Chapter 6

Discussion

6.1 Summary of Results

The work presented in this thesis revolves around the Stem Cell (SC) composition of colorectal neoplasia and pre-malignant lesions, and how it determines the molecular characteristics and micro-environmental composition of the lesions. In chapter 3, I proposed a framework to classify Colorectal Cancer (CRC) according to the proportion of progenitors present in each tumour, and taking the conventional Lgr5+ Crypt Base Columnar (CBC) and the Regenerative Stem Cell (RSC) as extreme phenotypic references. In Chapter 4, I analysed how reactive stroma can re-shape the homeostatic Wnt gradients and fuel colorectal transformation in a model of intestinal polyposis, the Vil1-*Grem1* mouse. Finally, in Chapter 5, I studied the link between WNT activation, stem characteristics and immune exclusion in mouse models of colorectal transformation. Furthermore, I proposed a mechanism by which WNT may be mediating an immune exclusion phenotype in progenitors from a WNT ligand-dependent model of colorectal polyposis, the *Lgr5-Rspo3* mouse. Overall, this work aims to highlight how the stem characteristics embedded within cancer-initiating cells can shape the selective acquisition of mutations and the interactions that neoplastic cells establish with their microenvironment, which ultimately dictate tumour evolution (Fig.50).

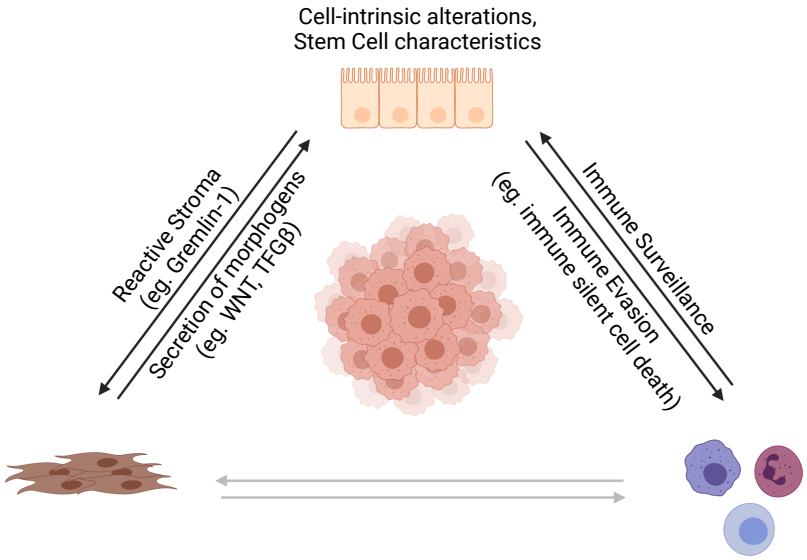

Figure 50: The cell-intrinsic characteristics of the intestinal epithelium condition and in turn are affected by the composition of the microenvironment. These interactions guide cancer-initiation and evolution.

6.2 Discussion

6.2.1 Different Pools of Progenitors Select for Cell-Extrinsic or Cell-Intrinsic forms of WNT disruption

Cancer is initiated by cells that possess stem-like characteristics. That is to say, self-renewal capacity and multi-directional differentiation potential. Years ago, experiments in APC-driven models demonstrated that colorectal adenomas were driven by acquisition of cell-intrinsic WNT alterations in Lgr5+ CBC[231, 125]. Despite this holding true for the majority of cases, it is not universal. Indeed, CRC can arise from different pools of progenitors that may acquire cell-intrinsic (eg. *APC* mutations) or cell-extrinsic (eg. *Rspo* fusions) forms of WNT disruption.

According to the Fearon and Vogelstein model of colorectal tumorigenesis[98], normal tissue transitions towards adenomas and, later, carcinomas, by successive accumulation of driver mutations. Distinct pre-cancerous lesions can be classified based on their histopathological characteristics into Tubulovillous (TVA) or serrated adenomas. Interestingly, the distribution of WNT alterations as well as the progenitor com-

position of these groups of lesions are not comparable. As previous studies show[231, 125], TVA have a CBC cell of origin and commonly acquire ligand-independent (LI) WNT mutations (eg. *APC, CTNNB1*). Contrarily, serrated polyps tend to have ligand-dependent (LD) WNT alterations (eg. *RNF43* mutations and *RSPO2/3* fusions), and minimal expression of common stem cell markers (i.e.*LGR5* and *ANXA1*), although sporadic populations of RSC can be observed within luminal areas of the lesions. The observation that early transformation in serrated models of colorectal polyposis (i.e. *Lgr5-Rspo3* and Vil1-*Grem1*) is driven by *Lgr5-*, *Anxa1-* progenitors, suggests that acquisition of RSC and/or CBC traits may be a later event in serrated polyposis, which matches the later acquisition of WNT mutations in the sequence of events described by Fearon and Vogelstein. Interestingly, the differential distribution of WNT alterations is maintained in advanced forms of colorectal neoplasia, with RSC cancers having higher numbers of LD mutations than their CBC counterparts and vice versa.

The reason why certain progenitor populations select for specific forms of WNT disruption is not clear, but this work provides some new evidence which may help to interpret this variation. The long life-span of CBC may allow for cell-intrinsic mutations (eg. *CTNNB1, APC*) to fixate within a crypt. Indeed, Flanagan et al demonstrated that *APC* mutations are selected in CBC cells, as they confer a supercompetitor phenotype and result in niche succession[234] (Fig.51). Contrarily, as observed in the *Lgr5-Rspo3* model, activation of the Lgr-Rspo axis (i.e. through *Rspo3* overexpression) within conventional crypts drives the acquisition of a "crypt-trapping" phenotype[142, 64], which hampers the expansion of CBC clones. This may be the reason why *RNF43* mutations and *RSPO3* fusions are not commonly observed in CBC-driven malignancies. Furthermore, LI forms of WNT disruption may hamper CBC to RSC conversion. For example, *APC* and *CTNNB1* mutations shelter cells from YAP-mediated β-catenin inhibition (See Fig. 3 in Chapter 1).

Instead of WNT activation, other mutations may confer a fitness advantage to cells outside of the crypts. Following this line of thought, mutations in *KRAS* and *BRAF* may be selected for in luminal areas, where they may activate YAP signaling and drive acquisition of RSC characteristics[160] (Fig.51). This could generate a pool of progenitor cells able to accumulate mutations and initiate serrated transformation. It is only in later stages of the disease that serrated tumours acquire WNT alterations, and these tend to be LD more frequently than in CBC-initiated lesions. Since acquisition of RSC characteristics requires the partial repression of the WNT transcriptomic programme[77], and YAP activation can effectively inhibit β-catenin

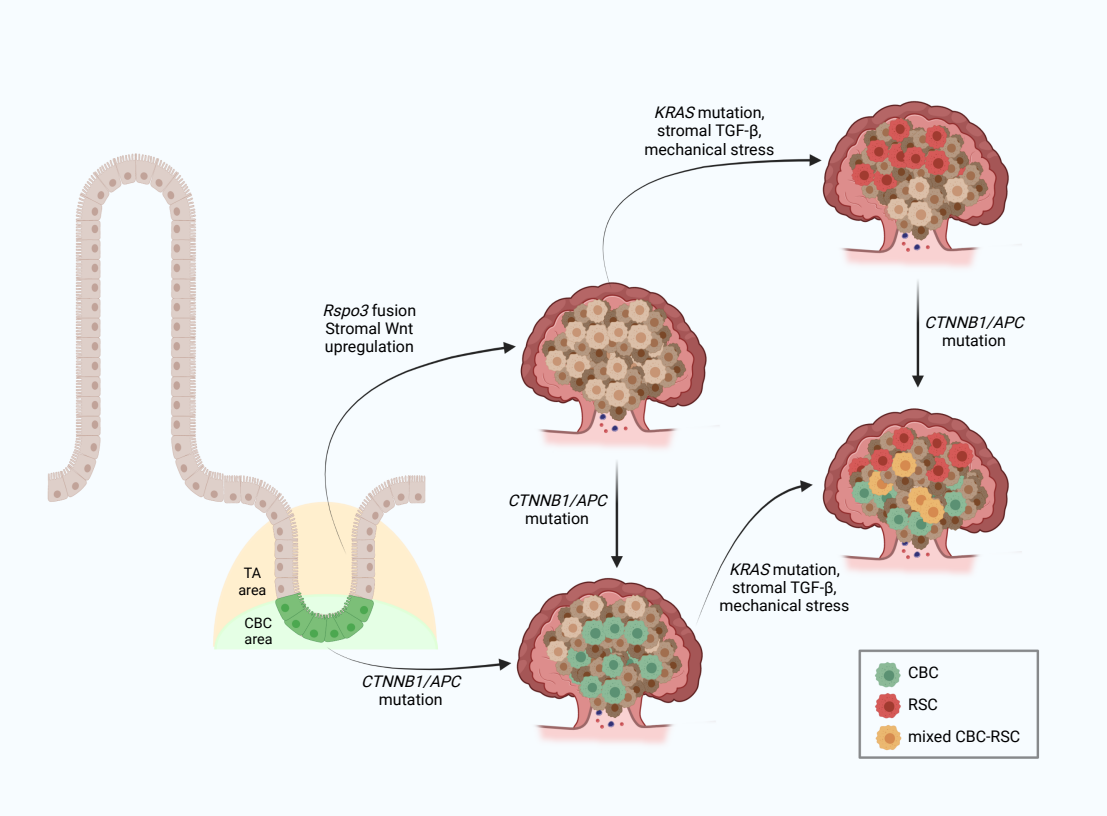

Figure 51: Hypothesis: different populations of progenitors select for specific forms of WNT disruption, which in turn conditions the SC composition and molecular characteristics of the tissue.

in cells that have LD mutations (See Fig. 3 in Chapter 1), selective acquisition of LD WNT alterations may help obtain a "just right" level of WNT activation. Moreover, *RNF43* mutations and *RSPO3* fusions are "altruistic", in the sense that they have paracrine effects and can encourage stem properties in neighbouring cells. Taking all together, ligand-dependent WNT activation may enable the maintenance of RSC characteristics in cells with cell-intrinsic YAP activating alterations, whereas neighbour cells that do not present YAP activation might acquire SC characteristics through cell-extrinsic WNT activation.

Interestingly, some animal models, like the APC^{Min} mouse, had regional differences in their SC composition, which indicates that the structural and molecular characteristics of the stroma may select for specific forms of progenitors over others. For example, it may be that the WNT high environment at the base of the crypts favour CBC phenotypes, whereas abundant TFG-β at the edges of the polyps might drive RSC conversion. Moreover, advanced lesions in complex tumorigenesis models, like the $Vil1\text{-}CreER^{T2}; Apc^{fl/+}; Kras^{G12D}; p53^{fl/fl}; Tgfbr1^{fl/fl}$ mouse, had a mixed

CBC-RSC composition, with some cells expressing simultaneously genes from the CBC and RSC signatures. This suggests that these SC phenotypes are not mutually exclusive, and that accumulation of enough alterations in combination with external cues, may drive a the expression of both transcriptomic programmes. In this example, *Apc* ablation may induce acquisition of CBC characteristics, whereas *Kras* and *Tgfbr1* mutations may activate RSC traits. Further studies will be needed to validate this hypothesis and to understand how WNT and plastic pathways interact to drive advanced forms of CRC.

6.2.2 Stem Cell Plastic Behaviour is a Useful Outcome of Therapy Response

Plasticity is the capacity of cells to reprogram in order to adapt to external cues. In the context of cancer treatment, cell plasticity can buffer the effects of a given drug, which may limit the net effect of the therapy. This was evidenced by Lgr5+ CBC ablation in APC^{Min} animals, which resulted in plastic adaptation by expansion of RSC progenitors. As a result, no differences in polyp size nor number of proliferative cells were detected in the treated samples. Similarly, in the FOxTROT human cohort, plastic properties correlated with a lack of response to therapy. Based on this, it becomes evident that the adaptive capacity of a given lesion carries important clinical implications. However, no index of cell plasticity is currently used in the clinic. In this piece of work, I propose a framework by which to assess adaptive changes in the SC composition of a tumour, which can be read as a surrogate of plasticity.

Currently, genomic sequencing of pre and post-treatment samples allows to assess changes in the clonality of a given lesion in response to selective pressure[100]. This strategy aims to identify the drivers behind resistance acquisition. Given the importance of plasticity for tumours adaptation, studying the pathways that drive interconversion between SC phenotypes could aid the search of these resistance determinants.

Importantly, the nature of the SC populations that sustain a given malignancy could inform the choice of treatment. Porcupine inhibition is a potential treatment to target cells with LD WNT alterations. However, it has important side effects in bone metabolism, which cause a loss of bone mass and strength[210]. In this study, WNT blockage in *Lgr5-Rspo3* animals evidenced that Lgr5+ and Lgr5- cells have different sensitivities to WNT inhibitions, which could be exploited therapeutically in early

tumours driven by expansion of Lgr5- progenitors. Furthermore, given the WNT-driven immune exclusion observed in Lgr5-Rspo3 mice, a combination of Porcupine inhibition and immune checkpoint blockage could increase the efficacy of this strategy.

6.2.3 The Epithelial and Stromal Compartments co-evolve during Colorectal Tumorigenesis

The intestinal epithelial and stromal compartments are entangled already from fetal stages. Elegant work by Shyer et al evidenced how changes in tissue architecture alter the distribution of cell populations and, consequently, the nature of the inter-compartmental interactions that drive intestinal development[241]. As the authors demonstrated, the formation of the villi generates an area of smaller surface-area-to-volume ratio at the tip of these structures. This causes an accumulation of Shh signals secreted by the epithelium, which leads to an increase in stromal Bmp ligands. Consequently, cells at the tip of the villi differentiate, and the SC characteristic of the tissue are transferred entirely to the epithelial population inhabiting the base of the crypts, where the surface-area-to-volume ratio is higher.

In adult intestines, cells co-exist in a dynamic equilibrium. However, when this balance is perturbed, tissues experience a temporal remodelling aimed to the re-establishment of homeostasis. This entails the coordinated effort of distinct cell compartments: upon epithelial injury, signals by damaged cells activate the surrounding fibroblasts and immune populations, whereas stromal cues drive the de-differentiation of epithelial cells needed for tissue regeneration[37, 29, 68].

This inter-compartmental dependency extends to settings of malignancy. Several stromal cues, like Hepatocyte Growth Factor, stromal-derived factor 1α, IL-17, PGE2 and TGF-β can shape the properties of the epithelium[124, 172, 173, 82, 158]. In turn, the epithelium can also secrete factors that modify the stroma, as observed in the VG mouse. In this HMPS model, a cell-intrinsic mutation results in the aberrant upregulation of the secreted BMP inhibitor Gremlin-1, which not only acts on epithelial cells, but also drives a stromal remodelling, with activation of fibroblasts populations and ectopic secretion of Wnt ligands. Interestingly, work from Allaire et al. suggested a profound alteration of the colon immune microenvironment upon stromal BMP inhibition, with infiltration of lymphocytes, monocytes and granulocytes[240]. The study of the immune compartment in the VG model awaits further research.

Importantly, treatment with a blocking Gremlin-1 antibody was enough to restore the original tissue architecture in VG intestines, which exemplifies the level of dependency between these two compartments in pathologic settings. Following from that, strategies aimed towards external cues, like the Gremlin-1 blocking antibody, may be efficient to prevent disease progression.

Drug resistance is the most important factor limiting response to treatment in cancer patients[100]. One important determinant of drug resistance is tumour heterogeneity, which increases as tumours progress. Consequently, the best clinical outcomes are achieved when tissue transformation is detected at early or even pre-malignant stages[100]. In this line of thought, Gremlin-1 blocking antibody treatment could constitute a successful strategy for HMPS patients with early forms of the disease. However, some advanced VG polyps resisted antibody treatment, which suggests that HMPS lesions may become independent from the stroma as the disease progresses.

6.2.4 WNT-driven Stem Cell Identity may Include Immune Evasion Characteristics

Previous work by Agudo et al suggested that only non-cycling SC possessed Immune Privilege, defined as the set of cell-intrinsic characteristics that enable cells to escape immune detection[14]. However, in this study, immune evasion was detected in different intestinal progenitor compartments (TA, CBC) in homeostatic and pathological settings, suggesting that certain degree of immune privilege is granted as part of the SC identity.

