Viewpoint

New insights into integrin signalling: implications for rheumatoid arthritis synovial fibroblasts

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Introduction

Fibronectin is an important component of the articular extracellular matrix (ECM). Both fibronectin itself and fragments of fibronectin bind to integrin receptors on mesenchymal cells and exert a variety of effects. Of these, regulation of cell growth, migration and survival are most prominent. However, it has also been demonstrated that injection of fibronectin fragments into joints may cause depletion of proteoglycans [1] and induce the production of matrix degrading enzymes [2,3]. Binding of fibronectin to integrin receptors results in the activation of tyrosine phosphorylation signals, and it is now accepted that the focal adhesion-associated tyrosine kinase (FAK) plays a central role in this process. Interactions of FAK with the src family of protein tyrosine kinases (Src-PTKs) have been described as being crucial for the initiation of signalling cascades that ultimately mediate the effects of integrins. Despite this general concept, early molecular events that regulate the association of FAK with Src-PTKs and thus link integrin signalling to cellular activation are unclear. Specifically, little is known about the role of receptor protein tyrosine phosphatases (PTPs), which have been implicated as positive and negative regulators of integrin signalling.

A recent report from Zeng and coworkers [4] sheds new light on the involvement of PTPs in early integrin signalling. Autophosphorylation of FAK at Tyr397 is a key initial step in the formation of Src-PTK/FAK complexes, which in turn mediate the phosphorylation of FAK associated proteins. The establishment of this multi-phosphocomponent signalling complex appears to be regulated by several intracellular PTPs, one of which is PTP-α. PTP-α can be found in focal adhesions and is involved in the spreading of cells on fibronectin. As shown in earlier studies, expression of PTP-α correlates with Src-PTK activity, and PTP-α acts as a physiological upstream regulator of Scr-PTKs [5].

Zheng and coworkers [4] compared wild-type, normal PTP-$\alpha^{+/+}$ and PTP-$\alpha^{-/-}$ mouse embryonic fibroblasts with respect to their nonspecific cell migration as well as haptotactic migration toward fibronectin. In addition, they analyzed the effects of PTP-α on integrin-mediated FAK phosphorylation. Those investigators observed abnormalities of PTP-$\alpha^{-/-}$ embryonic fibroblasts in migrating into space on cell culture dishes. They showed that the migratory defects of PTP-$\alpha^{-/-}$ fibroblasts are associated with altered cell morphology at the leading edge of migrating cells. These changes are linked to reduced FAK Tyr397 phosphorylation during closure of artificial wounds. Their finding that the haptotaxis of immortalized embryonic fibroblasts to fibronectin critically depends on PTP-α is of special interest. Fibronectin-induced rearrangement of the cytoskeleton is retarded in PTP-$\alpha^{-/-}$ cells, but reintroduction of PTP-α through adenoviral gene transfer partly restores the migration of PTP-$\alpha^{-/-}$ toward fibronectin. Although no data on the expression of PTP-α following gene transfer are presented, the authors suggest that the lower levels of PTP-α protein in AdPTP-α transduced PTP-$\alpha^{-/-}$ fibroblasts as compared with wild-type PTP-$\alpha^{+/+}$ cells are responsible for the incomplete effects of adenoviral delivery of PTP-α. Importantly, fibronectin-induced association of FAK with Scr-PTKs is reduced also in PTP-$\alpha^{-/-}$ fibroblasts. The association of FAK with Src-PTKs depends on the autophosphorylation status of FAK. Therefore, the phosphorylation of FAK at Tyr397 in PTP-$\alpha^{-/-}$ fibroblasts was investigated; FAK Tyr397 phosphorylation in response to fibronectin-induced integrin activation is impaired in the PTP-$\alpha^{-/-}$ cells but can be restored by expression of catalytically active PTP-α. Of interest, the delay in cell spreading and the altered morphology of PTP-$\alpha^{-/-}$ cells were reproduced by addition of Src-PTK inhibitors.

Based on these data, Zheng and coworkers concluded that FAK Tyr397 phophorylation is an early event in integrin signalling and is mediated by PTP-α. Defects in PTP-α activity result in the impaired formation of Src-PTK/FAK complexes

ECM = extracellular matrix; FAK = focal adhesion-associated tyrosine kinase; PTP = protein tyrosine phosphatase; RA = rheumatoid arthritis; SF = synovial fibroblast; Src-PTK = src protein tyrosine kinase.

and affect cytoskeletal rearrangement, cell spreading and haptotaxis to ECM molecules. However, FAK interacts with different members of Src-PTK family, and the precise nature of these interactions requires further investigation. In addition, the question of how PTP-α acts as an Scr-PTK activator should now be addressed. Nevertheless, these data highlight the role played by PTP-α as a key upstream regulator of integrin-mediated signalling, linking ECM signals to cell migration and Src-FAK signalling.

Integrin-mediated signal transduction is of considerable interest in a variety of conditions that are associated with altered attachment of fibroblasts-like cells to ECM. In rheumatoid arthritis (RA), attachment of synovial fibroblast to the ECM is an important initiating step in the progressive destruction of articular cartilage [6]. Following early morphological observations [7], several studies have established the notion that the invasion of RA synovial fibroblasts (SFs) into articular cartilage requires their attachment to the cartilage surface. Integrins have been identified as important receptors for ECM molecules in RA, and the increased expression of integrins on RA-SFs has been associated with their enhanced binding to ECM [8]. Functional data support the concept that integrin-mediated signalling events contribute to the invasiveness of RA-SFs [9]. In addition, cartilage-specific fragments of fibronectin have been identified as potent activators of articular chondrocytes [3,10] and fibroblasts [11]. However, little is known about regulation of integrin signalling in RA-SFs and the relevance of Src-PTK/FAK formation for synovial cell activation. This is in striking contrast to the multitude of data illustrating the importance of cytokine-mediated activation, as well as accumulating evidence for stable alterations in the intracellular signalling of RA-SFs. Thus, a recent study linked cytokine-mediated expression of vascular cell adhesion molecule-1 in RA-SFs to Src-dependent pathways [12], and data have been reported that suggest that inhibition of Src-PTKs suppresses RA-SF proliferation and interleukin-6 production [13]. In addition, PTEN, a tyrosine phosphatase that interacts with FAK and negatively regulates integrin-mediated cell spreading, is not expressed in RA-SFs of the most superficial lining layer and at sites of invasion [14].

It is intriguing to speculate that alterations in Src-PTK/FAK complex formation are present in RA-SFs, and it is clear that this aspect of fibroblasts activation requires further attention. By focusing on cytoskeletal rearrangement and cell migration, Zeng and coworkers [4] address only part of the several pathways that have been linked to Src and FAK signalling and that are of interest for enhancing our understanding the complex nature of activated RA-SF behaviour. This paper, together with data suggesting a role for Src-FAK signalling in tumour cell metastasis [15], should stimulate studies focusing on the role of FAK-mediated signalling, and specifically the role of PTPs, in RA-SFs.

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