A newly identified protein controls endothelial barrier function by acting as a cellular glue

The endothelial barrier function maintains vascular and tissue homeostasis, and therefore modulates many cardinal physiological processes such as angiogenesis, immune responses, and dynamic fluid exchanges throughout organs. Blood vessels rely on endothelial cell-cell adhesion to generate a barrier between the blood and underlying tissue. Accordingly, the dysregulation of this finely tuned function of endothelial cells plays a prominent role in the pathogenesis of human diseases ranging from inflammation to cancer and diabetes. The full list of the cellular and molecular actors involved in the establishment and maintenance of functional blood vessels is unknown.

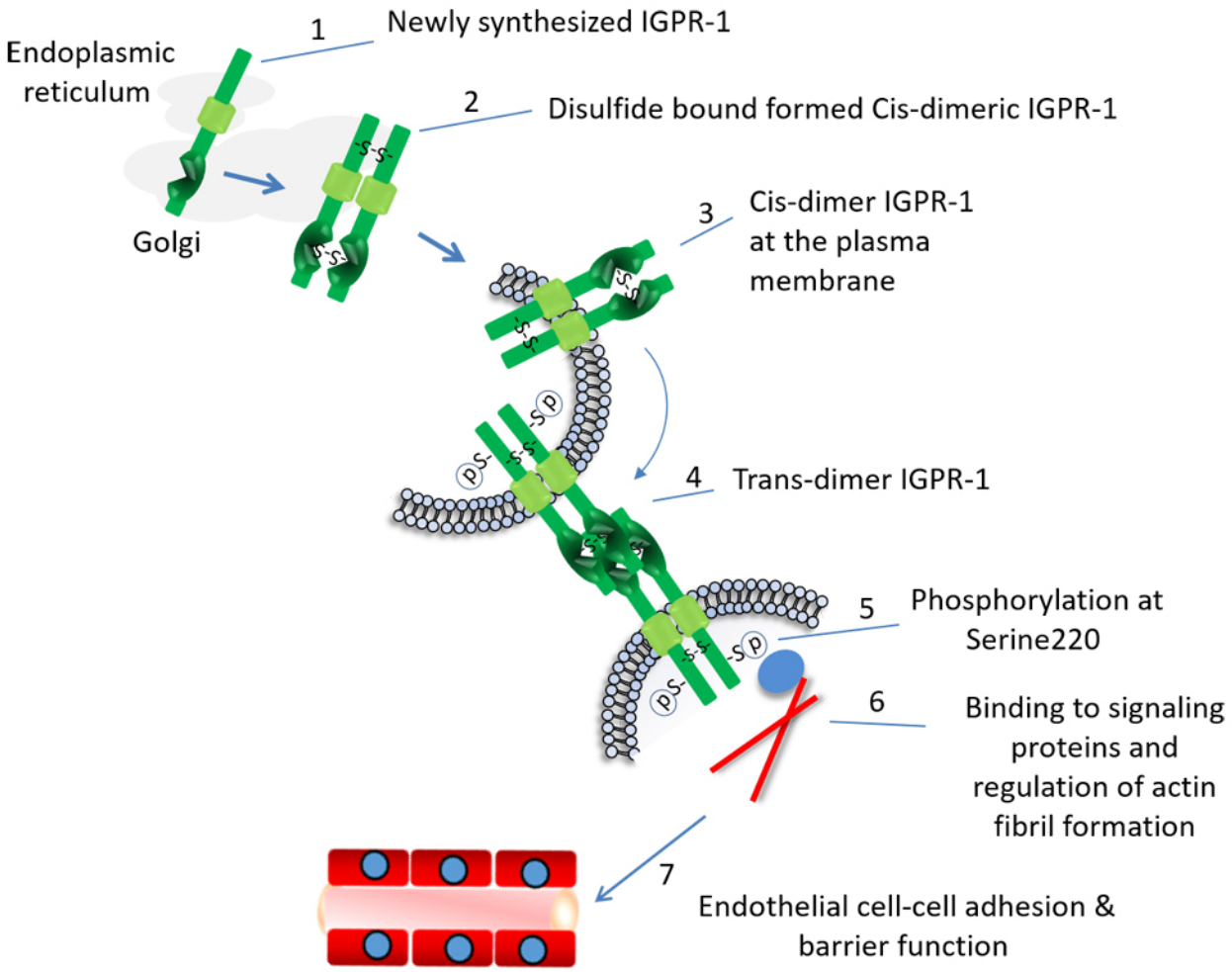

Fig. 1. IGPR-1 is localized to endothelial adherens junctions and through trans-homophilic dimerization regulates endothelial cell-cell adhesion and barrier function. Trans-homophilic dimerization of IGPR-1 stimulates phosphorylation of serine 220 (Ser220), which is required for

IGPR-1 to regulate endothelial barrier function and angiogenesis. pSer220 likely recruits signaling proteins to IGPR-1 and links IGPR-1 to actin fibril assembly, leading to formation of stable blood vessels.

During angiogenesis, multiple cellular and molecular processes simultaneously and, in a highly coordinated manner, direct endothelial cells to break off from the main vessel and begin new contacts such as gap, tight and adherent junctions. Blood vessels rely on endothelial cell-cell adhesion to generate the barrier between the blood and underlying tissue. Dysregulation of blood vessels is associated with the pathogenesis of cancer, inflammation and diabetes. Immunoglobulin (Ig) containing and proline-rich receptor-1 (IGPR-1) was recently identified as a novel Ig-cell adhesion molecule (Ig-CAM) expressed in endothelial cells. IGPR-1 regulates actin fibril formation and cell adhesion through interaction with Src-homology 3 (SH3) domain containing proteins, in a manner that is distinctly different from that of the classical CAMs such as E-cadherin and VE-cadherin. In this issue, Wang, et al., demonstrated that IGPR-1 is required for endothelial cell barrier function. The mechanism underlying the function of IGPR-1 in endothelial cell barrier function appears to involve the presentation of IGPR-1 on the surface of endothelial cells as a cis-dimer, which allows IGPR-1 to interact and undergo trans-homophilic dimerization. Once trans-homophilic dimers are formed, IGPR-1 induces phosphorylation of Serine 220 at its cytoplasmic domain, and this likely contributes to the observed adhesive function and signaling.

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