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Review

Signaling via PINCH: Functions, binding partners and implications in human diseases

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ABSTRACT

Particularly interesting new cysteine-histidine-rich protein (PINCH) is a LIM-domain-only adaptor that plays important roles in cytoskeletal organization and extracellular matrix adhesion, migration, proliferation and survival. Mammalian cells have two functional PINCH proteins, PINCH1 and PINCH2. PINCH not only binds to Nck2 and engages in the signaling of growth factor receptors, but also forms a ternary complex with ILK and parvin (IPP complex). Normally, the IPP complex locates to focal adhesions participating in the signaling of integrins and mediating the interaction of cytoskeleton and extracellular matrix (ECM). Accumulative evidence indicates that abnormalities in PINCH signaling are involved in the pathogenesis of important diseases, such as cancers, renal diseases, cardiomyopathy, and HIV. Therefore, clarifying the functions of PINCH and its interactions with key factors is important for better understanding of signaling events both in health and disease.

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Contents

Abbreviations: PINCH, particularly interesting new cysteine-histidine-rich protein; EMT, epithelial-to-mesenchymal transition; ECM, extracellular matrix; IPP, ILK-PINCH-parvin; FA, focal adhesion; ILK, integrin-linked kinase; EGFR, epidermal growth factor receptor; PDGFR-β, platelet-derived growth factor receptor β; IRS-1, insulin receptor substrate 1; Rsu1, Ras suppressor-1; Tβ4, thymosin beta 4; NCK2, NCK adaptor protein 2; WT1, Wilms Tumor 1.

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1. PINCH and binding partners

1.1. Structure and expression

PINCH was originally found and named in 1994 during search for senescent cell antigens (Rearden, 1994). Following the discovery of PINCH, in 2003, another member of the family, PINCH2, was discovered. PINCH was renamed to PINCH1 afterwards. There is a high sequence similarity between the two PINCH proteins, with 82% of their amino acid sequences being identical. Both proteins are composed of five LIM domains and a C-terminal putative nuclear localization/export signal (Fig. 1) (Braun et al., 2003; Wang et al., 2011). LIM domain is a specialized double-zinc finger motif, through which PINCH associates with other proteins, thus serving to mediate protein-protein interactions (Dawid et al., 1998). PINCH1/2 have more LIM domains than any other members in the LIM domain-containing family. Neither PINCH1 nor PINCH2 has a catalytic domain. These features make them ideal adaptor molecules to mediate the formation of multiprotein complexes. Both PINCH1 and PINCH2 are ubiquitously expressed in most mammalian tissues and organs, including the heart, lung, liver, kidney, and bladder. During mouse embryogenesis, PINCH1 expression begins at E8.5, while the expression of PINCH2 starts at E14.5. This time difference probably explains, in part, the dramatic differences between the phenotypes of their knockout mice (Braun et al., 2003).

1.2. PINCH protein complexes

Although PINCH proteins have no catalytic activity, they form multiple complexes with other proteins via their five LIM domains. This largely explains how they exert their signaling function in cells. For this reason, it is of great significance to know which proteins interact with PINCH, and what the functions of the complexes are.

1.2.1. ILK-PINCH-parvin (IPP) complex

Integrins, a group of transmembrane cell adhesion receptors, play an important role in mediation of the interaction of cell and extracellular matrix (ECM). On one hand, the extracellular domain of integrin interacts with components of ECM (Fig. 2). On the other hand, the cytoplasmic tail of it recruits a number of adaptors and signaling proteins, which together form a structure called focal adhesion (FA). Through FAs, integrins physically contact with the cytoskeleton and transduce signals into the cell (Karakose et al., 2015). Integrin-linked kinase (ILK) was found to be able to bind the cytoplasmic tail of integrin β1 by yeast two-hybrid analysis. It was thought that ILK can not only bind to, but also phosphorylate the cytoplasmic tail of integrin β1 (Hannigan et al., 1996). However, recent structural and genetic studies support that ILK is actually a pseudokinase that acts as an adaptor protein in FAs (Qin and Wu, 2012). Wu group was the first to demonstrate that PINCH can interact with ILK through its LIM1 domain (Fig. 2). Besides, binding with PINCH is the prerequisite for ILK to locate to integrin-rich FAs (Tu et al., 1999; Li et al., 1999). Later, ILK was found to be able to bind to parvin; thus together with PINCH, they form a ternary complex known as the IPP (**I**LK-**P**INCH-**p**arvin) (Fig. 2). The formation of the IPP complex is crucial for the stability of the three proteins, and is the prerequisite for them to locate to the cell-ECM adhesion sites. Any mutations in PINCH, ILK or parvin that disrupt the formation of the complex will prevent other members from locating to FAs (Zhang et al., 2002a). One exception was from a recent study in that PINCH1 in ILK-deficient keratinocytes could still gather within the adhesion sites and recruited EPLIN to modulate the function of FAs (Karakose et al., 2015). This suggests that some of the PINCH1 function is independent upon the presence of the IPP complex.

