Mindin your own business

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Published online: 30 May 2012
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The extracellular matrix (ECM) consists of a complex glycoprotein assortment and proteoglycan networks that are produced locally by cells in the matrix and are assembled into an organized meshwork, composing the interstitial matrix and the basement membrane. The ECM serves not only as a structural support scaffold for tissues but also regulates cell behavior. Interactions between cells and ECM components influence cell migration, adhesion, differentiation, and proliferation. Inflammatory cell recruitment is mediated by interactions between integrins and several ECM proteins, including fibronectin, vitronectin, and laminin, which function as integrin ligands. Mindin is an F-spondin (FS) family member, multidomain ECM protein, with numerous functions. The FS domain resides at the N-terminus, while the C-terminus features a thrombospondin type 1 repeat. Li and colleagues [1] demonstrated that the FS domain mediates integrin binding and identified the binding site by mutagenesis. Li et al. further showed that mindin recognizes lipopolysaccharide through the thrombospondin repeat domain, and presented evidence that C-mannosylation of this domain influences lipopolysaccharide binding [1]. These complex interactions raised the possibility that mindin could promote activation of both adaptive and innate immune responses. Tan and Lawler [2] investigated the crystal structure of the FS domain and found that the FS domain may be responsible for membrane targeting that could explain mindin's regulation of axonal development. Indeed, mindin and other FS members were

shown to promote the outgrowth and adhesion of embryonic hippocampal neurons [3].

Mice lacking mindin have an impaired ability to clear bacterial infections, and mindin-deficient macrophages show defective responses to microbial stimuli [4, 5]. Mindin binds directly to bacteria and their components and functions as an opsonin for macrophage phagocytosis. Thus, mindin represents a unique pattern recognition molecule in the ECM, as shown in Fig. 1A. Mindin-deficient mice also displayed severely impaired recruitment of neutrophils and macrophages to inflammation sites. Mindin—integrin interactions were also found to have a key function in T cell priming by dendritic cells. The mindin-deficient mice had defective humoral immune responses to T cell-dependent antigens. The dendritic cells from mindin-deficient mice exhibited an impaired capacity to prime CD4⁺ T cells due to inefficient engagement of T lymphocytes. With this broad role in innate and acquired immunity, it comes as no surprise that mindin has turned in numerous disease processes. For instance, mindin was found in podocytes in a rodent model of diabetic nephropathy [6]. Mindin was also found to modify airway responses in response to noxious agents [7], and now, mindin turns up as an important ECM protein in the heart.

In this issue, Bian and colleagues [8] report on the role of mindin in cardiac hypertrophy. They relied on the mindin gene-deleted mouse model. The authors induced cardiac hypertrophy by thoracic aortic banding or angiotensin II (Ang II) infusion in mindin gene-deleted and wild-type mice. Bian et al. found that mindin gene-deleted mice were more susceptible to cardiac hypertrophy and fibrosis in response to thoracic aortic banding or Ang II stimulation than wild-type mice [8]. The mindin-deleted mice also had worsened cardiac function during both systole and diastole, compared to wild-type

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Fig. 1 **A** Mindin is secreted into the ECM and binds to bacteria through sugar moieties found in the bacterial cell wall, which results in the opsonization and agglutination of the bacteria. The binding of bacteria by mindin promotes phagocytosis and stimulates the proinflammatory cytokine production by the macrophage. Possibly mindin binds to a cell surface receptor activating synergistic signal transduction pathways stimulating cytokine production (adapted from [4]).

B Shown is the signaling system including protein kinase B/AKT that drives cell growth and proliferation largely via mTOR pathway. The system is commonly activated by receptor tyrosine kinases (insulin receptor for instance). Postulated is an AKT inhibitory mechanism signaled by mindin through as yet unclear pathways that diminishes AKT. GSK3 is negatively regulated by AKT/PKB (protein kinase B) and by the WNT signaling pathways

mice. Western blotting showed that the activation of AKT/glycogen synthase kinase 3 β (GSK3 β) signaling in response to hypertrophic stimuli was significantly increased in mindin gene-deleted mice. The authors claim that by blocking AKT/GSK3 β signaling pharmacologically, the cardiac abnormalities in mindin gene-deleted mice were reversed. Bian et al. [8] suggest that mindin is an intrinsic cardioprotective factor that prevents maladaptive remodeling and the transition to heart failure by blocking AKT/GSK3 β signaling. How are we supposed to put all this information together? Can we accept mindin as a protein kinase B/AKT inhibitor?

This work is in line with an earlier study by these authors [9]. In that paper, they used cultured neonatal rat cardiomyocytes with gain and loss of mindin function and also cardiac-specific mindin-overexpressing transgenic mice. In the cultured cardiomyocytes, mindin abrogated Ang II-mediated hypertrophic growth. The authors again relied on thoracic aortic banding or Ang II infusion in the transgenic and control mice. Mindin overexpression in the heart markedly attenuated cardiac hypertrophy, fibrosis, and left ventricular dysfunction in response to both maneuvers. Analysis of the signaling events in vitro and in vivo in these earlier studies also indicated that the beneficial effects of mindin were associated with the interruption of AKT/GSK3 β and transforming growth factor- β 1-Smad signaling.

The mechanisms how mindin specifically blocks AKT signaling remains unknown. Mindin is a ligand for integrins and could alter integrin-signaling complexes that regulate AKT activation. Integrin signaling is essential for both normal cardiac function and compensatory hypertrophy. Thus,

it is unlikely that mindin inhibits integrin signaling directly. Mindin may modulate integrin signaling or an integrin complex in a manner that specifically regulates AKT. The FS domain for instance blocks integrin α v β 3 and inhibits tyrosine phosphorylation of focal adhesion kinase and activation of AKT in vascular endothelial growth factor-stimulated human endothelial cells. AKT is a member of totally nonspecific pathways. AKT is crucial to insulin receptor signaling. AKT is a survival signal that relies on NF- κ B. Surely, regulation of AKT by mindin must require subtle and very highly regulated signals. A speculation is shown in Fig. 1B.

A change in AKT pathway is likely to be an indicator much more than a true determinant and a pharmacological target. Perhaps a more indirect signaling mechanism could involve the macrophage, dendritic cell, and T cell-signaling pathways that have been identified for mindin. Mice deficient in T lymphocytes but not in B lymphocytes are resistant to blood pressure-raising effects of Ang II [10]. We found that mice deficient in the transcription factor required for dendritic cell development were also resistant to infused Ang II [11]. The authors unfortunately did not report on blood pressure responses after Ang II infusion in their mindin-deficient and mindin-overexpressing models. An interaction between mindin, immune mechanisms, and cardiac hypertrophic responses could provide additional answers.

Respectfully,

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