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Review article

Roles of integrin-linked kinase in cell signaling and its perspectives as a therapeutic target

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ABSTRACT

Integrin-linked kinase (ILK) localizes to focal adhesions, and interacts with the cytoplasmic tail of β subunits of integrins and couples them to the actin cytoskeleton. ILK may act as a kinase and transmit the signals in a phosphatidylinositol 3-kinase-dependent manner, or can act as a scaffold protein to function through cell–matrix interactions, cell signaling, and cytoskeletal organization. Within this pivotal position, ILK mediates many important cellular processes, including survival, proliferation, differentiation, adhesion, migration, contractility, etc. Besides, ILK plays some role in the activation of endothelial progenitor cells and neovascularization, and may also enhance vascular endothelial growth factor expression. Increased ILK activity may promote epithelial-to-mesenchymal transition and induce a transformed, tumorigenic phenotype. Higher expression of ILK was frequently noted in human malignancies. ILK may also be important for mitotic-spindle assembly. Inhibition of ILK causes proliferative defects, induces cell-cycle arrest and apoptosis, and is embryonically lethal. New concepts of gene or cell-based therapy working on the up- or downregulation of ILK have emerged as a valid therapeutic approach for cancer treatment, and also a new hope for vasculogenesis in the ischemic area. The current review will discuss some known mechanisms, and the role of ILK in the modulation of tumorigenesis and reproduction, based on an extensive literature survey.

Introduction

Integrin-linked kinase (ILK) is a key scaffold protein that localizes to focal adhesions, acts as a central component of a heterotrimer (the ILK–PINCH–parvin complex). Since its discovery, ILK has been demonstrated to have an essential role in connecting the cytoplasmic tail of β subunits of integrins to the actin cytoskeleton, and in regulating actin polymerization.[1] Within this pivotal position, ILK has been shown to interact with many intracellular proteins through PINCH or parvin to mediate diverse arrays of biological events,[2] or to mediate cell responses induced by the interaction of integrins with the extracellular matrix (ECM).[2,3] ILK is involved in the regulation of cell growth, survival, adhesion, invasion, and migration. Increased ILK activity may promote epithelial–mesenchymal transition (EMT)[4] and angiogenesis; aberrantly overexpressed or activated ILK has also been found in many types of human malignancies.[5]

The female reproductive system is strongly governed and influenced by the cyclic ovarian hormones, and the endometrium exhibits rapid cyclical shedding and regrowth throughout the female reproductive life. During the menstrual cycle, the endometrium undergoes cell proliferation and then decidualization, a process of tissue remodeling for the preparation of embryo implantation that includes molecular differentiation, morphological transformation, ECM reorganization, as well as variations in integrin moiety expression, which is called “integrin switching.”[6] Three integrins, α1β1, α4β1, and αvβ3, coexpress at the window of implantation.[7,8] In addition, endometriosis and adenomyosis, which are common pathologies of the female reproductive system that induces significant pelvic pain and subfertility, are caused by

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the ectopic spread and growth of the endometrium; however, the exact mechanism of pathogenesis remains elusive despite many research efforts.[9] Although endometriosis and adenomyosis are generally thought to be benign diseases, malignancy can occur unexpectedly in rare situations.[10]

As ILK acts in the center stage of cell–matrix adhesion, and a cyclic integrin switching takes place in endometrial cells throughout the menstrual cycle, it is reasonable to assume that ILK can play some important roles in endometrial functions of decidualization and implantation, as well as in its unique pathology of ectopic spread, or even in malignant transformation. In the current review, a literature search was conducted to discuss some known mechanisms by which ILK functions, the possible roles of ILK in tumorigenesis and reproduction, and some prospects of ILK as a therapeutic target.

ILK is in the center stage of cell–matrix adhesion and signaling

Integrins are the major cell surface receptors that recognize and bind ECM proteins, on which the communication between the cells and ECM is based. Integrins are the prototypic transmembrane receptors that induce the formation of focal adhesions. Upon binding to its extracellular ligand, integrin would induce intracellular signaling processes, involving molecules such as ILK or focal adhesion kinase.[11]

ILK is a highly evolutionarily conserved intracellular protein,[12] and is required for embryogenesis and tissue homeostasis, as mice with ILK-conditional knockout are embryonic lethal shortly after implantation due to defective epiblast polarization and abnormal F-actin accumulation.[13]

Although there is a consensus that ILK is biologically important, it remains controversial as to how ILK can confer its functions. Recent structural, biochemical, and genetic analyses have revealed that the protein kinase domain of ILK lacks some amino-acid residues thought to be essential for phosphotransferase activity; instead, it contains multiple pseudoactive site features, including the unusually short and rigid activation segment that lacks a conserved phosphorylation site, altered magnesium coordination topology, and a severely degraded catalytic loop. Although initially named as a kinase, ILK is frequently questioned to be a pseudokinase.[2]

