

Pro-survival p53 target genes have evolved clusters of interacting polymorphic response elements that can affect cancer risk

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The p53 tumour suppressor is best known for its inhibition of cell survival through regulating transcription of anti-survival genes and ~50% of cancers exhibit mutated p53, which promotes tumorigenesis. However, p53 also has pro-survival target genes and recent data from mice suggest that cancers retaining wild type p53 benefit from the activation of these genes. In humans, we find that pro-survival p53 target genes are more likely than anti-survival targets to have evolved clusters of polymorphic response elements that interact and affect cancer susceptibility. Using targeted genome editing, we evaluated a cluster of four genetically linked polymorphic p53 response elements and show that p53-dependent up-regulation of a pro-survival gene can promote cancer cell survival through c-kit-mediated signaling. Our results provide human genetic evidence supporting a tumor-promoting role of pro-survival activities of p53. This urges re-thinking of p53's role in tumorigenesis and could support the development of more effective therapy combinations.