In addition to its role controlling stem characteristics, or perhaps because of it, WNT has been proposed as one of the main mediators of immune exclusion. Others have demonstrated this link in melanoma[197] and glioma[194]. The experiments presented here demonstrate that CRC lesions also acquire WNT-driven immune evasion. Indeed, treatment of a ligand-dependent model of colorectal polyposis with a WNT blocking agent was enough to drive T cell infiltration into transformed areas.

Cell death control is exerted by a plethora of mechanisms that differ between intestinal cell pools. Importantly, these differences translate into a higher or lower levels of immune surveillance. Different stimuli, like irradiation[6], staurosporine administration[84] or DTR-mediated ablation, cause CBC to die by apoptosis, a silent type of cell death that does not drive T cell infiltration into the tissue. Contrarily, immunogenic forms of cell death, like necroptosis or necrosis, involve the exposure

of damage signals and inflammatory mediators, which result in recruitment of immune cells into the tissue. Among them, pyroptosis is a type of cell death normally restricted to settings of pathogenic infiltration or tissue damage[85].

Gasdermins are mediators of pyroptosis that form pores in the membrane and induce cell lysis, with the consequent release of pro-inflammatory mediators. Despite the existence of various Gasdermin family members, all of them have a very similar N-terminal pore-forming domain, suggesting that they cause cell lysis by comparable mechanisms[88]. In this study, I focused on *Gsdmc4*, one of the top dysregulated genes in animal models of WNT disruption. This transcript, which expression is restricted to the TA compartment within WT intestines, was repressed in a ligand-dependent model of WNT-driven polyposis. However, WNT inhibition caused the upregulation of *Gsdmc4*, which was associated with the death of ECF progenitors and an influx of immune cells into the tissue. Based on these observation, it is plausible that WNT is mediating immune-exclusion at least partially through *Gsdmc4*-dependent down-regulation of pyroptosis in ligand-dependent polyps.

Interestingly, there was a clear dichotomy between the response of Lgr5+ and Lgr5- cells to WNT inhibition, which might be explained by a different susceptibility to specific forms of cell death. Given their vital role in intestinal homeostasis, CBC may be protected against immune-mediated killing by suppression of immunogenic cell death. Contrarily, later progenitors and differentiated cells may select for the most adequate cell death mechanisms depending on the context. For example, cells may die by apoptosis in homeostatic settings, but switch to pyroptosis when Pattern Recognition Receptors are engaged, so that the immune system becomes activated and mediates the elimination of the noxious stimuli (Fig.52)[85].

In the Lgr5-Rspo3 mouse model, hyper-proliferative progenitors self-organize forming ectopic crypts. The high turn-over within these structures might allow for the accumulation of mutations which, in an immune active environment, could drive the activation of cytotoxic cells. In this context, WNT-mediated repression of pyroptosis might mitigate the immune surveillance which ectopic crypts are subjected to, this way favouring their persistence over time. However, WNT blockage would cause cells to release that break, which might facilitate the activation of pyroptosis and the consequent recruitment of immune populations.

In recent years, the research community has made a collective effort to understand the link between WNT and the immune exclusion phenotype observed across malignancies[197, 194, 199, 200]. In this piece of work, I propose a mechanisms by which WNT activation may be protecting progenitors from cell death in malignancies

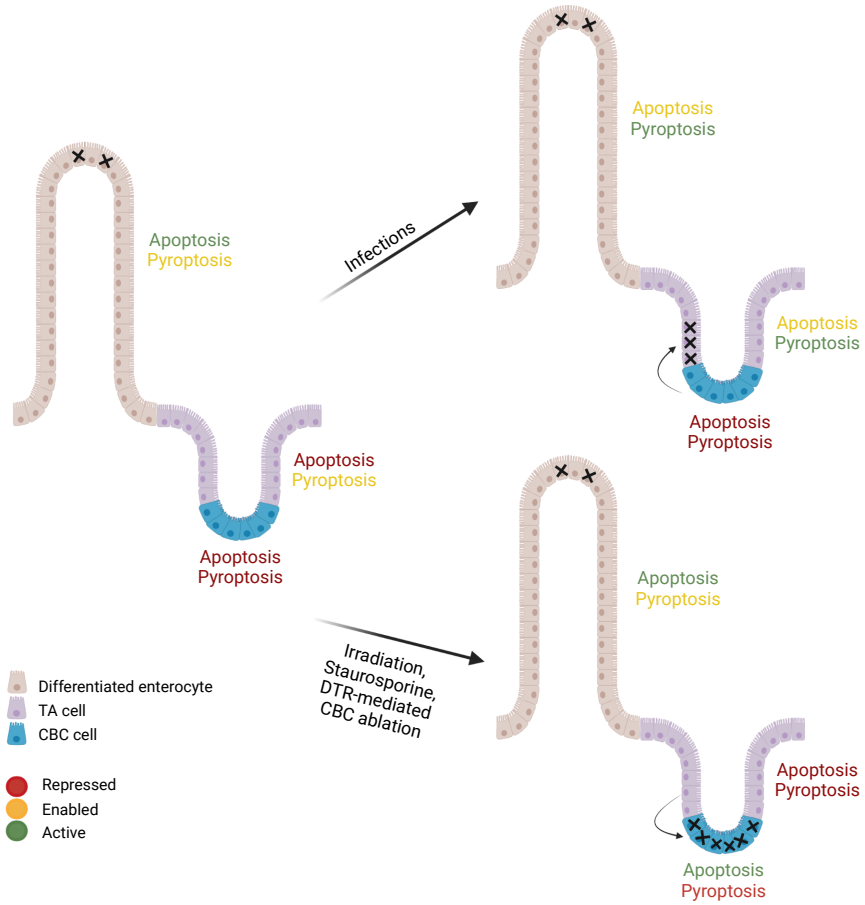

Figure 52: Distinct populations of Intestinal Epithelial Cells are subjected to different forms of programmed cell death.

driven by Lgr5- progenitors, but only additional research can tell the extend to which this mechanisms operates in other neoplastic models.

Unlike in *Lgr5-Rspo3* mice, T cell infiltration into APC^{Min} polyps was not associated to changes in *Gsdmc4*. Given the cell-intrinsic differences between the existing pools of intestinal progenitors, it may be that CBC acquire their WNT-induced immune evasion phenotype through alternative mechanisms. Consequently, future studies regarding WNT-driven immune exclusion could benefit from considering the progenitor composition of the lesion.

6.3 Concluding Remarks

The work presented within this thesis aims to highlight how the stem characteristics embedded within malignancies can shape the interactions that cancer epithelial cells establish with their environment, which ultimately dictate tumour evolution, and

emphasizes how this understanding can improve clinical practice. To do so, I first proposed a framework that permitted the classification of polyps and tumours based on their stem characteristics, and then used this set of tools to understand how these properties relate to important aspects of colorectal transformation, like cancer initiation, tumour-stromal interactions and selection for particular molecular drives.

The analysis presented within this thesis highlight the complexity of colorectal neoplasia and, without disregarding the vast predominance of tumours initiated by CBC progenitors, emphasizes the role that alternative stem cell populations may be playing in serrated polyps and their correspondent advanced lesions, thus fuelling the top-down models of colorectal tumorigenesis.

Furthermore, this work brings up the importance of integrating new clinical read-outs that account for the plastic characteristics embedded within colorectal tumours, for they have been shown to have important implications in therapy response. Indeed, the implementations of a tool like the Stem Cell Index into clinical practice could guide cancer adaptive therapy or, alternatively, be used to corner cancers down a evolutionary bottleneck which, if combined with therapeutic agents that compromise the plastic characteristics of the tissue, could result in successful cancer eradication.

Finally, given the different characteristics of the existing pools of intestinal progenitors, and how they shape the dynamics of the tissue, I propose that tools like the Stem Cell Index may help researchers classify their models according to relevant epithelial cell-intrinsic characteristics, which will hopefully aid CRC research in the future.

Appendix A

Supplementary Figures and Tables

EnsembleID	Gene name	Human EnsenbleID	Human Gene
ENSMUSG00000026831	1700007K13Rik	ENSG00000160345	C9orf116
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ENSMUSG00000028970	Abcb1b	ENSG00000085563	ABCB1
ENSMUSG00000018381	Abi3	ENSG00000108798	ABI3
ENSMUSG00000030935	Acsm3	ENSG00000005187	ACSM3
ENSMUSG00000061758	Akr1b10	ENSG00000198074	AKR1B10
ENSMUSG00000001642	Akr1b3	ENSG00000085662	AKR1B1
ENSMUSG00000029762	Akr1b8	ENSG00000198074	AKR1B10
ENSMUSG00000022636	Alcam	ENSG00000170017	ALCAM
ENSMUSG00000024659	Anxa1	ENSG00000135046	ANXA1
ENSMUSG00000029484	Anxa3	ENSG00000138772	ANXA3
ENSMUSG00000027712	Anxa5	ENSG00000164111	ANXA5
ENSMUSG00000054702	Ap1s3	ENSG00000152056	AP1S3
ENSMUSG00000033389	Arhgap44	ENSG00000006740	ARHGAP44
ENSMUSG00000037509	Arhgef4	ENSG00000136002	ARHGEF4
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ENSMUSG00000049866	Arl4c	ENSG00000188042	ARL4C
ENSMUSG00000018821	Avpi1	ENSG00000119986	AVPI1
ENSMUSG00000018126	Baiap2l2	ENSG00000128298	BAIAP2L2
ENSMUSG00000045763	Basp1	ENSG00000176788	BASP1
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ENSMUSG00000020785	Camkk1	ENSG00000004660	CAMKK1
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ENSMUSG00000021373	Cap2	ENSG00000112186	CAP2
ENSMUSG00000035547	Capn5	ENSG00000149260	CAPN5
ENSMUSG00000032373	Car12	ENSG00000074410	CA12
ENSMUSG00000027562	Car2	ENSG00000104267	CA2

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ENSMUSG00000019997	Ccn2	ENSG00000118523	CCN2
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ENSMUSG00000015093	Clic3	ENSG00000169583	CLIC3
ENSMUSG00000004665	Cnn2	ENSG00000064666	CNN2
ENSMUSG00000019866	Crybg1	ENSG00000112297	CRYBG1
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ENSMUSG00000029154	Cwh43	ENSG00000109182	CWH43
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ENSMUSG00000018920	Cxcl16	ENSG00000161921	CXCL16
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ENSMUSG00000090877	Hspa1b	ENSG00000204388	HSPA1B
ENSMUSG00000059970	Hspa2	ENSG00000126803	HSPA2
ENSMUSG00000004951	Hspb1	ENSG00000106211	HSPB1
ENSMUSG00000029657	Hsph1	ENSG00000120694	HSPH1
ENSMUSG00000010051	Hyal1	ENSG00000114378	HYAL1
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ENSMUSG00000037405	Icam1	ENSG00000090339	ICAM1
ENSMUSG00000020644	Id2	ENSG00000115738	ID2
ENSMUSG00000025492	Ifitm3	ENSG00000142089	IFITM3
ENSMUSG00000043088	Il17re	ENSG00000163701	IL17RE
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ENSMUSG00000024810	Il33	ENSG00000137033	IL33
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ENSMUSG00000018899	Irf1	ENSG00000125347	IRF1
ENSMUSG00000015533	Itga2	ENSG00000164171	ITGA2
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ENSMUSG00000020758	Itgb4	ENSG00000132470	ITGB4
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ENSMUSG00000021025	Nfkbia	ENSG00000100906	NFKBIA
ENSMUSG00000035356	Nfkbiz	ENSG00000144802	NFKBIZ
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ENSMUSG00000032860	P2ry2	ENSG00000175591	P2RY2
ENSMUSG00000048779	P2ry6	ENSG00000171631	P2RY6
ENSMUSG00000025931	Paqr8	ENSG00000170915	PAQR8
ENSMUSG00000028716	Pdzk1ip1	ENSG00000162366	PDZK1IP1
ENSMUSG00000020205	Phlda1	ENSG00000139289	PHLDA1
ENSMUSG00000010760	Phlda2	ENSG00000181649	PHLDA2
ENSMUSG00000020808	Pimreg	ENSG00000129195	PIMREG
ENSMUSG00000021822	Plau	ENSG00000122861	PLAU
ENSMUSG00000046223	Plaur	ENSG00000011422	PLAUR

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EnsembleID	Gene name	Human EnsenbleID	Human Gene
ENSMUSG00000020937	Plcd3	ENSG00000161714	PLCD3
ENSMUSG00000035818	Plekhs1	ENSG00000148735	PLEKHS1
ENSMUSG00000021701	Plk2	ENSG00000145632	PLK2
ENSMUSG00000038400	Pmepa1	ENSG00000124225	PMEPA1
ENSMUSG00000024538	Ppic	ENSG00000168938	PPIC
ENSMUSG00000039457	Ppl	ENSG00000118898	PPL
ENSMUSG00000068744	Psrc1	ENSG00000134222	PSRC1
ENSMUSG00000032487	Ptgs2	ENSG00000073756	PTGS2
ENSMUSG00000051343	Rab11fip5	ENSG00000135631	RAB11FIP5
ENSMUSG00000021062	Rab15	ENSG00000139998	RAB15
ENSMUSG00000020372	Rack1	ENSG00000204628	RACK1
ENSMUSG00000037110	Ralgapa2	ENSG00000188559	RALGAPA2
ENSMUSG00000026970	Rbms1	ENSG00000153250	RBMS1
ENSMUSG00000002458	Rgs19	ENSG00000171700	RGS19
ENSMUSG00000041845	Rhod	ENSG00000173156	RHOD
ENSMUSG00000041135	Ripk2	ENSG00000104312	RIPK2
ENSMUSG00000092837	Rpph1	ENSG00000277209	RPPH1
ENSMUSG00000022952	Runx1	ENSG00000159216	RUNX1
ENSMUSG00000042306	S100a14	ENSG00000189334	S100A14
ENSMUSG00000001020	S100a4	ENSG00000196154	S100A4
ENSMUSG00000001025	S100a6	ENSG00000197956	S100A6
ENSMUSG00000060487	Samd5	ENSG00000203727	SAMD5
ENSMUSG00000088689	Scarna17	ENSG00000251992	SCARNA17
ENSMUSG00000022123	Scel	ENSG00000136155	SCEL
ENSMUSG00000038264	Sema7a	ENSG00000138623	SEMA7A
ENSMUSG00000021403	Serpinb9b	ENSG00000170542	SERPINB9
ENSMUSG00000032261	Sh3bgrl2	ENSG00000198478	SH3BGRL2
ENSMUSG00000040918	Slc19a2	ENSG00000117479	SLC19A2
ENSMUSG00000025986	Slc39a10	ENSG00000196950	SLC39A10
ENSMUSG00000057193	Slc44a2	ENSG00000129353	SLC44A2
ENSMUSG00000040010	Slc7a5	ENSG00000103257	SLC7A5
ENSMUSG00000038963	Slco4a1	ENSG00000101187	SLCO4A1
ENSMUSG00000017002	Slpi	ENSG00000124107	SLPI
ENSMUSG00000064637	Snora20	ENSG00000207392	SNORA20
ENSMUSG00000064387	Snora73a	ENSG00000274266	SNORA73A
ENSMUSG00000065353	Snora73b	ENSG00000200087	SNORA73B
ENSMUSG00000065126	Snord104	ENSG00000199753	SNORD104
ENSMUSG00000064899	Snord118	ENSG00000200463	SNORD118
ENSMUSG00000105167	Snord43	ENSG00000263764	SNORD43
ENSMUSG00000093289	Snord92	ENSG00000264994	SNORD92
ENSMUSG00000053113	Socs3	ENSG00000184557	SOCS3

