FEATURES

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In MSCs Composition Matters

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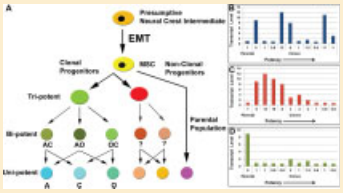

Research conducted over the past several decades has revealed that mesenchymal stem cells (MSCs) derived from adult bone marrow function as connective tissue progenitors, contribute to the HSC niche, and exhibit potent angiogenic, trophic, anti-inflammatory and immuno-modulatory activity. These findings have spurred tremendous growth in the clinical application of mesenchymal stem cell (MSC)-based therapies, which aim to exploit these properties to treat a broad array of diseases. However, scant information exists regarding how the different functional attributes ascribed to MSCs are specified within populations and, more importantly, how donor-to-donor and intra-population heterogeneity limits the overall therapeutic potential of cells. Heterogeneity at the population level poses significant obstacles both in research and in efforts to develop clinical manufacturing protocols that reproducibly generate functionally equivalent clinical cell doses for patient administration. Indeed, despite successes in several human clinical trials, MSC-based therapies lack a clear dose response and outcomes are poorly predicted based on in vitro metrics of cell potency. To address these issues, this article reviews data demonstrating that MSC populations are intrinsically heterogeneous, elaborates on the molecular basis for this heterogeneity, and discusses how heterogeneity affects both clinical manufacturing and the therapeutic potency of MSCs.

Nuclear Factors and Forces

Alison D. Walters, Ananth Bommakanti, and Orna Cohen-Fix

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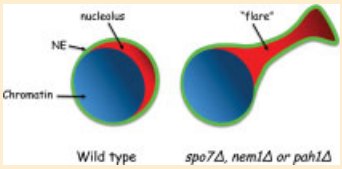

A fundamental unanswered question in cell biology is what determines organelle shape and size. Indeed, certain diseases are associated with abnormal organelle morphology, but the underlying mechanisms that link altered organelle morphology and disease states are unknown. In this issue, Walters *et al.* discuss the factors and forces that affect nuclear morphology. While in most cell types nuclei are either round or oval, certain conditions, such as cancer and aging, are associated with abnormal nuclear morphology. The authors describe how nuclear envelope-associated proteins affect nuclear shape, and discuss the possible relationship between nuclear morphology, lipid metabolism, and organization of the endoplasmic reticulum. They then raise the interesting possibility that nuclear shape is determined, in part, by constraints on nuclear size. Their model is based on observations that in a variety of organisms, nuclear size scales with cell size. The authors speculate that under conditions where the surface area of the nucleus is increased, the requirement to adhere to a specific nuclear/cell volume ratio will lead to nuclear invaginations and protrusions. This and other ideas discussed in the article provide a framework for further investigations into the regulation of nuclear shape and size.

Journal of Cellular Biochemistry

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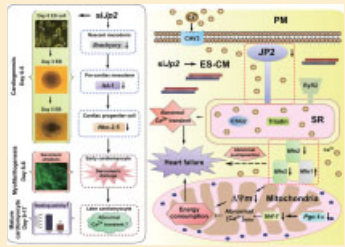
Junctophilin2 (JP2) is of vital importance to cardiac cell function and associated with cardiac hypertrophy. In their paper, Liang *et al.* comprehensively analyze *Jp2* knockdown interference with mitochondrium status in ES cell-derived cardiomyocytes (ESC-CMs) and cardiogenesis of ES cells, revealing that mitochondria within si*Jp2* ESC-CMs were de-energized, the essential juxtaposition structure of mitochondrium with sarcoplasmic reticulum (SR) was destroyed, accompanied by abnormal Ca^{2+} homeostasis and down-regulation of Pgc1α, Nrf1 and Mfn2. *Jp2* knockdown selectively decreased gene transcription towards cardiogenesis, subsequently weakened beating activity and exhibited impaired colocalization of the *JP2* and sarcomeres. Liang *et al.* provide a novel insight into the links between *JP2* and mitochondrium-SR interaction, as well as the role of *JP2* in cardiogenesis of ES cells. Evidence provided indicates that reducing *JP2* expression resulted in impaired mitochondrial status, and a sensitive time window of *JP2* necessary in cardiac differentiation was found at early stage via an extra non-TTs/SR anchor-dependent role. .



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FGFR1 is the essential mediator of the novel nuclear signaling module, Integrative Nuclear FGFR1 Signaling (INFS), which is central to neuronal development. INFS is activated by diverse cell surface receptors involving canonical signal transduction pathways. On the other hand, retinoic acid (RA), a well-known mediator of neuronal differentiation that acts via dual function proteins serving as nuclear receptors and sequence specific transcription factors, does not involve typical signaling cascades. In this study, Lee *et al.* demonstrate that RA mediated nuclear targeting of FGFR1 plays a central role in retinoid-scripted neuronal programming of embryonic stem cells. FGFR1 interacts with ligand-dependent RAR/RXR and orphan Nur nuclear receptors to form complexes with RA-activated genes in transcriptionally active chromatin at target genomic sequences. This study establishes further the role of INFS as a universal driver of cell development and provides a new mechanism for developmental gene regulation. The INFS, RAR, RXR, Nur developmental module offers an important new target for neuronal programming of embryonic stem cells and for augmenting the efficacy of INFS-reactivation of endogenous neurogenesis in adult brain. Efforts to facilitate and harness these interactions are relevant for emerging treatments of a broad range of neural diseases.