Review of: "Vimentin Regulates Collagen Remodeling Through Interaction with Myosin 10"

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Increased complexity in cytoskeletal network interactions

Background

Myosin-X (MYO10) is an unconventional myosin motor protein which has been studied to some extent with the regard to relationship to cell adhesion and filopodia formation and extension[1]. Myosin-X is widely expressed but at low levels. The total knockout mouse has been reported to have a complex phenotype affecting melanocyte function on the belly, vasculature in the eye and digit formation, in addition to a neuronal defect. At the cellular level, lack of myosin X leads to reduced filopodia formation and increased cell spreading[2].

Vimentin is an intermediate filament protein expressed in mesenchymal cells and is often used as a marker for fibroblasts. Early knockout studies suggested a mild phenotype for vimentin deficient mouse[3] but with a distinct wound healing defect[4] later explained at molecular level, to be in part due to an effect related to altered TGF-beta signaling[5]. At the molecular level the role of vimentin has recently attracted increasing interest.

Although distinct cytoskeletal networks exist, they often interact, and vimentin has been demonstrated to interact with both the actin cytoskeleton and the microtubuli network. When analyzing the contractility of cells lacking vimentin, fibroblasts lacking vimentin demonstrated reduced migration and decreased contractility of collagen gels[3]. Curiously, separate studies have later shown that cells lacking vimentin contain more stress fibers, enlarged focal adhesions and increased integrin activity[6].

When relating cytoskeletal events with the cell surface integrins are key molecules to act as nodal point for cytoskeleton attachments. A study from 2004 demonstrated that myosin X interact with the NPXY motif in integrin beta chains to regulate filopodia formation[7]. Later studies have clarified the role of the interaction to demonstrate that myosin-X, by binding both the conserved GFFKR motif in integrin alpha chains and the NPXY motif in integrin beta subunits, is able to activate integrins at the tip of filopodia and hence increase cell adhesive events[8]. Regarding vimentin-integrin interactions a recent study suggest that vimentin also can interact with collagen-binding beta1 integrins and affect activation and clustering of collagen-binding integrins, although exact nature of molecular interaction has not been clarified[9].

Article

In the current study "**Vimentin Regulates Collagen Remodeling Through Interaction with Myosin 10**" by *Zofia*

Ostrowska-Podhorodecka, Isabel Ding, Sevil Abbasi, Masoud Norouzi, Aiman Ali, Pamma D. Arora, Timothy H.F. Wong, Marco Magalhaes, Christopher A. McCulloch (Qeios, CC-BY 4.0 · Article, April 30, 2022), the interesting observation is made that vimentin filaments interact with myosin-X. The study is made in the context of colorectal carcinoma cells, but a large part of studies is made using fibroblasts from vimentin- and myosin- X knockout mouse models. In the studies advanced microscopy, co-precipitation and cross-linking are used to demonstrate an interaction between vimentin and myosin-X. Data is presented that vimentin promote myosin-X localization to the filopodia tip. When analyzing cell behavior on collagen gels, a reduced alignment of collagen fibrils is observed in the absence of either vimentin or myosin. Finally, the authors also note that there is a decreased collagen proteolysis via MM-P14, which seems to depend on both vimentin and myosin X.

Comments

The study is interesting and raises several questions including:

1. Which specific collagen-binding integrins are involved in mediating the observed effects on the cell surface?
2. Are the beta1 integrin collagen receptors implicated in these events also present on tumor cells*in vivo*, and not just in de-differentiated tumor cell lines cultured *in vitro*?
3. The findings of myosin-X at the filopodia tip, which has been observed before, is thus now expanded with a new interactor, namely vimentin. At the tip, myosin-X has been shown to interact directly and activate integrins[8], and it is thus possible that vimentin localization at the filopodia tip will depend on the myosin-X binding to integrins. Alternatively, vimentin could have a specific affinity for collagen-binding integrin alpha-chains, and if this is the case, this interaction might also offer an alternative route for myosin X localization to filopodia tips.
4. It would also be important to determine if the observed effects on collagen alignment and proteolysis are filopodia-dependent or if these effects indicate novel roles for myosin X at the cell membrane, independent of filopodia.
5. It is also interesting to note that one paradigm for cell-mediated collagen assembly and reorganization suggest a role of fibronectin in collagen matrix assembly[10], but the data from Ostrowska-Podhorodecka et al support a direct role for collagen-binding integrins.
6. It will also be important to sort out the biological relevance of these interactions. If I were to guess, I am not so sure that these mechanisms are foremost central in fibrosis but might me more relevant in dedifferentiated tumor cells initiating metastasis.

So, in summary, an interesting study that has raised many interesting follow-up questions.

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