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EnsembleID	Gene name	Human EnsenbleID	Human Gene
ENSMUSG00000049313	Sorl1	ENSG00000137642	SORL1
ENSMUSG00000034401	Spata6	ENSG00000132122	SPATA6
ENSMUSG00000029304	Spp1	ENSG00000118785	SPP1
ENSMUSG00000039232	Stx11	ENSG00000135604	STX11
ENSMUSG00000006800	Sulf2	ENSG00000196562	SULF2
ENSMUSG00000031098	Syt8	ENSG00000149043	SYT8
ENSMUSG00000056313	Tcim	ENSG00000176907	TCIM
ENSMUSG00000001750	Tcirg1	ENSG00000110719	TCIRG1
ENSMUSG00000035493	Tgfbi	ENSG00000120708	TGFBI
ENSMUSG00000037820	Tgm2	ENSG00000198959	TGM2
ENSMUSG00000017466	Timp2	ENSG00000035862	TIMP2
ENSMUSG00000028776	Tinagl1	ENSG00000142910	TINAGL1
ENSMUSG00000039005	Tlr4	ENSG00000136869	TLR4
ENSMUSG00000031617	Tmem184c	ENSG00000164168	TMEM184C
ENSMUSG00000030095	Tmem43	ENSG00000170876	TMEM43
ENSMUSG00000024401	Tnf	ENSG00000232810	TNF
ENSMUSG00000019850	Tnfaip3	ENSG00000118503	TNFAIP3
ENSMUSG00000062210	Tnfaip8	ENSG00000145779	TNFAIP8
ENSMUSG00000028599	Tnfrsf1b	ENSG00000028137	TNFRSF1B
ENSMUSG00000035678	Tnfsf9	ENSG00000125657	TNFSF9
ENSMUSG00000044162	Tnip3	ENSG00000050730	TNIP3
ENSMUSG00000031097	Tnni2	ENSG00000130598	TNNI2
ENSMUSG00000026414	Tnnt2	ENSG00000118194	TNNT2
ENSMUSG00000017607	Tns4	ENSG00000131746	TNS4
ENSMUSG00000041779	Tram2	ENSG00000065308	TRAM2
ENSMUSG00000050747	Trim15	ENSG00000204610	TRIM15
ENSMUSG00000073399	Trim40	ENSG00000204614	TRIM40
ENSMUSG00000025511	Tspan4	ENSG00000214063	TSPAN4
ENSMUSG00000067377	Tspan6	ENSG00000000003	TSPAN6
ENSMUSG00000072235	Tuba1a	ENSG00000167552	TUBA1A
ENSMUSG00000073002	Vamp5	ENSG00000168899	VAMP5
ENSMUSG00000026728	Vim	ENSG00000026025	VIM
ENSMUSG00000037440	Vnn1	ENSG00000112299	VNN1
ENSMUSG00000017723	Wfdc2	ENSG00000101443	WFDC2
ENSMUSG00000027803	Wwtr1	ENSG00000018408	WWTR1
ENSMUSG00000011267	Zfp296	ENSG00000170684	ZNF296
ENSMUSG00000085795	Zfp703	ENSG00000183779	ZNF703
ENSMUSG00000027663	Zmat3	ENSG00000172667	ZMAT3
ENSMUSG00000073421	H2-Ab1	ENSG00000179344	HLA-DQB1
ENSMUSG00000055413	H2-Q5	ENSG00000204632	HLA-G
ENSMUSG00000105743	Mir1949		

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EnsembleID	**Gene name**	**Human EnsenbleID**	**Human Gene**
ENSMUSG00000085972	1110028F11Rik		
ENSMUSG00000097651	4930461G14Rik		
ENSMUSG00000081793	5730416F02Rik		
ENSMUSG00000092517	Art2a		
ENSMUSG00000075010	AW112010		
ENSMUSG00000095562	Erdr1		
ENSMUSG00000035778	Ggta1		
ENSMUSG00000069804	Gm10277		
ENSMUSG00000087342	Gm12238		
ENSMUSG00000073555	Gm4951		
ENSMUSG00000094790	Gm6625		
ENSMUSG00000036594	H2-Aa		
ENSMUSG00000026535	Ifi202b		
ENSMUSG00000054072	Iigp1		
ENSMUSG00000043165	Lor		
ENSMUSG00000075602	Ly6a		
ENSMUSG00000079018	Ly6c1		
ENSMUSG00000022584	Ly6c2		
ENSMUSG00000022583	Ly6f		
ENSMUSG00000022226	Mcpt2		
ENSMUSG00000093336	Mir1954		
ENSMUSG00000076948	Mir467e		
ENSMUSG00000071203	Naip5		
ENSMUSG00000079092	Prl2c2		
ENSMUSG00000056457	Prl2c3		
ENSMUSG00000037071	Scd1		
ENSMUSG00000064968	Snord47		
ENSMUSG00000093880	Tmem181c-ps		
ENSMUSG00000079451	Tmprss11g		
ENSMUSG00000000983	Wfdc18		
ENSMUSG00000051341	Zfp52		

Table A.1: Curated list of RSC genes

Table A.2: Statistics: Mouse autochtonous tumours

group1	group2	p	p.adj	p.format	p.signif	method
APCmin	A	0.5237	1	0.5237	ns	Wilcoxon
APCmin	AK	0.01212	0.28	0.01212	*	Wilcoxon
APCmin	AKPT	0.01212	0.28	0.01212	*	Wilcoxon
APCmin	BA	0.00404	0.097	0.00404	**	Wilcoxon
APCmin	BPN	0.00373	0.093	0.00373	**	Wilcoxon
APCmin	KP	0.01212	0.28	0.01212	*	Wilcoxon
APCmin	KPN	1.6E-05	0.00044	1.60E-05	****	Wilcoxon
A	AK	0.03571	0.68	0.03571	*	Wilcoxon
A	AKPT	0.03571	0.68	0.03571	*	Wilcoxon
A	BA	0.01587	0.32	0.01587	*	Wilcoxon
A	BPN	0.00253	0.066	0.00253	**	Wilcoxon
A	KP	0.03571	0.68	0.03571	*	Wilcoxon
A	KPN	0.00032	0.0087	0.00032	***	Wilcoxon
AK	AKPT	0.7	1	0.7	ns	Wilcoxon
AK	BA	0.62857	1	0.62857	ns	Wilcoxon
AK	BPN	0.26667	1	0.26667	ns	Wilcoxon
AK	KP	0.1	1	0.1	ns	Wilcoxon
AK	KPN	0.44835	1	0.44835	ns	Wilcoxon
AKPT	BA	0.4	1	0.4	ns	Wilcoxon
AKPT	BPN	1	1	1	ns	Wilcoxon
AKPT	KP	0.1	1	0.1	ns	Wilcoxon
AKPT	KPN	0.18022	1	0.18022	ns	Wilcoxon
BA	BPN	0.10909	1	0.10909	ns	Wilcoxon
BA	KP	0.05714	0.86	0.05714	ns	Wilcoxon
BA	KPN	0.68352	1	0.68352	ns	Wilcoxon
BPN	KP	0.06667	0.93	0.06667	ns	Wilcoxon
BPN	KPN	0.03584	0.68	0.03584	*	Wilcoxon
KP	KPN	0.13626	1	0.13626	ns	Wilcoxon

Overall Anova	p.value
All groups	3.36E-06

Table A.3: Statistics: Tumour-derived organoids

group1	group2	p	p.adj	p.format	p.signif	method
A	AK	5.66E-03	0.062	0.0057	**	Wilcoxon
A	AKPT	9.49E-01	1	0.9495	ns	Wilcoxon
A	BPN	1.47E-03	0.021	0.0015	**	Wilcoxon
A	KP	3.85E-02	0.31	0.0385	*	Wilcoxon
A	KPN	2.65E-05	0.0004	2.60E-05	****	Wilcoxon
AK	AKPT	1.96E-02	0.2	0.0196	*	Wilcoxon
AK	BPN	8.25E-01	1	0.8252	ns	Wilcoxon
AK	KP	7.27E-01	1	0.7273	ns	Wilcoxon
AK	KPN	2.36E-01	1	0.2359	ns	Wilcoxon
AKPT	BPN	2.86E-02	0.26	0.0286	*	Wilcoxon
AKPT	KP	1.14E-01	0.8	0.1143	ns	Wilcoxon
AKPT	KPN	4.04E-03	0.053	0.004	**	Wilcoxon
BPN	KP	6.29E-01	1	0.6286	ns	Wilcoxon
BPN	KPN	4.04E-03	0.053	0.004	**	Wilcoxon
KP	KPN	7.76E-01	1	0.7758	ns	Wilcoxon

Overall anova all groups	p.value 7.78E-06

Table A.4: Statistics human pre-malignant lesions

group1	group2	pvalue	padj	p.significance	method
TVA	TSA	0.25	0.75	ns	Wilcoxon
TVA	SSL	0.000532	0.0032	***	Wilcoxon
TVA	IBD LGD	0.00779	0.039	**	Wilcoxon
TSA	SSL	0.315	0.75	ns	Wilcoxon
TSA	IBD LGD	0.698	0.75	ns	Wilcoxon
SSL	IBD LGD	0.176	0.7	ns	Wilcoxon

Overall anova all groups	p.value 0.00213

Table A.5: Statistics human pre-malignant tumours

CRIS-A	CRIS-B	0.074	0.3	ns
CRIS-A	CRIS-C	0.000000518	0.0000047	****
CRIS-A	CRIS-D	0.00178	0.0089	**
CRIS-A	CRIS-E	0.00267	0.0016	***
CRIS-B	CRIS-C	0.000000292	0.0000029	****
CRIS-B	CRIS-D	0.0000722	0.00051	****
CRIS-B	CRIS-E	0.00000598	0.000048	****
CRIS-C	CRIS-D	0.131	0.39	****
CRIS-C	CRIS-E	0.594	1	ns
CRIS-D	CRIS-E	0.531	1	ns

overall anova all groups	p.value 6.40E-12

Gene name	CBC number	RSC number	CBC %	RSC %
APC	26	9	0.684211	0.236842
TP53	17	10	0.447368	0.263158
KRAS	12	11	0.315789	0.289474
PIK3CA	7	7	0.184211	0.184211
FBXW7	4	5	0.105263	0.131579
SMAD4	2	3	0.052632	0.078947
TCF7L2	1	0	0.026316	0
NRAS	3	0	0.078947	0
SMAD2	1	3	0.026316	0.078947
ARID1A	3	5	0.078947	0.131579
ATM	0	3	0	0.078947
FN1	1	1	0.026316	0.026316
CTNNB1	2	3	0.052632	0.078947
PTPRU	0	3	0	0.078947
BRAF	2	15	0.052632	0.394737
CHD4	0	3	0	0.078947
SOX9	1	1	0.026316	0.026316
GNAS	0	2	0	0.052632
TGFBR2	0	2	0	0.052632
ELF3	0	1	0	0.026316
ACVR1B	0	1	0	0.026316
AXIN2	1	0	0.026316	0
RBM10	2	1	0.052632	0.026316
CAD	0	0	0	0
AKAP9	1	0	0.026316	0
PCBP1	1	2	0.026316	0.052632
NF1	2	1	0.052632	0.026316
CREBBP	0	4	0	0.105263
PIK3R1	2	2	0.052632	0.052632
EGFR	0	2	0	0.052632
CASP8	0	1	0	0.026316
CTCF	2	0	0.052632	0
IDH2	0	0	0	0
DIS3	1	1	0.026316	0.026316
MED12	0	1	0	0.026316
MED24	0	1	0	0.026316
ASPM	1	1	0.026316	0.026316
MAP3K4	1	1	0.026316	0.026316
CLSPN	2	2	0.052632	0.052632
SOS2	1	0	0.026316	0
PPP2R1A	1	1	0.026316	0.026316

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Gene name	CBC number	RSC number	CBC %	RSC %
CNOT1	1	2	0.026316	0.052632
CHD9	1	3	0.026316	0.078947
BRWD1	1	1	0.026316	0.026316
TRIO	1	1	0.026316	0.026316
GOLGA5	0	4	0	0.105263
TP53BP1	0	1	0	0.026316
SMC1A	0	2	0	0.052632
NTN4	0	1	0	0.026316
FOXP1	0	1	0	0.026316
RTN4	0	0	0	0
CDC73	1	0	0.026316	0
TAF1	0	0	0	0
CDK12	2	4	0.052632	0.105263
MGA	1	3	0.026316	0.078947
BCOR	0	2	0	0.052632
SRGAP3	1	1	0.026316	0.026316
PTEN	2	1	0.052632	0.026316
DNMT3A	1	0	0.026316	0
STAG2	0	1	0	0.026316
WT1	0	1	0	0.026316
ATRX	2	1	0.052632	0.026316
GATA3	0	3	0	0.078947
CDKN1B	0	0	0	0
RUNX1	1	3	0.026316	0.078947
MAP2K1	0	1	0	0.026316
CEP290	1	5	0.026316	0.131579
MSR1	1	2	0.026316	0.052632
MECOM	0	0	0	0
NUP98	1	1	0.026316	0.026316
ACO1	0	1	0	0.026316
ARNTL	0	0	0	0
BPTF	1	0	0.026316	0
NR2F2	0	0	0	0
ITSN1	0	4	0	0.105263
POLR2B	0	1	0	0.026316
CUL1	0	1	0	0.026316
ZC3H11A	1	0	0.026316	0
PTGS1	0	1	0	0.026316
NUP107	0	0	0	0
FXR1	0	1	0	0.026316
SF3B1	0	5	0	0.131579

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Gene name	**CBC number**	**RSC number**	**CBC %**	**RSC %**
WIPF1	0	0	0	0
TBX3	0	2	0	0.052632
SYNCRIP	0	0	0	0
TCF12	1	1	0.026316	0.026316
NR4A2	0	2	0	0.052632
ACSL6	0	0	0	0
RAD21	1	2	0.026316	0.052632
PTPN11	1	0	0.026316	0
BMPR2	0	7	0	0.184211
RNF43	0	6	0	0.157895
GSK3B	1	1	0.026316	0.026316
ZNRF3	0	2	0	0.052632
LGR4	0	1	0	0.026316
LGR5	1	2	0.026316	0.052632
LGR6	0	2	0	0.052632
POLA1	0	1	0	0.026316
POLA2	0	0	0	0
POLB	0	1	0	0.026316
POLD1	0	2	0	0.052632
POLD2	0	1	0	0.026316
POLD3	0	0	0	0
POLD4	0	0	0	0
POLDIP2	0	0	0	0
POLDIP3	0	1	0	0.026316
POLE	1	1	0.026316	0.026316
POLE2	0	0	0	0
POLE3	0	0	0	0
POLE4	0	0	0	0
RSPO3fusion	0	2	0	0.052632
APCloss	9	2	0.236842	0.052632
SMAD4loss	27	5	0.710526	0.131579
DCCloss	28	5	0.736842	0.131579

Table A.6: Number of alterations in top and bottom deciles.

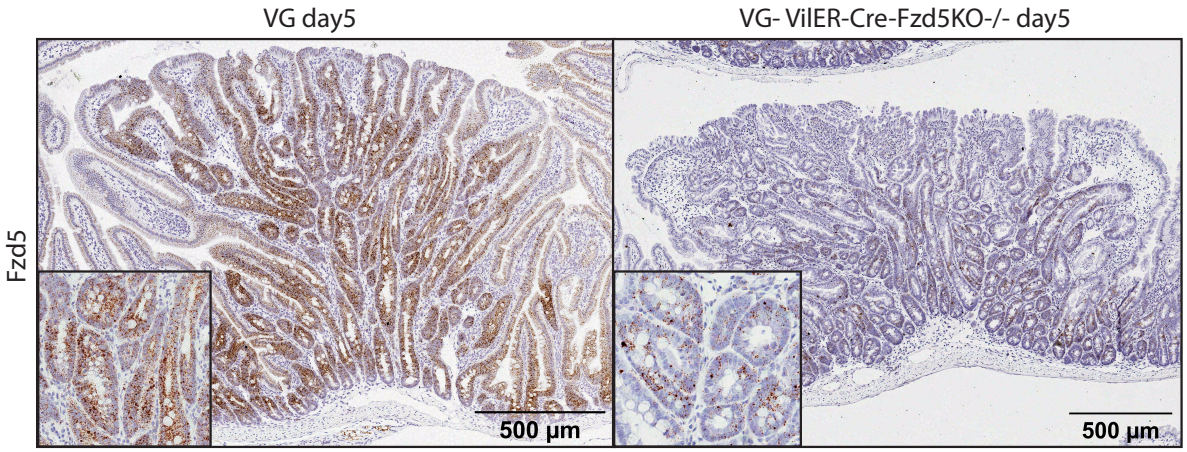

Figure S1: Levels of long-term *Fzd5* VG-VilER-Cre-Fzd5KO$^{-/-}$ animals. A-D *In Situ Hybridization* of *Fzd5* in VG (A) and VG-VilER-Cre-Fzd5KO$^{-/-}$(B) mice collected 5 days after the first injection.

