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PERSPECTIVES

The kindlin-2 double act

Q1 Xi Ye and Kim A. Dora
Department of Pharmacology, University of Oxford, Oxford, UK
Email: xi.ye@pharm.ox.ac.uk

A restricted and controlled ability of circulating ions, molecules and cells to pass through the endothelium lining all blood vessels is crucial for maintaining the correct balance of fluid within our circulation. Not only does the limited movement of water, ions and proteins generate our blood pressure and hence flow, it also prevents tissue oedema. Endothelial cell permeability can be altered in diseases, contributing to the development of retinopathies and cancer metastasis, and can be manipulated to improve the delivery of drugs to tissues. Therefore, an understanding of the processes involved has many potential therapeutic benefits.

To date, two key pathways are thought to govern endothelial cell permeability: the transcellular and paracellular pathways. Transcellular transport is determined by the movement of proteins through vesiculo-vacuolar organelles within cells, while paracellular movement is regulated by the opening and closing of proteins at endothelial cell junctions (Dejana *et al.* 2008).

The integrity of the paracellular permeability barrier is maintained by myriad proteins which interact to form the tight junctions and adherence junctions between endothelial cells. A number of pro-permeability factors such as histamine, vascular endothelial growth factor and bradykinin increase vascular leakage in a reversible manner and many believe these factors trigger such a phenomenon through the dynamic remodelling of both types of junctions.

VE-cadherin is one of the major adherence junction proteins in endothelial cells. Its cytoplasmic tail can interact with both β- and γ-catenin, which each in turn bind to α-catenin to then interact with the actin skeleton, providing the means to regulate the assembly of adherence junctions. However, one unresolved problem remains with this paradigm: although α-catenin has binding sites for both β-catenin and actin, the binding sites overlap, so it should not bind to both at the same time (Yamada *et al.* 2005), as is required. Therefore, it has been long postulated that a linker protein related to α-catenin may be required to enable the process.

Although a number of proteins have been suggested to fulfil the role of a linker between VE-cadherin and α-catenin, some of the obvious candidates on this list, such α-actinin, failed to fulfil the role and another protein, vinculin, only facilitates adherence junction formation when tension is applied. The study by Pluskota *et al.* (2017 in this issue of *The Journal of Physiology*) suggests kindlin-2 may solve this dilemma by forming an intermediate between β-catenin and actin filaments. Through a number of *in vitro* and *in vivo* assays, Pluskota *et al.* provide compelling evidence that kindlin-2 is an important regulator of adherence junction formation, and that removal of kindlin-2 not only weakens adherence junctions but also tight junctions. Vascular permeability in the ear skin and trachea was evidently higher in kindlin-2$^{+/-}$ animals with or without challenge by platelet activating factor, another reversible pro-permeability factor, and this observation was supported by *in vitro* data from transendothelial electrical resistance measurements. Following confirmation that kindlin-2 is required for adherence junction assembly, it is perhaps not surprising that kindlin-2 reduction also caused the disassembly of tight junctions, as it has been noted that the proper assembly of adherence junctions is required for the formation of tight junctions (Taddei *et al.* 2008). Interestingly, contrary to the traditional view of α-catenin as an adaptor protein facilitating contact with the cytoskeleton, the data support a role for kindlin-2 instead. Kindlin-2 does not directly interact with α-catenin, as confirmed by surface plasmon resonance, but instead binds to β- and γ-catenin as well as actin to form a pathway connecting VE-cadherin to actin, without any requirement for α-catenin. However, it is likely α-catenin still plays a role in adherence junction formation, but in different scenarios, such as when tension is applied. Even here it is proposed that kindlin-2 stabilizes the catenin complex.

This non-integrin role for kindlin-2 may extend beyond the vasculature, as β/γ-catenin can also interact with all known members of the cadherin family. E-cadherin for example, is repressed during epithelial–mesenchymal transition, a process that has been described to play pivotal roles during development, tissue repair and cancer metastasis (Kalluri & Weinberg 2009). In this case, one would speculate that reducing levels of kindlin-2 could promote the development of cancer by both promoting epithelial–mesenchymal transition and increasing vascular permeability, allowing both metastasis and oxygenation of cancer cells.

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Additional information

Competing interests

None

Author contributions

Both authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed. Q2

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