# FEATURES

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## Back to the Future: Moving Beyond "Mesenchymal Stem Cells"



*Paolo Bianco*

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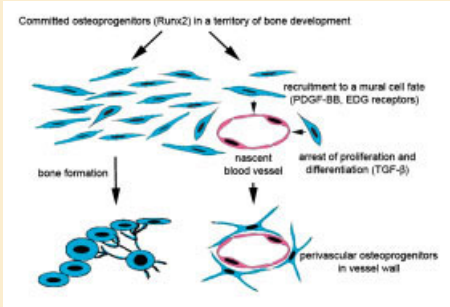
The last decade was dominated by the notion that postnatal ''mesenchymal stem cells,'' purportedly found in bone marrow but also in other tissues, can generate multiple skeletal and nonskeletal tissues. As a result, "MSCs" obtained in culture from virtually every tissue source have been seen as "building blocks" for virtually every tissue beyond the skeleton, in a perspective that has not found support in stringent experimental evidence. Consideration of fundamental developmental biology, recent experimental evidence, and a critical evaluation of the many attempts to restore non-skeletal tissues with "MSCs", together discloses a novel paradigm. Bone marrow stromal cells (the archetypal MSCs) are self-renewing skeletal stem cells; their native potency is restricted to skeletal tissues; they originate from committed skeletal progenitors; they are uniquely capable of establishing the hematopoietic microenvironment/niche; they are microvascular cells; they can organize nascent microvascular networks. Microvascular cells from tissues other than bone marrow, in contrast, are not equivalent to skeletal stem cells in potency, developmental origin, or other functions. Attempts to engineer tissues must be based on rigorously proven potency of each class of progenitor cells considered. The microenvironment-generating and angiopoietic functions of skeletal stem cells offer novel keys to treating as well as understanding diseases.




## PAK4 and Cell Cycle Progression



*Tanya Nekrasova and Audrey Minden*

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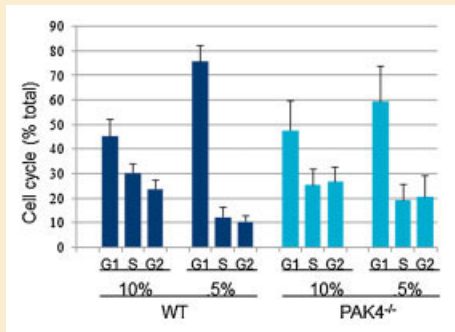
PAK4 is essential during embryonic development, but aberrant PAK4 overexpression is associated with a variety of human cancers. Overexpression of PAK4 has been linked to increased cell proliferation, but the molecular mechanisms by which PAK4 controls proliferation are not well understood. In this issue, Nekrasova and Minden analyze PAK4 function within the context of the cell cycle. Evidence from the study reveals that the cell cycle regulatory protein p21 is a novel target for PAK4. By comparing several wild type and *Pak4* knockout cell lines the authors show that deletion of PAK4 caused a substantial increase in p21 protein. They found that PAK4 regulates p21 mostly at the level of protein stability, though it also affects p21 mRNA levels. PAK4 expression was also explored during the cell cycle, revealing that it is strongly up-regulated as cells enter early G1 phase. Increase in p21 in *Pak4* knockout cells prevents cell quiescence, allows formation of active CDK4/p21/cyclin D1 complexes, and induces untimely progression of the cell cycle. These results indicate that PAK4 functions in early G1 to suppress p21 and prevent premature progression of the cell cycle.



Journal of Cellular Biochemistry

## AIMP1's Role in Adhesion and Cytoskeleton Remodeling



*Valentina Charlotte Jackson, Sarah Dewilde, Alessandra Giuliano Albo, Katarzyna Lis, Davide Corpillo, and Barbara Canepa*

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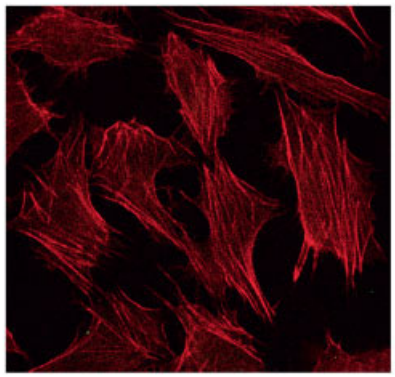

The cytokine properties of AIMP1 (*aminoacyl-tRNA synthetase complex-interacting multifunctional protein 1*) have become of great interest after the discovery of its secretion and activity on different target cells such as endothelial cells (ECs), macrophages and fibroblasts, also acting as an *in vivo* tumor growth suppressor. To clarify how AIMP1 exerts its complex extracellular activities, Jackson *et al.* conducted a series of *in vitro* experiments investigating the signaling pathways activated by exogenous AIMP1 in ECs. The authors demonstrate that AIMP1 decreases EC viability through an $\alpha 5\beta 1$ integrin-dependent mechanism and inhibits cell adhesion. Internalization of exogenous AIMP1 shows an asymmetric pattern of distribution and accumulation in cell protrusions. Moreover, AIMP1 was found to interact with cytoskeletal and cytoskeleton-related proteins and, interestingly, $\alpha$-tubulin phosphorylates upon cell treatment with AIMP1. Jackson *et al.* propose that AIMP1 interferes with the $\alpha 5\beta 1$ integrin signaling pathway and, upon cell uptake, interacts with a multiprotein complex composed of at least four proteins on the cytosolic face of the cell membrane. Interaction and/or activation of these proteins could regulate cellular architecture maintenance and remodelling, thus affecting endothelial cell adhesion and viability. Jackson *et al.* provide novel insight into the molecular mechanisms underlying the exogenous AIMP1 role in adhesion and cytoskeleton remodelling processes.

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## Protein Folding and the Order/Disorder Paradox



*Prakash Kulkarni, Krithika Rajagopalan, David Yeater, and Robert H. Getzenberg*

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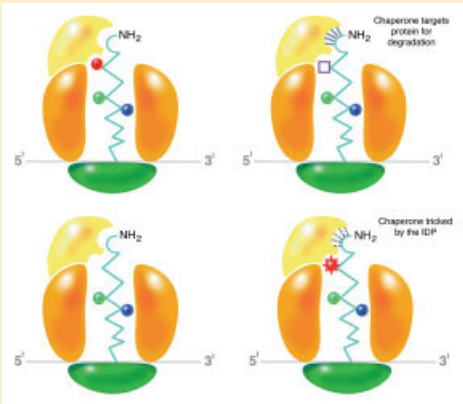


Intrinsically Disordered Proteins (IDPs) are proteins that lack rigid 3D structures and instead, exist as dynamic ensembles. The dynamic structures in the IDPs have many similarities to 'normal' globular proteins that posses a 3D structure such as the native (ordered), and non-native (molten globule, pre-molten globule, and coil-like) states seen during folding of the globular proteins. Paradoxically however, unlike nascent globular proteins that are culled and sent for degradation by the cellular 'quality control' machinery if misfolded, nascent IDPs evade being detected as misfolded and degraded. Kulkarni *et al.* refer to this paradox as the order/disorder paradox and postulate that one of the mechanisms by which the IDPs may escape the cell's surveillance machinery is by capitalizing on their intrinsic promiscuity and ability to undergo disorder-to-order transitions upon binding to biological targets (coupled folding and binding). Given that more than a third of the human proteome consists of IDPs and the important roles they play in human health and disease, the novel insight provided by Kulkarni et al on this fundamental problem is sure to spark a flurry of activity that should eventually help us understand the order/disorder paradox.