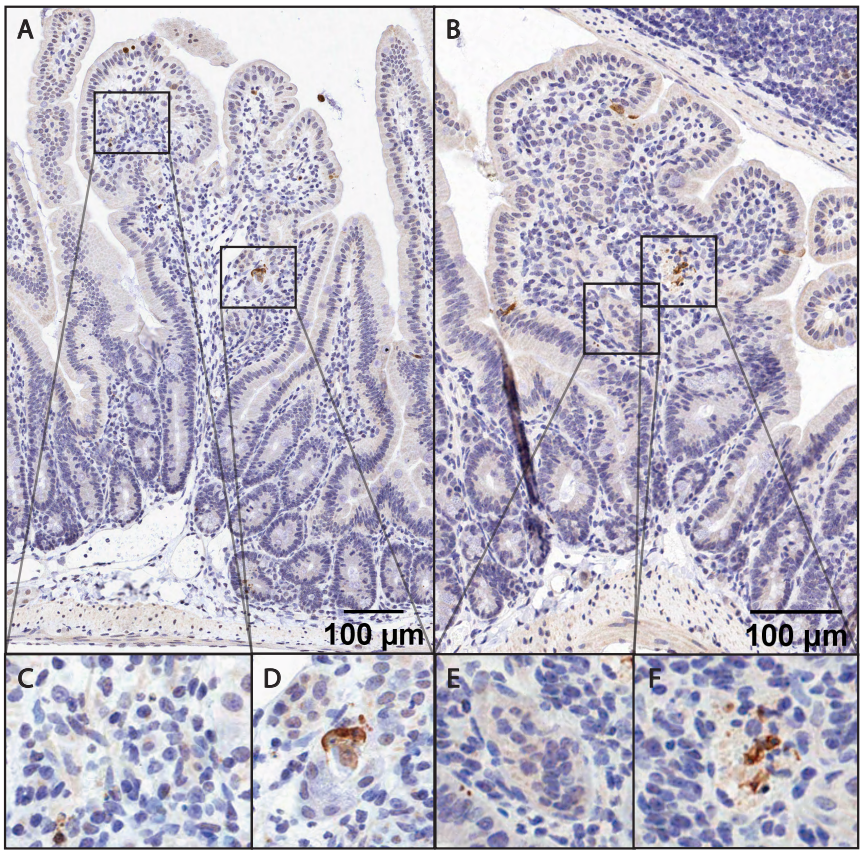

Figure S2: Caspase-3 is only sporadically expressed by cells in the ECF from RXC004-treated Lgr5-Rspo3 animals. A-F. IHC for Caspase-3 in polyps from Lgr5-Rspo3 animals treated for five days with RXC004.



Figure S3: *Gsdmc4* is mostly expressed by Enterocyte progenitors. t-SNE plots generated using the Broad Institute interface and the single cell RNAseq data generated by Haber et al [248]. A. Segregation of cell types using the t-SNE1 and t-SNE2 components. B. Expression levels of *Gsdmc4* per cell.

Bibliography

[1] Helmuth Gehart and Hans Clevers. "Tales from the crypt: new insights into intestinal stem cells". In: *Nature Reviews Gastroenterology Hepatology* 16.1 (2019), pp. 19–34. ISSN: 1759-5053. DOI: 10.1038/s41575-018-0081-y. URL: https://doi.org/10.1038/s41575-018-0081-y.

[2] C. Schiller et al. "Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging". In: *Aliment Pharmacol Ther* 22.10 (2005), pp. 971–9. ISSN: 0269-2813 (Print) 0269-2813. DOI: 10.1111/j.1365-2036.2005.02683.x.

[3] N. Sasaki et al. "Reg4+ deep crypt secretory cells function as epithelial niche for Lgr5+ stem cells in colon". In: *Proc Natl Acad Sci U S A* 113.37 (2016), E5399–407. ISSN: 0027-8424. DOI: 10.1073/pnas.1607327113.

[4] H. Cheng and C. P. Leblond. "Origin, differentiation and renewal of the four main epithelial cell types in the mouse small intestine. V. Unitarian Theory of the origin of the four epithelial cell types". In: *Am J Anat* 141.4 (1974), pp. 537–61. ISSN: 0002-9106 (Print) 0002-9106. DOI: 10.1002/aja.1001410407.

[5] Laurens G. Van der Flier et al. "The Intestinal Wnt/TCF Signature". In: *Gastroenterology* 132.2 (2007), pp. 628–632. ISSN: 0016-5085. DOI: 10.1053/j.gastro.2006.08.039. URL: https://doi.org/10.1053/j.gastro.2006.08.039.

[6] Nick Barker et al. "Identification of stem cells in small intestine and colon by marker gene Lgr5". In: *Nature* 449.7165 (2007), pp. 1003–1007. ISSN: 1476-4687. DOI: 10.1038/nature06196. URL: https://doi.org/10.1038/nature06196.

[7] J. Munoz et al. "The Lgr5 intestinal stem cell signature: robust expression of proposed quiescent '+4' cell markers". In: *Embo j* 31.14 (2012), pp. 3079–91. ISSN: 0261-4189. DOI: 10.1038/emboj.2012.166.

[8] Anna Merlos-Suárez et al. "The Intestinal Stem Cell Signature Identifies Colorectal Cancer Stem Cells and Predicts Disease Relapse". In: *Cell Stem Cell* 8.5 (2011), pp. 511–524. ISSN: 1934-5909. DOI: https://doi.org/10.1016/j.stem.2011.02.020. URL: http://www.sciencedirect.com/science/article/pii/S193459091100110X.

[9] Tea Fevr et al. “Wnt/-Catenin Is Essential for Intestinal Homeostasis and Maintenance of Intestinal Stem Cells”. In: *Molecular and Cellular Biology* 27.21 (2007), pp. 7551–7559. DOI: 10.1128/mcb.01034-07. URL: https://mcb.asm.org/content/mcb/27/21/7551.full.pdf.

[10] Allan McI Mowat. “To respond or not to respond — a personal perspective of intestinal tolerance”. In: *Nature Reviews Immunology* 18.6 (2018), pp. 405–415. ISSN: 1474-1741. DOI: 10.1038/s41577-018-0002-x. URL: https://doi.org/10.1038/s41577-018-0002-x.

[11] J. L. Coombes et al. “A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism”. In: *J Exp Med* 204.8 (2007), pp. 1757–64. ISSN: 0022-1007 (Print) 0022-1007. DOI: 10.1084/jem.20070590.

[12] M. Rimoldi et al. “Intestinal immune homeostasis is regulated by the crosstalk between epithelial cells and dendritic cells”. In: *Nat Immunol* 6.5 (2005), pp. 507–14. ISSN: 1529-2908 (Print) 1529-2908. DOI: 10.1038/ni1192.

[13] J. V. Forrester et al. “Immune privilege or privileged immunity?” In: *Mucosal Immunol* 1.5 (2008), pp. 372–81. ISSN: 1933-0219. DOI: 10.1038/mi.2008.27.

[14] J. Agudo et al. “Quiescent Tissue Stem Cells Evade Immune Surveillance”. In: *Immunity* 48.2 (2018), 271–285.e5. ISSN: 1074-7613 (Print) 1074-7613. DOI: 10.1016/j.immuni.2018.02.001.

[15] S. Takashima et al. “T cell-derived interferon- programs stem cell death in immune-mediated intestinal damage”. In: *Sci Immunol* 4.42 (2019). ISSN: 2470-9468. DOI: 10.1126/sciimmunol.aay8556.

[16] Jiaqiao Fan et al. “Adoptive Cell Transfer: Is it a Promising Immunotherapy for Colorectal Cancer?” In: *Theranostics* 8.20 (2018), pp. 5784–5800. ISSN: 1838-7640. DOI: 10.7150/thno.29035. URL: https://pubmed.ncbi.nlm.nih.gov/30555581%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6276301/.

[17] Toufic Mayassi and Bana Jabri. “Human intraepithelial lymphocytes”. In: *Mucosal Immunology* 11.5 (2018), pp. 1281–1289. ISSN: 1935-3456. DOI: 10.1038/s41385-018-0016-5. URL: https://doi.org/10.1038/s41385-018-0016-5.

[18] J. Rajagopal and B. Z. Stanger. “Plasticity in the Adult: How Should the Waddington Diagram Be Applied to Regenerating Tissues?” In: *Dev Cell* 36.2 (2016), pp. 133–7. ISSN: 1534-5807. DOI: 10.1016/j.devcel.2015.12.021.

[19] C. H. Waddington. *The strategy of the genes; a discussion of some aspects of theoretical biology*. London: Allen Unwin, 1957.

[20] K. Takahashi and S. Yamanaka. “Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors”. In: *Cell* 126.4 (2006), pp. 663–76. ISSN: 0092-8674 (Print) 0092-8674. DOI: 10.1016/j.cell.2006.07.024.

[21] Laila Ritsma et al. “Intestinal crypt homeostasis revealed at single-stem-cell level by in vivo live imaging”. In: *Nature* 507.7492 (2014), pp. 362–365. ISSN: 1476-4687. DOI: 10.1038/nature12972. URL: https://doi.org/10.1038/nature12972.

[22] J. H. van Es et al. “Dll1+ secretory progenitor cells revert to stem cells upon crypt damage”. In: *Nat Cell Biol* 14.10 (2012), pp. 1099–1104. ISSN: 1465-7392. DOI: 10.1038/ncb2581.

[23] H. Tian et al. “A reserve stem cell population in small intestine renders Lgr5-positive cells dispensable”. In: *Nature* 478.7368 (2011), pp. 255–9. ISSN: 0028-0836. DOI: 10.1038/nature10408.

[24] K. S. Yan et al. “The intestinal stem cell markers Bmi1 and Lgr5 identify two functionally distinct populations”. In: *Proc Natl Acad Sci U S A* 109.2 (2012), pp. 466–71. ISSN: 0027-8424. DOI: 10.1073/pnas.1118857109.

[25] F. de Sousa e Melo et al. “A distinct role for Lgr5(+) stem cells in primary and metastatic colon cancer”. In: *Nature* 543.7647 (2017), pp. 676–680. ISSN: 0028-0836. DOI: 10.1038/nature21713.

[26] C. Benedikt Westphalen et al. “Long-lived intestinal tuft cells serve as colon cancer-initiating cells”. In: *The Journal of clinical investigation* 124.3 (2014), p. 1283. DOI: 10.1172/JCI73434.

[27] P. W. Tetteh et al. “Replacement of Lost Lgr5-Positive Stem Cells through Plasticity of Their Enterocyte-Lineage Daughters”. In: *Cell Stem Cell* 18.2 (2016), pp. 203–13. ISSN: 1875-9777. DOI: 10.1016/j.stem.2016.01.001.

[28] S. Yu et al. “Paneth Cell Multipotency Induced by Notch Activation following Injury”. In: *Cell Stem Cell* 23.1 (2018), 46–59.e5. ISSN: 1875-9777. DOI: 10.1016/j.stem.2018.05.002.

[29] Christine Harnack et al. “R-spondin 3 promotes stem cell recovery and epithelial regeneration in the colon”. In: *Nature Communications* 10.1 (2019), p. 4368. ISSN: 2041-1723. DOI: 10.1038/s41467-019-12349-5. URL: https://doi.org/10.1038/s41467-019-12349-5.

[30] Tae-Hee Kim et al. “Broadly permissive intestinal chromatin underlies lateral inhibition and cell plasticity”. In: *Nature* 506.7489 (2014), pp. 511–515. ISSN: 1476-4687. DOI: 10.1038/nature12903. URL: https://doi.org/10.1038/nature12903.

[31] Lucas T. J. Kaaij et al. “DNA methylation dynamics during intestinal stem cell differentiation reveals enhancers driving gene expression in the villus”. In: *Genome Biology* 14.5 (2013), R50. ISSN: 1474-760X. DOI: 10.1186/gb-2013-14-5-r50. URL: https://doi.org/10.1186/gb-2013-14-5-r50.

[32] Shiro Yui et al. "YAP/TAZ-Dependent Reprogramming of Colonic Epithelium Links ECM Remodeling to Tissue Regeneration". In: *Cell stem cell* 22.1 (2018), 35–49.e7. ISSN: 1875-9777 1934-5909. DOI: 10.1016/j.stem.2017.11.001. URL: https://pubmed.ncbi.nlm.nih.gov/29249464%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5766831/.

[33] Ysbrand M. Nusse et al. "Parasitic helminths induce fetal-like reversion in the intestinal stem cell niche". In: *Nature* 559.7712 (2018), pp. 109–113. ISSN: 1476-4687. DOI: 10.1038/s41586-018-0257-1. URL: https://doi.org/10.1038/s41586-018-0257-1.

[34] Arshad Ayyaz et al. "Single-cell transcriptomes of the regenerating intestine reveal a revival stem cell". In: *Nature* 569.7754 (2019), pp. 121–125. ISSN: 1476-4687. DOI: 10.1038/s41586-019-1154-y. URL: https://doi.org/10.1038/s41586-019-1154-y.

[35] S. Date and T. Sato. "Mini-gut organoids: reconstitution of the stem cell niche". In: *Annu Rev Cell Dev Biol* 31 (2015), pp. 269–89. ISSN: 1081-0706. DOI: 10.1146/annurev-cellbio-100814-125218.

[36] Toshiro Sato et al. "Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche". In: *Nature* 459.7244 (2009), pp. 262–265. ISSN: 1476-4687. DOI: 10.1038/nature07935. URL: https://doi.org/10.1038/nature07935.

[37] J. H. Hageman et al. "Intestinal Regeneration: Regulation by the Microenvironment". In: *Dev Cell* 54.4 (2020), pp. 435–446. ISSN: 1534-5807. DOI: 10.1016/j.devcel.2020.07.009.

[38] R. Takada et al. "Monounsaturated fatty acid modification of Wnt protein: its role in Wnt secretion". In: *Dev Cell* 11.6 (2006), pp. 791–801. ISSN: 1534-5807 (Print) 1534-5807. DOI: 10.1016/j.devcel.2006.10.003.

[39] Rene Jackstadt, Michael Charles Hodder, and Owen James Sansom. "WNT and -Catenin in Cancer: Genes and Therapy". In: *Annual Review of Cancer Biology* 4.1 (2020), pp. 177–196. DOI: 10.1146/annurev-cancerbio-030419-033628. URL: https://www.annualreviews.org/doi/abs/10.1146/annurev-cancerbio-030419-033628.

[40] E. Dekker et al. "Colorectal cancer". In: *Lancet* 394.10207 (2019), pp. 1467–1480. ISSN: 0140-6736. DOI: 10.1016/s0140-6736(19)32319-0.

[41] Vladimir Korinek et al. "Depletion of epithelial stem-cell compartments in the small intestine of mice lacking Tcf-4". In: *Nature Genetics* 19.4 (1998), pp. 379–383. ISSN: 1546-1718. DOI: 10.1038/1270. URL: https://doi.org/10.1038/1270.

[42] D. Pinto et al. "Canonical Wnt signals are essential for homeostasis of the intestinal epithelium". In: *Genes Dev* 17.14 (2003), pp. 1709–13. ISSN: 0890-9369 (Print) 0890-9369. DOI: 10.1101/gad.267103.

[43] Frank Kuhnert et al. “Essential requirement for Wnt signaling in proliferation of adult small intestine and colon revealed by adenoviral expression of Dickkopf-1”. In: *Proceedings of the National Academy of Sciences* 101.1 (2004), pp. 266–271. DOI: 10.1073/pnas.2536800100. URL: https://www.pnas.org/content/pnas/101/1/266.full.pdf.