ILK may function as an adaptor/scaffold protein

Evidence has shown that ILK, a central piece of the ILK–PINCH–parvin complex in connecting integrins to the actin cytoskeleton and other signaling proteins, functions primarily as an adaptor/scaffold protein and works through protein–protein interactions.[12] Dynamic interactions between cells and their environments can also regulate their morphogenesis and functions. Through the protein–protein interaction mechanism, the ILK scaffold transduces signals through its attachment to focal adhesions and reorganization of the actin cytoskeleton and catalytic proteins, and thereby regulates focal adhesion assembly, cytoskeleton organization, and signaling (Fig. 1). ILK is activated through cellular interactions with the ECM and growth factors to mediate many intracellular functional effects and cellular processes, including growth, proliferation, survival, differentiation, migration, invasion, and angiogenesis.[14,15] Several studies have reported proliferative defects upon ILK depletion.[16] ILK also has central roles to play in cardiac and smooth-muscle contractility, and ILK dysregulation causes cardiomyopathies in humans.[12] Increased ILK activity may induce a transformed, tumorigenic phenotype, and may also enhance vascular endothelial growth factor (VEGF) expression, whereas inhibition of ILK induces apoptosis and cell-cycle arrest.[5]

ILK interacts directly with cytoplasmic domains of the β1 or β3 integrin subunits.[15] Integrins (α1β1, α4β1, and αvβ3) coexpress in the endometrium at the window of implantation,[7,8] and the expression of integrin α3β1 is also increased in cancer progression[17]; these integrins may be correlated to the ILK expression. ILK regulates transmembrane signals bidirectionally,[18,19] as they also modulate extracellular fibronectin fibrillogenesis[20] and fibronectin matrix assembly and deposition.[21,22]

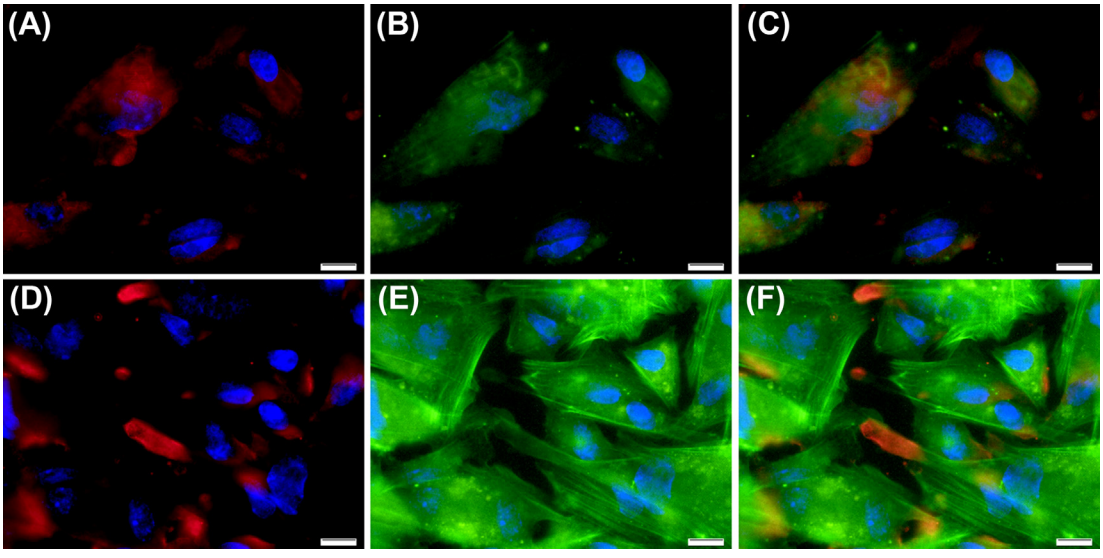

Fig. 1. Immunofluorescent staining of the intracellular distribution of ILK and actin fibers. Representative micrographs are ESCs obtained in one isolation and cultured (A–C) without *in vitro* decidualization (treated with estradiol) and (D–F) with *in vitro* decidualization (treated with estradiol plus medroxyprogesterone acetate) for 8 days. ILK was stained with Texas-red labeling (in red), intracellular actin stress fibers with phalloidin-FITC (in green), and the nucleus with DAPI (in blue). ILK in ESC without decidualization was expressed in a disperse fashion and the staining was fainter; however, in ESC with decidualization, the expression of ILK was significantly increased and more assembled (shown in a dot or spot fashion). Bar = 10 μm. DAPI = 4',6-diamidino-2-phenylindole; ESC = endometrial stromal cell; ILK = integrin-linked kinase.