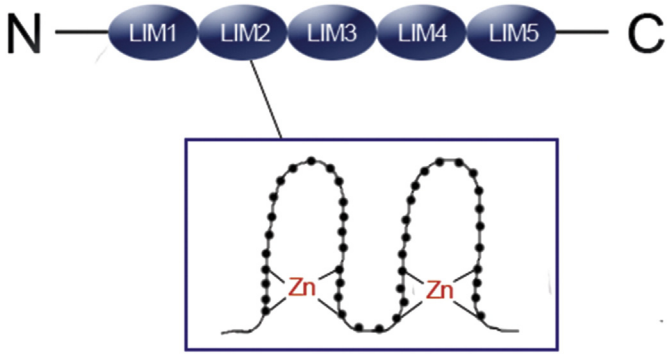

Fig. 1. Schematic of PINCH showing its five LIM domain structure.

What are the roles of IPP complex in FAs? In mice, deleting each of the three proteins resulted in embryonic lethality (Li et al., 2005; Sakai et al., 2003; Montanez et al., 2009). Some common features of the knockout animals include defects in cell polarity, migration, viability and cell-ECM adhesion, which are quite similar to those caused by integrin deficiency. These results further demonstrate that the IPP complex plays a critical role in integrin-mediated cell-ECM interaction network.

In contrast to PINCH1, PINCH2 knockout mice have no obvious phenotypes. This is likely due to a compensation by PINCH1 as the expression of PINCH1 is up-regulated in tissues of the PINCH2 KO mice (Stanchi et al., 2005). PINCH2 can bind to ILK and form the PINCH2-ILK-parvin complex just like PINCH1 does. But this does not mean that they can completely replace each other (Zhang et al., 2002b). Overexpression of PINCH2 in HeLa cells did prevent the down-regulation of ILK and parvin resulted from loss of PINCH1; but it failed to rescue the defects in cell spreading and cell survival signaling (Fukuda et al., 2003). Furthermore, overexpression of PINCH2 in 293 cells inhibited cell spreading and migration, which may be due to destruction of the PINCH1-ILK-parvin complex (Zhang et al., 2002b). Although a functional redundancy between the two proteins does exists as they are often co-expressed and structurally similar, PINCH1 and PINCH2 have their own unique roles in cells as well.

Apart from binding with integrins on the membrane, IPP complex can interact with the cytoskeleton as well as many signaling proteins inside the cell. Up to now, dozens of IPP complex-related proteins have been identified. One of these proteins is parvin that binds to F-actin, thus connecting ECM with cytoskeleton (Olski et al., 2001). In the following, we will discuss PINCH-interacting proteins and their roles.

1.2.2. PINCH-Nck2 complex

Cytoplasmic protein Nck2 is one of the first proteins that was discovered to be related to PINCH. It consists of three N-terminal SH3 domains and one C-terminal SH2 domain (Fig. 2). The two proteins bind to each other through the fourth LIM domain of PINCH1 and the third SH3 domain of Nck2 (Fig. 2). Apart from associating with PINCH1, Nck2 can also interact with components of the growth factor receptor signaling pathways (Fig. 2), such as epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor β (PDGFR-β), and insulin receptor substrate 1 (IRS-1). So through its interaction with Nck2, PINCH1 links the integrin signaling pathways with the growth factor receptor signaling pathways (Fig. 2) (Tu et al., 1998). Besides, Nck2 binds to and activates N-WASP, a molecule related to actin polymerization. Thus, the interaction of PINCH1 and Nck2 drives cytoskeleton assembly at cell-ECM adhesions (Wu, 2005).

Studies using NMR spectroscopy revealed that the binding between PINCH1 and Nck2 was highly specific, but weak, which changes rapidly. The association is so weak that it cannot be detected by GST pull-down and Co-IP assays. Nevertheless, the interaction of PINCH1 and Nck2 is important for the formation of FAs. A mutation in LIM4 domain that disrupts PINCH1 binding to Nck2 prevented PINCH1 from locating to FAs (Velyvis et al., 2003). Furthermore, knocking down Nck2 in HeLa cells led to spreading defect. Overexpression of mutant Nck2 that is defective

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