[44] Z. Kabiri et al. “Stroma provides an intestinal stem cell niche in the absence of epithelial Wnts”. In: *Development* 141.11 (2014), pp. 2206–15. ISSN: 0950-1991. DOI: 10.1242/dev.104976.

[45] Joel Johansson et al. “RAL GTPases Drive Intestinal Stem Cell Function and Regeneration through Internalization of WNT Signalosomes”. In: *Cell Stem Cell* 24.4 (2019), 592–607.e7. ISSN: 1934-5909. DOI: https://doi.org/10.1016/j.stem.2019.02.002. URL: https://www.sciencedirect.com/science/article/pii/S193459091930044X.

[46] K. Murata et al. “Ascl2-Dependent Cell Dedifferentiation Drives Regeneration of Ablated Intestinal Stem Cells”. In: *Cell Stem Cell* 26.3 (2020), 377–390.e6. ISSN: 1934-5909 (Print) 1875-9777. DOI: 10.1016/j.stem.2019.12.011.

[47] Jurian Schuijers et al. “Ascl2 Acts as an R-spondin/Wnt-Responsive Switch to Control Stemness in Intestinal Crypts”. In: *Cell Stem Cell* 16.2 (2015), pp. 158–170. ISSN: 1934-5909. DOI: 10.1016/j.stem.2014.12.006.

[48] Toshiro Sato et al. “Paneth cells constitute the niche for Lgr5 stem cells in intestinal crypts”. In: *Nature* 469.7330 (2011), pp. 415–418. ISSN: 1476-4687 0028-0836. DOI: 10.1038/nature09637. URL: https://pubmed.ncbi.nlm.nih.gov/21113151%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3547360/.

[49] M. Shoshkes-Carmel et al. “Subepithelial telocytes are an important source of Wnts that supports intestinal crypts”. In: *Nature* (2018). ISSN: 0028-0836. DOI: 10.1038/s41586-018-0084-4.

[50] B. Degirmenci et al. “GLI1-expressing mesenchymal cells form the essential Wnt-secreting niche for colon stem cells”. In: *Nature* 558.7710 (2018), pp. 449–453. ISSN: 0028-0836. DOI: 10.1038/s41586-018-0190-3.

[51] Gediminas Greicius et al. “PDGFRα pericryptal stromal cells are the critical source of Wnts and RSPO3 for murine intestinal stem cells in vivo”. In: *Proceedings of the National Academy of Sciences* (2018). DOI: 10.1073/pnas.1713510115. URL: http://www.pnas.org/content/pnas/early/2018/03/19/1713510115.full.pdf.

[52] M. Ozawa, H. Baribault, and R. Kemler. “The cytoplasmic domain of the cell adhesion molecule uvomorulin associates with three independent proteins structurally related in different species”. In: *The EMBO journal* 8.6 (1989), pp. 1711–1717. ISSN: 0261-4189 1460-2075. URL: https://pubmed.ncbi.nlm.nih.gov/2788574%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC401013/.

[53] T. Zhan, N. Rindtorff, and M. Boutros. "Wnt signaling in cancer". In: *Oncogene* 36.11 (2017), pp. 1461–1473. ISSN: 1476-5594. DOI: 10.1038/onc.2016.304. URL: https://doi.org/10.1038/onc.2016.304.

[54] E. Gómez-Orte et al. "Multiple functions of the noncanonical Wnt pathway". In: *Trends Genet* 29.9 (2013), pp. 545–53. ISSN: 0168-9525 (Print) 0168-9525. DOI: 10.1016/j.tig.2013.06.003.

[55] H. Miyoshi et al. "Wnt5a potentiates TGF-beta signaling to promote colonic crypt regeneration after tissue injury". In: *Science* 338.6103 (2012), pp. 108–13. ISSN: 0036-8075. DOI: 10.1126/science.1223821.

[56] Wim B. M. de Lau, Berend Snel, and Hans C. Clevers. "The R-spondin protein family". In: *Genome Biology* 13.3 (2012), p. 242. ISSN: 1474-760X. DOI: 10.1186/gb-2012-13-3-242. URL: https://doi.org/10.1186/gb-2012-13-3-242.

[57] O. Kazanskaya et al. "R-Spondin2 is a secreted activator of Wnt/beta-catenin signaling and is required for Xenopus myogenesis". In: *Dev Cell* 7.4 (2004), pp. 525–34. ISSN: 1534-5807 (Print) 1534-5807. DOI: 10.1016/j.devcel.2004.07.019.

[58] W. de Lau et al. "Lgr5 homologues associate with Wnt receptors and mediate R-spondin signalling". In: *Nature* 476.7360 (2011), pp. 293–7. ISSN: 0028-0836. DOI: 10.1038/nature10337.

[59] K. S. Carmon et al. "R-spondins function as ligands of the orphan receptors LGR4 and LGR5 to regulate Wnt/beta-catenin signaling". In: *Proc Natl Acad Sci U S A* 108.28 (2011), pp. 11452–7. ISSN: 0027-8424. DOI: 10.1073/pnas.1106083108.

[60] Andrei Glinka et al. "LGR4 and LGR5 are R-spondin receptors mediating Wnt/-catenin and Wnt/PCP signalling". In: *EMBO reports* 12.10 (2011), pp. 1055–1061. ISSN: 1469-221X. DOI: 10.1038/embor.2011.175. URL: https://www.embopress.org/doi/abs/10.1038/embor.2011.175.

[61] H. F. Farin et al. "Visualization of a short-range Wnt gradient in the intestinal stem-cell niche". In: *Nature* 530.7590 (2016), pp. 340–3. ISSN: 0028-0836. DOI: 10.1038/nature16937.

[62] Elaine E. Storm et al. "Targeting PTPRK-RSPO3 colon tumours promotes differentiation and loss of stem-cell function". In: *Nature* 529.7584 (2016), pp. 97–100. ISSN: 1476-4687. DOI: 10.1038/nature16466. URL: https://doi.org/10.1038/nature16466.

[63] D. J. Huels et al. "Wnt ligands influence tumour initiation by controlling the number of intestinal stem cells". In: *Nature Communications* 9.1 (2018), p. 1132. ISSN: 2041-1723. DOI: 10.1038/s41467-018-03426-2. URL: https://doi.org/10.1038/s41467-018-03426-2.

[64] K. S. Yan et al. “Non-equivalence of Wnt and R-spondin ligands during Lgr5(+) intestinal stem-cell self-renewal”. In: *Nature* 545.7653 (2017), pp. 238–242. ISSN: 0028-0836. DOI: 10.1038/nature22313.

[65] Richard N. Wang et al. “Bone Morphogenetic Protein (BMP) signaling in development and human diseases”. In: *Genes Diseases* 1.1 (2014), pp. 87–105. ISSN: 2352-3042. DOI: https://doi.org/10.1016/j.gendis.2014.07.005. URL: http://www.sciencedirect.com/science/article/pii/S2352304214000105.

[66] Zhen Qi et al. “BMP restricts stemness of intestinal Lgr5+ stem cells by directly suppressing their signature genes”. In: *Nature Communications* 8.1 (2017), p. 13824. ISSN: 2041-1723. DOI: 10.1038/ncomms13824. URL: https://doi.org/10.1038/ncomms13824.

[67] N. McCarthy et al. “Distinct Mesenchymal Cell Populations Generate the Essential Intestinal BMP Signaling Gradient”. In: *Cell Stem Cell* 26.3 (2020), 391–402.e5. ISSN: 1934-5909 (Print) 1875-9777. DOI: 10.1016/j.stem.2020.01.008.

[68] Martijn A. J. Koppens et al. “BMP pathway antagonism by lt;emgt;Grem1lt;/emgt; regulates epithelial cell fate in intestinal regeneration”. In: *bioRxiv* (2021), p. 2021.01.06.425570. DOI: 10.1101/2021.01.06.425570. URL: http://biorxiv.org/content/early/2021/01/07/2021.01.06.425570.abstract.

[69] S. Rakoff-Nahoum et al. “Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis”. In: *Cell* 118.2 (2004), pp. 229–41. ISSN: 0092-8674 (Print) 0092-8674. DOI: 10.1016/j.cell.2004.07.002.

[70] F. R. Greten et al. “IKKbeta links inflammation and tumorigenesis in a mouse model of colitis-associated cancer”. In: *Cell* 118.3 (2004), pp. 285–96. ISSN: 0092-8674 (Print) 0092-8674. DOI: 10.1016/j.cell.2004.07.013.

[71] A. Nenci et al. “Epithelial NEMO links innate immunity to chronic intestinal inflammation”. In: *Nature* 446.7135 (2007), pp. 557–61. ISSN: 0028-0836. DOI: 10.1038/nature05698.

[72] C. A. Richmond et al. “JAK/STAT-1 Signaling Is Required for Reserve Intestinal Stem Cell Activation during Intestinal Regeneration Following Acute Inflammation”. In: *Stem Cell Reports* 10.1 (2018), pp. 17–26. ISSN: 2213-6711. DOI: 10.1016/j.stemcr.2017.11.015.

[73] Marco Marini et al. “TNF-neutralization ameliorates the severity of murine Crohn’s-like ileitis by abrogation of intestinal epithelial cell apoptosis”. In: *Proceedings of the National Academy of Sciences* 100.14 (2003), pp. 8366–8371. DOI: 10.1073/pnas.1432897100. URL: https://www.pnas.org/content/pnas/100/14/8366.full.pdf.

[74] Porfirio Nava et al. “Interferon-gamma regulates intestinal epithelial homeostasis through converging beta-catenin signaling pathways”. In: *Immunity* 32.3 (2010), pp. 392–402. ISSN: 1097-4180 1074-7613. DOI: 10.1016/j.immuni.2010.03.001. URL: https://pubmed.ncbi.nlm.nih.gov/20303298%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2859189/.

[75] Mahima Swamy et al. “Intestinal intraepithelial lymphocyte activation promotes innate antiviral resistance”. In: *Nature Communications* 6.1 (2015), p. 7090. ISSN: 2041-1723. DOI: 10.1038/ncomms8090. URL: https://doi.org/10.1038/ncomms8090.

[76] Jing Cai et al. “The Hippo signaling pathway restricts the oncogenic potential of an intestinal regeneration program”. In: *Genes development* 24.21 (2010), pp. 2383–2388. ISSN: 1549-5477 0890-9369. DOI: 10.1101/gad.1978810. URL: https://pubmed.ncbi.nlm.nih.gov/21041407%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2964748/.

[77] Alex Gregorieff et al. “Yap-dependent reprogramming of Lgr5+ stem cells drives intestinal regeneration and cancer”. In: *Nature* 526.7575 (2015), pp. 715–718. ISSN: 1476-4687. DOI: 10.1038/nature15382. URL: https://doi.org/10.1038/nature15382.

[78] Koji Taniguchi et al. “A gp130–Src–YAP module links inflammation to epithelial regeneration”. In: *Nature* 519.7541 (2015), pp. 57–62. ISSN: 1476-4687. DOI: 10.1038/nature14228. URL: https://doi.org/10.1038/nature14228.

[79] Shenghong Ma et al. “The Hippo Pathway: Biology and Pathophysiology”. In: *Annual Review of Biochemistry* 88.1 (2019), pp. 577–604. DOI: 10.1146/annurev-biochem-013118-111829. URL: https://www.annualreviews.org/doi/abs/10.1146/annurev-biochem-013118-111829.

[80] Tito Panciera et al. “Mechanobiology of YAP and TAZ in physiology and disease”. In: *Nature Reviews Molecular Cell Biology* 18.12 (2017), pp. 758–770. ISSN: 1471-0080. DOI: 10.1038/nrm.2017.87. URL: https://doi.org/10.1038/nrm.2017.87.

[81] Masayuki Fukata et al. “Toll-like receptor-4 promotes the development of colitis-associated colorectal tumors”. In: *Gastroenterology* 133.6 (2007), pp. 1869–1881. ISSN: 1528-0012 0016-5085. DOI: 10.1053/j.gastro.2007.09.008. URL: https://pubmed.ncbi.nlm.nih.gov/18054559%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2180834/.

[82] Manolis Roulis et al. “Paracrine orchestration of intestinal tumorigenesis by a mesenchymal niche”. In: *Nature* 580.7804 (2020), pp. 524–529. ISSN: 1476-4687. DOI: 10.1038/s41586-020-2166-3. URL: https://doi.org/10.1038/s41586-020-2166-3.

[83] D. E. Pefani et al. “TGF- Targets the Hippo Pathway Scaffold RASSF1A to Facilitate YAP/SMAD2 Nuclear Translocation”. In: *Mol Cell* 63.1 (2016), pp. 156–66. ISSN: 1097-2765. DOI: 10.1016/j.molcel.2016.05.012.

[84] Elle Koren et al. “ARTS mediates apoptosis and regeneration of the intestinal stem cell niche”. In: *Nature Communications* 9.1 (2018), p. 4582. ISSN: 2041-1723. DOI: 10.1038/s41467-018-06941-4. URL: https://doi.org/10.1038/s41467-018-06941-4.

[85] Jay V. Patankar and Christoph Becker. “Cell death in the gut epithelium and implications for chronic inflammation”. In: *Nature Reviews Gastroenterology Hepatology* 17.9 (2020), pp. 543–556. ISSN: 1759-5053. DOI: 10.1038/s41575-020-0326-4. URL: https://doi.org/10.1038/s41575-020-0326-4.

[86] Nobuhiko Kayagaki et al. “Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling”. In: *Nature* 526.7575 (2015), pp. 666–671. ISSN: 1476-4687. DOI: 10.1038/nature15541. URL: https://doi.org/10.1038/nature15541.

[87] Jianjin Shi et al. “Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death”. In: *Nature* 526.7575 (2015), pp. 660–665. ISSN: 1476-4687. DOI: 10.1038/nature15514. URL: https://doi.org/10.1038/nature15514.

[88] Petr Broz, Pablo Pelegrín, and Feng Shao. “The gasdermins, a protein family executing cell death and inflammation”. In: *Nature Reviews Immunology* 20.3 (2020), pp. 143–157. ISSN: 1474-1741. DOI: 10.1038/s41577-019-0228-2. URL: https://doi.org/10.1038/s41577-019-0228-2.

[89] Aimée Parker et al. “Elevated apoptosis impairs epithelial cell turnover and shortens villi in TNF-driven intestinal inflammation”. In: *Cell Death Disease* 10.2 (2019), p. 108. ISSN: 2041-4889. DOI: 10.1038/s41419-018-1275-5. URL: https://doi.org/10.1038/s41419-018-1275-5.

[90] M. C. Liebl and T. G. Hofmann. “The Role of p53 Signaling in Colorectal Cancer”. In: *Cancers (Basel)* 13.9 (2021). ISSN: 2072-6694 (Print) 2072-6694. DOI: 10.3390/cancers13092125.

[91] H. Sung et al. “Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries”. In: *CA Cancer J Clin* (2021). ISSN: 0007-9235. DOI: 10.3322/caac.21660.

[92] Yuan-Hong Xie, Ying-Xuan Chen, and Jing-Yuan Fang. “Comprehensive review of targeted therapy for colorectal cancer”. In: *Signal Transduction and Targeted Therapy* 5.1 (2020), p. 22. ISSN: 2059-3635. DOI: 10.1038/s41392-020-0116-z. URL: https://doi.org/10.1038/s41392-020-0116-z.

[93] S. Syngal et al. “ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes”. In: *Am J Gastroenterol* 110.2 (2015), 223–62, quiz 263. ISSN: 0002-9270. DOI: 10.1038/ajg.2014.435.

[94] I. Nishisho et al. “Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients”. In: *Science* 253.5020 (1991), pp. 665–9. ISSN: 0036-8075 (Print) 0036-8075. DOI: 10.1126/science.1651563.

[95] Y. Miki et al. "Disruption of the APC gene by a retrotransposal insertion of L1 sequence in a colon cancer". In: *Cancer Res* 52.3 (1992), pp. 643–5. ISSN: 0008-5472 (Print) 0008-5472.

[96] R. Houlston et al. "Mutations in DPC4 (SMAD4) cause juvenile polyposis syndrome, but only account for a minority of cases". In: *Hum Mol Genet* 7.12 (1998), pp. 1907–12. ISSN: 0964-6906 (Print) 0964-6906. DOI: 10.1093/hmg/7.12.1907.

[97] J. R. Howe et al. "Germline mutations of the gene encoding bone morphogenetic protein receptor 1A in juvenile polyposis". In: *Nat Genet* 28.2 (2001), pp. 184–7. ISSN: 1061-4036 (Print) 1061-4036. DOI: 10.1038/88919.

[98] Eric R. Fearon and Bert Vogelstein. "A genetic model for colorectal tumorigenesis". In: *Cell* 61.5 (1990), pp. 759–767. ISSN: 0092-8674. DOI: https://doi.org/10.1016/0092-8674(90)90186-I. URL: https://www.sciencedirect.com/science/article/pii/009286749090186I.

[99] Dung T. Le et al. "PD-1 Blockade in Tumors with Mismatch-Repair Deficiency". In: *New England Journal of Medicine* 372.26 (2015), pp. 2509–2520. DOI: 10.1056/NEJMoa1500596. URL: https://www.nejm.org/doi/full/10.1056/NEJMoa1500596.

[100] Neil Vasan, José Baselga, and David M. Hyman. "A view on drug resistance in cancer". In: *Nature* 575.7782 (2019), pp. 299–309. ISSN: 1476-4687. DOI: 10.1038/s41586-019-1730-1. URL: https://doi.org/10.1038/s41586-019-1730-1.

[101] A. Sadanandam et al. "A colorectal cancer classification system that associates cellular phenotype and responses to therapy". In: *Nat Med* 19.5 (2013), pp. 619–25. ISSN: 1078-8956. DOI: 10.1038/nm.3175.

[102] E. Melo Felipe De Sousa et al. "Poor-prognosis colon cancer is defined by a molecularly distinct subtype and develops from serrated precursor lesions". In: *Nature Medicine* 19.5 (2013), p. 614. ISSN: 1078-8956. DOI: 10.1038/nm.3174.

[103] Laetitia Marisa et al. "Gene Expression Classification of Colon Cancer into Molecular Subtypes: Characterization, Validation, and Prognostic Value (Molecular Classification of Colon Cancer)". In: 10.5 (2013), e1001453. DOI: 10.1371/journal.pmed.1001453.

[104] A. Schlicker et al. "Subtypes of primary colorectal tumors correlate with response to targeted treatment in colorectal cell lines". In: *BMC Med Genomics* 5 (2012), p. 66. ISSN: 1755-8794. DOI: 10.1186/1755-8794-5-66.

[105] E. Budinska et al. "Gene expression patterns unveil a new level of molecular heterogeneity in colorectal cancer". In: *J Pathol* 231.1 (2013), pp. 63–76. ISSN: 0022-3417. DOI: 10.1002/path.4212.

[106] P. Roepman et al. “Colorectal cancer intrinsic subtypes predict chemotherapy benefit, deficient mismatch repair and epithelial-to-mesenchymal transition”. In: *Int J Cancer* 134.3 (2014), pp. 552–62. ISSN: 0020-7136. DOI: 10.1002/ijc.28387.

[107] Guinney Justin et al. “The consensus molecular subtypes of colorectal cancer”. In: *Nature Medicine* 21.11 (2015). ISSN: 1078-8956. DOI: 10.1038/nm.3967.

[108] D. V. F. Tauriello et al. “TGFbeta drives immune evasion in genetically reconstituted colon cancer metastasis”. In: *Nature* 554.7693 (2018), pp. 538–543. ISSN: 0028-0836. DOI: 10.1038/nature25492.

[109] A. Sveen et al. “Colorectal Cancer Consensus Molecular Subtypes Translated to Preclinical Models Uncover Potentially Targetable Cancer Cell Dependencies”. In: *Clin Cancer Res* 24.4 (2018), pp. 794–806. ISSN: 1078-0432 (Print) 1078-0432. DOI: 10.1158/1078-0432.ccr-17-1234.

[110] Heinz-Josef Lenz et al. “Impact of Consensus Molecular Subtype on Survival in Patients With Metastatic Colorectal Cancer: Results From CALGB/SWOG 80405 (Alliance)”. In: *Journal of Clinical Oncology* 37.22 (2019), pp. 1876–1885. DOI: 10.1200/jco.18.02258. URL: https://ascopubs.org/doi/abs/10.1200/JCO.18.02258.

[111] J. K. Mooi et al. “The prognostic impact of consensus molecular subtypes (CMS) and its predictive effects for bevacizumab benefit in metastatic colorectal cancer: molecular analysis of the AGITG MAX clinical trial”. In: *Annals of Oncology* 29.11 (2018), pp. 2240–2246. ISSN: 0923-7534. DOI: 10.1093/annonc/mdy410. URL: https://doi.org/10.1093/annonc/mdy410.

[112] Claudio Isella et al. “Stromal contribution to the colorectal cancer transcriptome”. In: *Nature Genetics* 47.4 (2015), pp. 312–319. ISSN: 1546-1718. DOI: 10.1038/ng.3224. URL: https://doi.org/10.1038/ng.3224.

[113] Claudio Isella et al. “Selective analysis of cancer-cell intrinsic transcriptional traits defines novel clinically relevant subtypes of colorectal cancer”. In: *Nature Communications* 8.1 (2017), p. 15107. ISSN: 2041-1723. DOI: 10.1038/ncomms15107. URL: https://doi.org/10.1038/ncomms15107.

[114] Jul Cohnheim. “Congenitales, quergestreiftes Muskelsarkom der Nieren”. In: *Archiv für pathologische Anatomie und Physiologie und für klinische Medicin* 65.1 (1875), pp. 64–69. ISSN: 1432-2307. DOI: 10.1007/BF01978936. URL: https://doi.org/10.1007/BF01978936.

[115] R. Virchow. “Editorial archive für pathologische”. In: *Anat Physiol Klin Med* 8 (1855), pp. 23–54.

[116] M. Askanazy. “Die Teratome nach ihrem Bau, ihrem Verlauf, ihrer Genese und im Vergleich zum experimentellen Teratoid”. In: *Deutsch Pathol* 11 (1907), pp. 39–82.

[117] T. Lapidot et al. “A cell initiating human acute myeloid leukaemia after transplantation into SCID mice”. In: *Nature* 367.6464 (1994), pp. 645–8. ISSN: 0028-0836 (Print) 0028-0836. DOI: 10.1038/367645a0.

[118] D. Bonnet and J. E. Dick. “Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell”. In: *Nat Med* 3.7 (1997), pp. 730–7. ISSN: 1078-8956 (Print) 1078-8956. DOI: 10.1038/nm0797-730.

[119] M. Al-Hajj et al. “Prospective identification of tumorigenic breast cancer cells”. In: *Proc Natl Acad Sci U S A* 100.7 (2003), pp. 3983–8. ISSN: 0027-8424 (Print) 0027-8424. DOI: 10.1073/pnas.0530291100.

[120] S. K. Singh et al. “Identification of human brain tumour initiating cells”. In: *Nature* 432.7015 (2004), pp. 396–401. ISSN: 0028-0836. DOI: 10.1038/nature03128.

[121] Catherine A. O’Brien et al. “A human colon cancer cell capable of initiating tumour growth in immunodeficient mice”. In: *Nature* 445.7123 (2007), pp. 106–110. ISSN: 1476-4687. DOI: 10.1038/nature05372. URL: https://doi.org/10.1038/nature05372.

[122] Lucia Ricci-Vitiani et al. “Identification and expansion of human colon-cancer-initiating cells”. In: *Nature* 445.7123 (2007), pp. 111–115. ISSN: 1476-4687. DOI: 10.1038/nature05384. URL: https://doi.org/10.1038/nature05384.

[123] P. Dalerba et al. “Phenotypic characterization of human colorectal cancer stem cells”. In: *Proc Natl Acad Sci U S A* 104.24 (2007), pp. 10158–63. ISSN: 0027-8424 (Print) 0027-8424. DOI: 10.1073/pnas.0703478104.

[124] Louis Vermeulen et al. “Wnt activity defines colon cancer stem cells and is regulated by the microenvironment”. In: *Nature Cell Biology* 12.5 (2010), pp. 468–476. ISSN: 1476-4679. DOI: 10.1038/ncb2048. URL: https://doi.org/10.1038/ncb2048.

[125] Nick Barker et al. “Crypt stem cells as the cells-of-origin of intestinal cancer”. In: *Nature* 457.7229 (2009), pp. 608–611. ISSN: 1476-4687. DOI: 10.1038/nature07602. URL: https://doi.org/10.1038/nature07602.

[126] Samuel Asfaha et al. “Krt19+/Lgr5 Cells Are Radioresistant Cancer-Initiating Stem Cells in the Colon and Intestine”. In: *Cell Stem Cell* 16.6 (2015), pp. 627–638. ISSN: 1934-5909. DOI: https://doi.org/10.1016/j.stem.2015.04.013. URL: http://www.sciencedirect.com/science/article/pii/S193459091500171X.

[127] A. E. Powell et al. “Inducible loss of one Apc allele in Lrig1-expressing progenitor cells results in multiple distal colonic tumors with features of familial adenomatous polyposis”. In: *Am J Physiol Gastrointest Liver Physiol* 307.1 (2014), G16–23. ISSN: 0193-1857. DOI: 10.1152/ajpgi.00358.2013.

[128] O. J. Sansom et al. “Loss of Apc in vivo immediately perturbs Wnt signaling, differentiation, and migration”. In: *Genes Dev* 18.12 (2004), pp. 1385–90. ISSN: 0890-9369 (Print) 0890-9369. DOI: 10.1101/gad.287404.

[129] I. M. Shih et al. “Top-down morphogenesis of colorectal tumors”. In: *Proc Natl Acad Sci U S A* 98.5 (2001), pp. 2640–5. ISSN: 0027-8424 (Print) 0027-8424. DOI: 10.1073/pnas.051629398.

[130] E. E. Torlakovic et al. “Sessile serrated adenoma (SSA) vs. traditional serrated adenoma (TSA)”. In: *Am J Surg Pathol* 32.1 (2008), pp. 21–9. ISSN: 0147-5185 (Print) 0147-5185. DOI: 10.1097/PAS.0b013e318157f002.

[131] Anna-Pavlina G. Haramis et al. “De Novo Crypt Formation and Juvenile Polyposis on BMP Inhibition in Mouse Intestine”. In: *Science* 303.5664 (2004), pp. 1684–1686. DOI: 10.1126/science.1093587. URL: https://science.sciencemag.org/content/sci/303/5664/1684.full.pdf.

[132] H. Davis et al. “Aberrant epithelial GREM1 expression initiates colonic tumorigenesis from cells outside the stem cell niche”. In: (2015).

[133] S. Schwitalla et al. “Intestinal tumorigenesis initiated by dedifferentiation and acquisition of stem-cell-like properties”. In: *Cell* 152.1-2 (2013), pp. 25–38. ISSN: 0092-8674. DOI: 10.1016/j.cell.2012.12.012.

[134] A. S. Tsukamoto et al. “Expression of the int-1 gene in transgenic mice is associated with mammary gland hyperplasia and adenocarcinomas in male and female mice”. In: *Cell* 55.4 (1988), pp. 619–25. ISSN: 0092-8674 (Print) 0092-8674. DOI: 10.1016/0092-8674(88)90220-6.

[135] K. W. Kinzler et al. “Identification of FAP locus genes from chromosome 5q21”. In: *Science* 253.5020 (1991), pp. 661–5. ISSN: 0036-8075 (Print) 0036-8075. DOI: 10.1126/science.1651562.

[136] V. Korinek et al. “Constitutive transcriptional activation by a beta-catenin-Tcf complex in APC-/- colon carcinoma”. In: *Science* 275.5307 (1997), pp. 1784–7. ISSN: 0036-8075 (Print) 0036-8075. DOI: 10.1126/science.275.5307.1784.

[137] P. J. Morin et al. “Activation of beta-catenin-Tcf signaling in colon cancer by mutations in beta-catenin or APC”. In: *Science* 275.5307 (1997), pp. 1787–90. ISSN: 0036-8075 (Print) 0036-8075. DOI: 10.1126/science.275.5307.1787.

[138] Donna M. Muzny et al. “Comprehensive molecular characterization of human colon and rectal cancer”. In: *Nature* 487.7407 (2012), pp. 330–337. ISSN: 1476-4687. DOI: 10.1038/nature11252. URL: https://doi.org/10.1038/nature11252.

[139] Seshagiri Somasekar et al. “Recurrent R-spondin fusions in colon cancer”. In: *Nature* 488.7413 (2012), p. 660. ISSN: 0028-0836. DOI: 10.1038/nature11282.

[140] Sam O. Kleeman et al. “Exploiting differential Wnt target gene expression to generate a molecular biomarker for colorectal cancer stratification”. In: *Gut* (2019), gutjnl-2019–319126. DOI: 10.1136/gutjnl-2019-319126. URL: http://gut.bmj.com/content/early/2019/09/27/gutjnl-2019-319126.abstract.

[141] S. Sekine et al. “Frequent PTPRK-RSPO3 fusions and RNF43 mutations in colorectal traditional serrated adenoma”. In: *J Pathol* 239.2 (2016), pp. 133–8. ISSN: 0022-3417. DOI: 10.1002/path.4709.

[142] John Hilkens et al. “RSPO3 expands intestinal stem cell and niche compartments and drives tumorigenesis”. In: *Gut* 66.6 (2017), pp. 1095–1105. DOI: 10.1136/gutjnl-2016-311606. URL: https://gut.bmj.com/content/gutjnl/66/6/1095.full.pdf.

[143] N. Beerenwinkel et al. “Genetic progression and the waiting time to cancer”. In: *PLoS Comput Biol* 3.11 (2007), e225. ISSN: 1553-734x. DOI: 10.1371/journal.pcbi.0030225.

[144] Teng Han et al. “R-Spondin chromosome rearrangements drive Wnt-dependent tumour initiation and maintenance in the intestine”. In: *Nature Communications* 8.1 (2017), p. 15945. ISSN: 2041-1723. DOI: 10.1038/ncomms15945. URL: https://doi.org/10.1038/ncomms15945.

[145] Lukas E Dow et al. “Apc Restoration Promotes Cellular Differentiation and Reestablishes Crypt Homeostasis in Colorectal Cancer”. In: *Cell* 161.7 (2015), pp. 1539–1552. ISSN: 0092-8674. DOI: https://doi.org/10.1016/j.cell.2015.05.033. URL: http://www.sciencedirect.com/science/article/pii/S0092867415006236.

[146] Marcus M. Fischer et al. “RSPO3 antagonism inhibits growth and tumorigenicity in colorectal tumors harboring common Wnt pathway mutations”. In: *Scientific Reports* 7.1 (2017), p. 15270. ISSN: 2045-2322. DOI: 10.1038/s41598-017-15704-y. URL: https://doi.org/10.1038/s41598-017-15704-y.

[147] Xi C. He et al. “BMP signaling inhibits intestinal stem cell self-renewal through suppression of Wnt–-catenin signaling”. In: *Nature Genetics* 36.10 (2004), pp. 1117–1121. ISSN: 1546-1718. DOI: 10.1038/ng1430. URL: https://doi.org/10.1038/ng1430.

[148] L. L. Kodach et al. “The bone morphogenetic protein pathway is inactivated in the majority of sporadic colorectal cancers”. In: *Gastroenterology* 134.5 (2008), pp. 1332–41. ISSN: 0016-5085. DOI: 10.1053/j.gastro.2008.02.059.

[149] I. P. Tomlinson et al. “Multiple common susceptibility variants near BMP pathway loci GREM1, BMP4, and BMP2 explain part of the missing heritability of colorectal cancer”. In: *PLoS Genet* 7.6 (2011), e1002105. ISSN: 1553-7390 (Print) 1553-7390. DOI: 10.1371/journal.pgen.1002105.

[150] K. Loh et al. “Bone morphogenic protein 3 inactivation is an early and frequent event in colorectal cancer development”. In: *Genes Chromosomes Cancer* 47.6 (2008), pp. 449–60. ISSN: 1045-2257. DOI: 10.1002/gcc.20552.

[151] P. W. Voorneveld et al. “Loss of SMAD4 alters BMP signaling to promote colorectal cancer cell metastasis via activation of Rho and ROCK”. In: *Gastroenterology* 147.1 (2014), 196–208.e13. ISSN: 0016-5085. DOI: 10.1053/j.gastro.2014.03.052.

[152] S. Ouahoud et al. “Bidirectional tumor/stroma crosstalk promotes metastasis in mesenchymal colorectal cancer”. In: *Oncogene* 39.12 (2020), pp. 2453–2466. ISSN: 0950-9232. DOI: 10.1038/s41388-020-1157-z.

[153] Shazia Irshad et al. “Bone morphogenetic protein and Notch signalling crosstalk in poor-prognosis, mesenchymal-subtype colorectal cancer”. In: *The Journal of Pathology* 242.2 (2017), pp. 178–192. ISSN: 0022-3417. DOI: https://doi.org/10.1002/path.4891. URL: https://doi.org/10.1002/path.4891.

[154] Louise R. Dutton et al. “Fibroblast-derived Gremlin1 localises to epithelial cells at the base of the intestinal crypt”. In: *Oncotarget* 10.45 (2019), pp. 4630–4639. ISSN: 1949-2553. DOI: 10.18632/oncotarget.27050. URL: https://pubmed.ncbi.nlm.nih.gov/31384391%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6659803/.

[155] Hiroki Kobayashi et al. “The balance of stromal BMP signaling mediated by GREM1 and ISLR drives colorectal carcinogenesis”. In: *Gastroenterology* (2020). ISSN: 0016-5085. DOI: https://doi.org/10.1053/j.gastro.2020.11.011. URL: http://www.sciencedirect.com/science/article/pii/S0016508520354007.

[156] Jaeger Emma et al. “Hereditary mixed polyposis syndrome is caused by a 40-kb upstream duplication that leads to increased and ectopic expression of the BMP antagonist GREM1”. In: *Nature Genetics* 44.6 (2012), p. 699. ISSN: 1061-4036. DOI: 10.1038/ng.2263.

[157] Francesca Zanconato, Michelangelo Cordenonsi, and Stefano Piccolo. “YAP and TAZ: a signalling hub of the tumour microenvironment”. In: *Nature Reviews Cancer* 19.8 (2019), pp. 454–464. ISSN: 1474-1768. DOI: 10.1038/s41568-019-0168-y. URL: https://doi.org/10.1038/s41568-019-0168-y.

[158] Teng Han et al. “Lineage Reversion Drives WNT Independence in Intestinal Cancer”. In: *Cancer Discovery* 10.10 (2020), p. 1590. DOI: 10.1158/2159-8290.CD-19-1536. URL: http://cancerdiscovery.aacrjournals.org/content/10/10/1590.abstract.

[159] Anne-France Le Rolle et al. “Oncogenic KRAS activates an embryonic stem cell-like program in human colon cancer initiation”. In: *Oncotarget* 7.3 (2016), pp. 2159–2174. ISSN: 1949-2553. DOI: 10.18632/oncotarget.6818. URL: https://pubmed.ncbi.nlm.nih.gov/26744320%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4823026/.

[160] Joshua D. G. Leach et al. “Oncogenic BRAF, unrestrained by TGF-receptor signalling, drives right-sided colonic tumorigenesis”. In: *Nature Communications* 12.1 (2021), p. 3464. ISSN: 2041-1723. DOI: 10.1038/s41467-021-23717-5. URL: https://doi.org/10.1038/s41467-021-23717-5.

[161] F. Hu et al. “Potential of RASSF1A promoter methylation as a biomarker for colorectal cancer: Meta-analysis and TCGA analysis”. In: *Pathol Res Pract* 216.8 (2020), p. 153009. ISSN: 0344-0338. DOI: 10.1016/j.prp.2020.153009.

[162] Yuki Nakanishi et al. “Simultaneous Loss of Both Atypical Protein Kinase C Genes in the Intestinal Epithelium Drives Serrated Intestinal Cancer by Impairing Immunosurveillance”. In: *Immunity* 49.6 (2018), 1132–1147.e7. ISSN: 1074-7613. DOI: https://doi.org/10.1016/j.immuni.2018.09.013. URL: https://www.sciencedirect.com/science/article/pii/S107476131830428X.

[163] Hyun Woo Park et al. “Alternative Wnt Signaling Activates YAP/TAZ”. In: *Cell* 162.4 (2015), pp. 780–794. ISSN: 1097-4172 0092-8674. DOI: 10.1016/j.cell.2015.07.013. URL: https://pubmed.ncbi.nlm.nih.gov/26276632%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4538707/.

[164] Luca Azzolin et al. “YAP/TAZ Incorporation in the -Catenin Destruction Complex Orchestrates the Wnt Response”. In: *Cell* 158.1 (2014), pp. 157–170. ISSN: 0092-8674. DOI: https://doi.org/10.1016/j.cell.2014.06.013. URL: http://www.sciencedirect.com/science/article/pii/S009286741400734X.

[165] X. Varelas et al. “The Hippo pathway regulates Wnt/beta-catenin signaling”. In: *Dev Cell* 18.4 (2010), pp. 579–91. ISSN: 1534-5807. DOI: 10.1016/j.devcel.2010.03.007.

[166] Feihong Deng et al. “YAP triggers the Wnt/-catenin signalling pathway and promotes enterocyte self-renewal, regeneration and tumorigenesis after DSS-induced injury”. In: *Cell Death Disease* 9.2 (2018), p. 153. ISSN: 2041-4889. DOI: 10.1038/s41419-017-0244-8. URL: https://doi.org/10.1038/s41419-017-0244-8.

[167] Shi Jiao et al. “VGLL4 targets a TCF4–TEAD4 complex to coregulate Wnt and Hippo signalling in colorectal cancer”. In: *Nature Communications* 8.1 (2017), p. 14058. ISSN: 2041-1723. DOI: 10.1038/ncomms14058. URL: https://doi.org/10.1038/ncomms14058.

[168] Joseph Rosenbluh et al. “-Catenin-Driven Cancers Require a YAP1 Transcriptional Complex for Survival and Tumorigenesis”. In: *Cell* 151.7 (2012), pp. 1457–1473. ISSN: 0092-8674. DOI: https://doi.org/10.1016/j.cell.2012.11.026. URL: http://www.sciencedirect.com/science/article/pii/S0092867412014110.

[169] N. Vlahov et al. “Alternate RASSF1 Transcripts Control SRC Activity, E-Cadherin Contacts, and YAP-Mediated Invasion”. In: *Curr Biol* 25.23 (2015), pp. 3019–34. ISSN: 0960-9822 (Print) 0960-9822. DOI: 10.1016/j.cub.2015.09.072.

[170] Angelos Papaspyropoulos et al. “RASSF1A uncouples Wnt from Hippo signalling and promotes YAP mediated differentiation via p73”. In: *Nature Communications* 9.1 (2018), p. 424. ISSN: 2041-1723. DOI: 10.1038/s41467-017-02786-5. URL: https://doi.org/10.1038/s41467-017-02786-5.

[171] Kristiaan J. Lenos et al. "Stem cell functionality is microenvironmentally defined during tumour expansion and therapy response in colon cancer". In: *Nature Cell Biology* 20.10 (2018), pp. 1193–1202. ISSN: 1476-4679. DOI: 10.1038/s41556-018-0179-z. URL: https://doi.org/10.1038/s41556-018-0179-z.

[172] F. Lotti et al. "Chemotherapy activates cancer-associated fibroblasts to maintain colorectal cancer-initiating cells by IL-17A". In: *J Exp Med* 210.13 (2013), pp. 2851–72. ISSN: 0022-1007. DOI: 10.1084/jem.20131195.

[173] M. Todaro et al. "CD44v6 is a marker of constitutive and reprogrammed cancer stem cells driving colon cancer metastasis". In: *Cell Stem Cell* 14.3 (2014), pp. 342–56. ISSN: 1875-9777. DOI: 10.1016/j.stem.2014.01.009.

[174] C. Morral et al. "Zonation of Ribosomal DNA Transcription Defines a Stem Cell Hierarchy in Colorectal Cancer". In: *Cell Stem Cell* 26.6 (2020), 845–861.e12. ISSN: 1875-9777. DOI: 10.1016/j.stem.2020.04.012.

[175] Franck Pagès et al. "Effector Memory T Cells, Early Metastasis, and Survival in Colorectal Cancer". In: *New England Journal of Medicine* 353.25 (2005), pp. 2654–2666. DOI: 10.1056/NEJMoa051424. URL: https://www.nejm.org/doi/full/10.1056/NEJMoa051424.

[176] J. Galon et al. "Type, density, and location of immune cells within human colorectal tumors predict clinical outcome". In: *Science* 313.5795 (2006), pp. 1960–4. ISSN: 0036-8075. DOI: 10.1126/science.1129139.

[177] F. Pagès et al. "International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study". In: *Lancet* 391.10135 (2018), pp. 2128–2139. ISSN: 0140-6736. DOI: 10.1016/s0140-6736(18)30789-x.

[178] Giovanni Germano et al. "Inactivation of DNA repair triggers neoantigen generation and impairs tumour growth". In: *Nature* 552.7683 (2017), pp. 116–120. ISSN: 1476-4687. DOI: 10.1038/nature24673. URL: https://doi.org/10.1038/nature24673.

[179] N. J. Llosa et al. "The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints". In: *Cancer Discov* 5.1 (2015), pp. 43–51. ISSN: 2159-8274 (Print) 2159-8274. DOI: 10.1158/2159-8290.cd-14-0863.

[180] E. Domingo et al. "Somatic POLE proofreading domain mutation, immune response, and prognosis in colorectal cancer: a retrospective, pooled biomarker study". In: *Lancet Gastroenterol Hepatol* 1.3 (2016), pp. 207–216. DOI: 10.1016/s2468-1253(16)30014-0.

[181] A. B. Schrock et al. "Tumor mutational burden is predictive of response to immune checkpoint inhibitors in MSI-high metastatic colorectal cancer". In: *Ann Oncol* 30.7 (2019), pp. 1096–1103. ISSN: 0923-7534. DOI: 10.1093/annonc/mdz134.

[182] C. S. Grasso et al. “Genetic Mechanisms of Immune Evasion in Colorectal Cancer”. In: *Cancer Discov* 8.6 (2018), pp. 730–749. ISSN: 2159-8274 (Print) 2159-8274. DOI: 10.1158/2159-8290.cd-17-1327.

[183] I. Catalano et al. “Immunogenomics of Colorectal Tumors: Facts and Hypotheses on an Evolving Saga”. In: *Trends Cancer* 5.12 (2019), pp. 779–788. ISSN: 2405-8025. DOI: 10.1016/j.trecan.2019.10.006.

[184] Peng Jiang et al. “Signatures of T cell dysfunction and exclusion predict cancer immunotherapy response”. In: *Nature Medicine* 24.10 (2018), pp. 1550–1558. ISSN: 1546-170X. DOI: 10.1038/s41591-018-0136-1. URL: https://doi.org/10.1038/s41591-018-0136-1.

[185] Yun-Qiang Tang et al. “The tumor immune microenvironment transcriptomic subtypes of colorectal cancer for prognosis and development of precise immunotherapy”. In: *Gastroenterology Report* 8.5 (2020), pp. 381–389. ISSN: 2052-0034. DOI: 10.1093/gastro/goaa045. URL: https://doi.org/10.1093/gastro/goaa045.

[186] J. N. Kather and N. Halama. “Harnessing the innate immune system and local immunological microenvironment to treat colorectal cancer”. In: *Br J Cancer* 120.9 (2019), pp. 871–882. ISSN: 0007-0920 (Print) 0007-0920. DOI: 10.1038/s41416-019-0441-6.

[187] Yosuke Togashi, Kohei Shitara, and Hiroyoshi Nishikawa. “Regulatory T cells in cancer immunosuppression — implications for anticancer therapy”. In: *Nature Reviews Clinical Oncology* 16.6 (2019), pp. 356–371. ISSN: 1759-4782. DOI: 10.1038/s41571-019-0175-7. URL: https://doi.org/10.1038/s41571-019-0175-7.

[188] Paul Salama et al. “Tumor-Infiltrating FOXP3+ T Regulatory Cells Show Strong Prognostic Significance in Colorectal Cancer”. In: *Journal of Clinical Oncology* 27.2 (2009), pp. 186–192. ISSN: 0732-183X. DOI: 10.1200/JCO.2008.18.7229. URL: https://doi.org/10.1200/JCO.2008.18.7229.

[189] F. A. Sinicrope et al. “Intraepithelial effector (CD3+)/regulatory (FoxP3+) T-cell ratio predicts a clinical outcome of human colon carcinoma”. In: *Gastroenterology* 137.4 (2009), pp. 1270–9. ISSN: 0016-5085 (Print) 0016-5085. DOI: 10.1053/j.gastro.2009.06.053.

[190] Taichi Kuwahara et al. “Intratumoural-infiltrating CD4+and FOXP3+T cells as strong positive predictive markers for the prognosis of resectable colorectal cancer”. In: *British Journal of Cancer* 121.8 (2019), pp. 659–665. ISSN: 1532-1827. DOI: 10.1038/s41416-019-0559-6. URL: https://doi.org/10.1038/s41416-019-0559-6.

[191] Takuro Saito et al. “Two FOXP3+CD4+ T cell subpopulations distinctly control the prognosis of colorectal cancers”. In: *Nature Medicine* 22.6 (2016), pp. 679–684. ISSN: 1546-170X. DOI: 10.1038/nm.4086. URL: https://doi.org/10.1038/nm.4086.

[192] S. Malladi et al. “Metastatic Latency and Immune Evasion through Autocrine Inhibition of WNT”. In: *Cell* 165.1 (2016), pp. 45–60. ISSN: 0092-8674 (Print) 0092-8674. DOI: 10.1016/j.cell.2016.02.025.

[193] Stefani Spranger and Thomas F. Gajewski. “Mechanisms of Tumor Cell–Intrinsic Immune Evasion”. In: *Annual Review of Cancer Biology* 2.1 (2018), pp. 213–228. ISSN: 2472-3428. DOI: 10.1146/annurev-cancerbio-030617-050606. URL: https://doi.org/10.1146/annurev-cancerbio-030617-050606.

[194] W. Yang et al. “MHC class I dysfunction of glioma stem cells escapes from CTL-mediated immune response via activation of Wnt/-catenin signaling pathway”. In: *Oncogene* 39.5 (2020), pp. 1098–1111. ISSN: 0950-9232. DOI: 10.1038/s41388-019-1045-6.

[195] Jitka Fucikova et al. “Detection of immunogenic cell death and its relevance for cancer therapy”. In: *Cell Death Disease* 11.11 (2020), p. 1013. ISSN: 2041-4889. DOI: 10.1038/s41419-020-03221-2. URL: https://doi.org/10.1038/s41419-020-03221-2.

[196] J. A. Joyce and D. T. Fearon. “T cell exclusion, immune privilege, and the tumor microenvironment”. In: *Science* 348.6230 (2015), pp. 74–80. ISSN: 0036-8075. DOI: 10.1126/science.aaa6204.

[197] S. Spranger, R. Bao, and T. F. Gajewski. “Melanoma-intrinsic -catenin signalling prevents anti-tumour immunity”. In: *Nature* 523.7559 (2015), pp. 231–5. ISSN: 0028-0836. DOI: 10.1038/nature14404.

[198] S. Spranger et al. “Tumor-Residing Batf3 Dendritic Cells Are Required for Effector T Cell Trafficking and Adoptive T Cell Therapy”. In: *Cancer Cell* 31.5 (2017), 711–723.e4. ISSN: 1535-6108 (Print) 1535-6108. DOI: 10.1016/j.ccell.2017.04.003.

[199] J. J. Luke et al. “WNT/-catenin Pathway Activation Correlates with Immune Exclusion across Human Cancers”. In: *Clin Cancer Res* 25.10 (2019), pp. 3074–3083. ISSN: 1078-0432 (Print) 1078-0432. DOI: 10.1158/1078-0432.ccr-18-1942.

[200] Qian Xiao et al. “DKK2 imparts tumor immunity evasion through -catenin-independent suppression of cytotoxic immune-cell activation”. In: *Nature medicine* 24.3 (2018), pp. 262–270. ISSN: 1546-170X 1078-8956. DOI: 10.1038/nm.4496. URL: https://pubmed.ncbi.nlm.nih.gov/29431745%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5840007/.

[201] S. Ganesh et al. “RNAi-Mediated -Catenin Inhibition Promotes T Cell Infiltration and Antitumor Activity in Combination with Immune Checkpoint Blockade”. In: *Mol Ther* 26.11 (2018), pp. 2567–2579. ISSN: 1525-0016 (Print) 1525-0016. DOI: 10.1016/j.ymthe.2018.09.005.

[202] S. Ahn and A. L. Joyner. “Dynamic changes in the response of cells to positive hedgehog signaling during mouse limb patterning”. In: *Cell* 118.4 (2004), pp. 505–16. ISSN: 0092-8674 (Print) 0092-8674. DOI: 10.1016/j.cell.2004.07.023.

[203] A. R. Moser, H. C. Pitot, and W. F. Dove. "A dominant mutation that predisposes to multiple intestinal neoplasia in the mouse". In: *Science* 247.4940 (1990), pp. 322–4. ISSN: 0036-8075 (Print) 0036-8075. DOI: 10.1126/science.2296722.

[204] A. R. Moser et al. "ApcMin: a mouse model for intestinal and mammary tumorigenesis". In: *Eur J Cancer* 31a.7-8 (1995), pp. 1061–4. ISSN: 0959-8049 (Print) 0959-8049. DOI: 10.1016/0959-8049(95)00181-h.

[205] H. Shibata et al. "Rapid colorectal adenoma formation initiated by conditional targeting of the Apc gene". In: *Science* 278.5335 (1997), pp. 120–3. ISSN: 0036-8075 (Print) 0036-8075. DOI: 10.1126/science.278.5335.120.

[206] Chunqiao Liu et al. "An essential role for Frizzled5 in neuronal survival in the parafascicular nucleus of the thalamus". In: *The Journal of neuroscience : the official journal of the Society for Neuroscience* 28.22 (2008), pp. 5641–5653. ISSN: 1529-2401 0270-6474. DOI: 10.1523/JNEUROSCI.1056-08.2008. URL: https://pubmed.ncbi.nlm.nih.gov/18509025%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6670808/.

[207] F. el Marjou et al. "Tissue-specific and inducible Cre-mediated recombination in the gut epithelium". In: *Genesis* 39.3 (2004), pp. 186–93. ISSN: 1526-954X (Print) 1526-954x. DOI: 10.1002/gene.20042.

[208] Huimin Yu et al. "Frizzled 2 and frizzled 7 function redundantly in convergent extension and closure of the ventricular septum and palate: evidence for a network of interacting genes". In: *Development* 139.23 (2012), pp. 4383–4394. ISSN: 0950-1991. DOI: 10.1242/dev.083352. URL: https://doi.org/10.1242/dev.083352.

[209] G. E. Truett et al. "Preparation of PCR-quality mouse genomic DNA with hot sodium hydroxide and tris (HotSHOT)". In: *Biotechniques* 29.1 (2000), pp. 52, 54. ISSN: 0736-6205 (Print) 0736-6205. DOI: 10.2144/00291bm09.

[210] Youn-Sang Jung and Jae-Il Park. "Wnt signaling in cancer: therapeutic targeting of Wnt signaling beyond -catenin and the destruction complex". In: *Experimental Molecular Medicine* 52.2 (2020), pp. 183–191. ISSN: 2092-6413. DOI: 10.1038/s12276-020-0380-6. URL: https://doi.org/10.1038/s12276-020-0380-6.

[211] R. Rudling et al. "A simple device to rapidly prepare whole mounts of murine intestine". In: *Cell Prolif* 39.5 (2006), pp. 415–20. ISSN: 0960-7722 (Print) 0960-7722. DOI: 10.1111/j.1365-2184.2006.00391.x.

[212] Johannes Schindelin et al. "Fiji: an open-source platform for biological-image analysis". In: *Nature Methods* 9.7 (2012), pp. 676–682. ISSN: 1548-7105. DOI: 10.1038/nmeth.2019. URL: https://doi.org/10.1038/nmeth.2019.

[213] R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing. Vienna, Austria, 2017. URL: https://www.R-project.org/.

[214] H. Li and R. Durbin. "Fast and accurate long-read alignment with Burrows-Wheeler transform". In: *Bioinformatics* 26.5 (2010), pp. 589–95. ISSN: 1367-4803. DOI: 10.1093/bioinformatics/btp698.

[215] H. Li et al. "The Sequence Alignment/Map format and SAMtools". In: *Bioinformatics* 25.16 (2009), pp. 2078–9. ISSN: 1367-4803. DOI: 10.1093/bioinformatics/btp352.

[216] Mark A. DePristo et al. "A framework for variation discovery and genotyping using next-generation DNA sequencing data". In: *Nature Genetics* 43.5 (2011), pp. 491–498. ISSN: 1546-1718. DOI: 10.1038/ng.806. URL: https://doi.org/10.1038/ng.806.

[217] M Oshima et al. "Loss of Apc heterozygosity and abnormal tissue building in nascent intestinal polyps in mice carrying a truncated Apc gene". In: *Proceedings of the National Academy of Sciences* 92.10 (1995), pp. 4482–4486. DOI: 10.1073/pnas.92.10.4482. URL: https://www.pnas.org/content/pnas/92/10/4482.full.pdf.

[218] Eri Sakai et al. "Combined Mutation of ¡em¿Apc, Kras¡/em¿, and ¡em¿Tgfbr2¡/em¿ Effectively Drives Metastasis of Intestinal Cancer". In: *Cancer Research* 78.5 (2018), pp. 1334–1346. DOI: 10.1158/0008-5472.can-17-3303. URL: https://cancerres.aacrjournals.org/content/canres/78/5/1334.full.pdf.

[219] Rene Jackstadt et al. "Epithelial NOTCH Signaling Rewires the Tumor Microenvironment of Colorectal Cancer to Drive Poor-Prognosis Subtypes and Metastasis". In: *Cancer Cell* 36.3 (2019), 319–336.e7. ISSN: 1535-6108. DOI: https://doi.org/10.1016/j.ccell.2019.08.003. URL: https://www.sciencedirect.com/science/article/pii/S153561081930371X.

[220] P. Bankhead et al. "QuPath: Open source software for digital pathology image analysis". In: *Sci Rep* 7.1 (2017), p. 16878. ISSN: 2045-2322. DOI: 10.1038/s41598-017-17204-5.

[221] Roxana C Mustata et al. "Identification of Lgr5-Independent Spheroid-Generating Progenitors of the Mouse Fetal Intestinal Epithelium". In: *Cell Reports* 5.2 (2013), pp. 421–432. ISSN: 2211-1247. DOI: https://doi.org/10.1016/j.celrep.2013.09.005. URL: https://www.sciencedirect.com/science/article/pii/S2211124713005135.

[222] Hae-Ock Lee et al. "Lineage-dependent gene expression programs influence the immune landscape of colorectal cancer". In: *Nature Genetics* 52.6 (2020), pp. 594–603. ISSN: 1546-1718. DOI: 10.1038/s41588-020-0636-z. URL: https://doi.org/10.1038/s41588-020-0636-z.

[223] Sonja Hänzelmann, Robert Castelo, and Justin Guinney. "GSVA: gene set variation analysis for microarray and RNA-Seq data". In: *BMC Bioinformatics* 14.1 (2013), p. 7. ISSN: 1471-2105. DOI: 10.1186/1471-2105-14-7. URL: https://doi.org/10.1186/1471-2105-14-7.

[224] Gennady Korotkevich et al. “Fast gene set enrichment analysis”. In: *bioRxiv* (2021), p. 060012. DOI: 10.1101/060012. URL: https://www.biorxiv.org/content/biorxiv/early/2021/02/01/060012.full.pdf.

[225] A. Loboda et al. “A gene expression signature of RAS pathway dependence predicts response to PI3K and RAS pathway inhibitors and expands the population of RAS pathway activated tumors”. In: *BMC Med Genomics* 3 (2010), p. 26. ISSN: 1755-8794. DOI: 10.1186/1755-8794-3-26.

[226] M. Ayers et al. “IFN--related mRNA profile predicts clinical response to PD-1 blockade”. In: *J Clin Invest* 127.8 (2017), pp. 2930–2940. ISSN: 0021-9738 (Print) 0021-9738. DOI: 10.1172/jci91190.

[227] Alexandre Calon et al. “Dependency of colorectal cancer on a TGF--driven program in stromal cells for metastasis initiation”. In: *Cancer cell* 22.5 (2012), pp. 571–584. ISSN: 1878-3686 1535-6108. DOI: 10.1016/j.ccr.2012.08.013. URL: https://pubmed.ncbi.nlm.nih.gov/23153532%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3512565/.

[228] D. H. Gonzalo et al. “Gene expression profiling of serrated polyps identifies annexin A10 as a marker of a sessile serrated adenoma/polyp”. In: *J Pathol* 230.4 (2013), pp. 420–9. ISSN: 0022-3417. DOI: 10.1002/path.4200.

[229] Jia-Huei Tsai et al. “Aberrant expression of annexin A10 is closely related to gastric phenotype in serrated pathway to colorectal carcinoma”. In: *Modern Pathology* 28.2 (2015), pp. 268–278. ISSN: 1530-0285. DOI: 10.1038/modpathol.2014.96. URL: https://doi.org/10.1038/modpathol.2014.96.

[230] Arianna Fumagalli et al. “Plasticity of Lgr5-Negative Cancer Cells Drives Metastasis in Colorectal Cancer”. In: *Cell Stem Cell* 26.4 (2020), 569–578.e7. ISSN: 1934-5909. DOI: https://doi.org/10.1016/j.stem.2020.02.008. URL: http://www.sciencedirect.com/science/article/pii/S1934590920300618.

[231] Arnout G. Schepers et al. “Lineage Tracing Reveals Lgr5¡sup¿+¡/sup¿ Stem Cell Activity in Mouse Intestinal Adenomas”. In: *Science* 337.6095 (2012), pp. 730–735. DOI: 10.1126/science.1224676. URL: https://science.sciencemag.org/content/sci/337/6095/730.full.pdf.

[232] Alexey A. Sergushichev. “An algorithm for fast preranked gene set enrichment analysis using cumulative statistic calculation”. In: *bioRxiv* (2016), p. 060012. DOI: 10.1101/060012. URL: https://www.biorxiv.org/content/biorxiv/early/2016/06/20/060012.full.pdf.

[233] Bob Chen et al. “Human colorectal pre-cancer atlas identifies distinct molecular programs underlying two major subclasses of pre-malignant tumors”. In: *bioRxiv* (2021), p. 2021.01.11.426044. DOI: 10.1101/2021.01.11.426044. URL: https://www.biorxiv.org/content/biorxiv/early/2021/01/13/2021.01.11.426044.full.pdf.

[234] Dustin J. Flanagan et al. "NOTUM from Apc-mutant cells biases clonal competition to initiate cancer". In: *Nature* 594.7863 (2021), pp. 430–435. ISSN: 1476-4687. DOI: 10.1038/s41586-021-03525-z. URL: https://doi.org/10.1038/s41586-021-03525-z.

[235] S. J. Lee et al. "Cross-regulation between oncogenic BRAF(V600E) kinase and the MST1 pathway in papillary thyroid carcinoma". In: *PLoS One* 6.1 (2011), e16180. ISSN: 1932-6203. DOI: 10.1371/journal.pone.0016180.

[236] F. M. Barriga et al. "Mex3a Marks a Slowly Dividing Subpopulation of Lgr5+ Intestinal Stem Cells". In: *Cell Stem Cell* 20.6 (2017), 801–816.e7. ISSN: 1934-5909 (Print) 1875-9777. DOI: 10.1016/j.stem.2017.02.007.

[237] A. Gregorieff et al. "Expression pattern of Wnt signaling components in the adult intestine". In: *Gastroenterology* 129.2 (2005), pp. 626–38. ISSN: 0016-5085 (Print) 0016-5085. DOI: 10.1016/j.gastro.2005.06.007.

[238] Sébastien A. B. Roy et al. "Loss of mesenchymal bone morphogenetic protein signaling leads to development of reactive stroma and initiation of the gastric neoplastic cascade". In: *Scientific Reports* 6.1 (2016), p. 32759. ISSN: 2045-2322. DOI: 10.1038/srep32759. URL: https://doi.org/10.1038/srep32759.

[239] B. A. Auclair et al. "Bone morphogenetic protein signaling is essential for terminal differentiation of the intestinal secretory cell lineage". In: *Gastroenterology* 133.3 (2007), pp. 887–96. ISSN: 0016-5085 (Print) 0016-5085. DOI: 10.1053/j.gastro.2007.06.066.

[240] J. M. Allaire et al. "Bmp signaling in colonic mesenchyme regulates stromal microenvironment and protects from polyposis initiation". In: *Int J Cancer* 138.11 (2016), pp. 2700–12. ISSN: 0020-7136. DOI: 10.1002/ijc.30001.

[241] Amy E Shyer et al. "Bending Gradients: How the Intestinal Stem Cell Gets Its Home". In: *Cell* 161.3 (2015), pp. 569–580. ISSN: 0092-8674. DOI: https://doi.org/10.1016/j.cell.2015.03.041. URL: https://www.sciencedirect.com/science/article/pii/S009286741500361X.

[242] R. Chetty and K. Gatter. "CD3: structure, function, and role of immunostaining in clinical practice". In: *J Pathol* 173.4 (1994), pp. 303–7. ISSN: 0022-3417 (Print) 0022-3417. DOI: 10.1002/path.1711730404.

[243] J. R. Groom and A. D. Luster. "CXCR3 in T cell function". In: *Exp Cell Res* 317.5 (2011), pp. 620–31. ISSN: 0014-4827 (Print) 0014-4827. DOI: 10.1016/j.yexcr.2010.12.017.

[244] Ying Ye, Qinjin Dai, and Hongbo Qi. "A novel defined pyroptosis-related gene signature for predicting the prognosis of ovarian cancer". In: *Cell death discovery* 7.1 (2021), pp. 71–71. ISSN: 2058-7716. DOI: 10.1038/s41420-021-00451-x. URL: https://pubmed.ncbi.nlm.nih.gov/33828074%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8026591/.

[245] J. Shi, W. Gao, and F. Shao. "Pyroptosis: Gasdermin-Mediated Programmed Necrotic Cell Death". In: *Trends Biochem Sci* 42.4 (2017), pp. 245–254. ISSN: 0968-0004 (Print) 0968-0004. DOI: 10.1016/j.tibs.2016.10.004.

[246] R. C. Mustata et al. "Lgr4 is required for Paneth cell differentiation and maintenance of intestinal stem cells ex vivo". In: *EMBO Rep* 12.6 (2011), pp. 558–64. ISSN: 1469-221X (Print) 1469-221x. DOI: 10.1038/embor.2011.52.

[247] M. S. Rooney et al. "Molecular and genetic properties of tumors associated with local immune cytolytic activity". In: *Cell* 160.1-2 (2015), pp. 48–61. ISSN: 0092-8674 (Print) 0092-8674. DOI: 10.1016/j.cell.2014.12.033.

[248] A. L. Haber et al. "A single-cell survey of the small intestinal epithelium". In: *Nature* 551.7680 (2017), pp. 333–339. ISSN: 0028-0836 (Print) 0028-0836. DOI: 10.1038/nature24489.

[249] Simon J Leedham et al. "A basal gradient of Wnt and stem-cell number influences regional tumour distribution in human and mouse intestinal tracts". In: *Gut* 62.1 (2013), pp. 83–93. DOI: 10.1136/gutjnl-2011-301601. URL: https://gut.bmj.com/content/gutjnl/62/1/83.full.pdf.