Gone with the Wnt/Notch: stem cells in laminopathies, progeria, and aging

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Specific mutations in the human gene encoding lamin A or in the lamin A–processing enzyme, Zmpste24, cause premature aging. New data on mice and humans suggest that these mutations affect adult stem cells by interfering with the Notch and Wnt signaling pathways.

Many premature aging diseases are caused by mutations in the lamin A gene, resulting in severe nuclear abnormalities, but, curiously, although some tissues show severe phenotypes, others are hardly affected. Two new studies, Scaffidi and Misteli (2008) and Espada et al. (see p. 27 of this issue), show that somatic stem cells are misregulated in premature aging, explaining some of the pathological defects observed in these situations.

Structure and function of nuclear lamins
The nuclear lamina underlies the inner membrane of the nuclear envelope (inner nuclear membrane [INM]). It is composed of lamins and lamin-associated proteins, including integral proteins of the INM. Lamins interact directly or indirectly with many known INM proteins, several nucleoplasm proteins, and proteins that bridge the inner and outer nuclear membranes and interact with cytoskeleton elements. These lamin-based complexes are involved in most nuclear activities, including determining nuclear structure, spacing of nuclear pores, replication of DNA, regulation of gene expression, transcription by RNA Pol II, nuclear positioning, segregation of chromosomes, meiosis, and apoptosis (Gruenbaum et al., 2005).

Lamins are type V intermediate filament proteins. They are found in all metazoans, and, like all intermediate filament proteins, they are composed of a short globular N-terminal (head) domain, an α-helical rod domain, and a globular C (tail) domain. The tail domain of lamins contains an Ig fold flanked by unstructured regions. Lamins form stable, fibrous structures both at the nuclear periphery and in the nucleoplasm (Moir et al., 2000; Wiesel et al., 2008).

Lamins are divided into A and B types based on their expression patterns and protein structure. A-type lamins are found only in more complex metazoans and are expressed in differenti-
Interestingly, the signaling pathways that operate in the different stem cell niches converge to four main pathways (Notch, Wnt, TGFβ, and Sonic hedgehog; Lowry and Richter, 2007), suggesting common mechanisms for adult stem cell regulation and maintenance. Most notable of these pathways are the Notch and Wnt signaling pathways, which are now shown to be implicated in premature aging (Espada et al., 2008; Scaffidi and Misteli, 2008).

Stem cells and lamins
Favreau et al. (2004) provided the first evidence that mutations in lamin A can interfere with muscle progenitor differentiation. Mouse C2C12 cells are capable of differentiation from myoblasts to myotubes, and expression of a mutant lamin A containing the Emery-Dreifuss muscular dystrophy--causing mutation R453W strongly delayed the ability of these cells to differentiate. Interestingly, mice that are homozygous for Zmpste24-null mutation and heterozygous for a deletion in LMNA have reduced levels of pre-lamin A and are apparently normal (Varela et al., 2005), suggesting that the toxicity of the permanent carboxyfarnesylated and methylated pre-lamin A depends on its expression levels.

Somatic stem cells
Unlike the pluripotent and highly proliferative embryonic stem cells, somatic (or adult) stem cells are tissue-specific residents that are usually self-renewing slowly or quiescent and are restricted in their differentiation potential, often giving rise to specific lineages of usually one germ layer origin. They are normally maintained as a small reservoir and provide a source of tissue replenishment and maintenance, especially during damage. They are present in a wide variety of tissues, including intestine, muscle, skin, brain, hair, blood, bone marrow, and more, and they seem to be highly dependent on their niche, from which they receive signals influencing their fate (Jones and Wagers, 2008). Interestingly, the signaling pathways that operate in the different stem cell niches converge to four main pathways (Notch, Wnt, TGFβ, and Sonic hedgehog; Lowry and Richter, 2007), suggesting common mechanisms for adult stem cell regulation and maintenance. Most notable of these pathways are the Notch and Wnt signaling pathways, which are now shown to be implicated in premature aging (Espada et al., 2008; Scaffidi and Misteli, 2008).

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Further insight into the connection between stem cells and progeria now come from two studies published by Scaffidi and Misteli (2008) and Espada et al. (2008). Although the two groups studied different systems (i.e., cell lines vs. mice), induced different mutations (i.e., truncated lamin A vs. Zmpste24/H11002/H11002/H11002), examined different niches (mesenchyme vs. hair follicle), and converged on different signaling pathways (i.e., Notch vs. Wnt), both studies demonstrate, for the first time, that progeria and age-related nuclear defects are directly linked with stem cell dysfunction.

To study the molecular mechanisms by which the truncated form of lamin A (progerin/LA\(\text{\textit{A}}\)) induces progeroid phenotypes, Scaffidi and Misteli (2008) prepared stable cell lines carrying inducible forms of either GFP-progerin/LA\(\text{\textit{A}}\) or GFP–wild-type lamin A and compared gene expression profiles after the transgenes’ induction. They found conspicuous activation of Notch signaling in progerin/LA\(\text{\textit{A}}\)-expressing cells. Curiously, this effect was limited to downstream targets of the Notch pathway, which is a major regulator of stem cell maintenance and fate. Directed differentiation of progerin/LA\(\text{\textit{A}}\)-expressing mesenchymal stem cells demonstrated enhanced inhibitor of adipocyte differentiation. Collectively, these results highlight the connection between lamins, especially lamin A and somatic stem cells, and demonstrate that mutations in lamin A cause somatic stem cell dysfunction.

**The progeria-stem cell connection**

The first hint that progeria might be connected with stem cell functioning was proposed by Hofer et al. (2005), who suggested a link between aberrant telomere functioning and accelerated aging in progeroid symptoms. They hypothesized that the fingernail atrophy and gray hair observed in progeria patients as well as in normal aging are the result of stem cell depletion caused by telomere shortening, which is enhanced in several progeroid syndromes. This idea was further developed by Gotzmann and Foisner (2006), who proposed the regeneration model, which argues that tissue degeneration in progeria is caused by mesenchymal stem cell self-renewal defects. This model explains the specificity of tissue degeneration, as most affected tissues in progeroid syndromes are of mesenchymal origin (Hennekam, 2006). Halaschek-Wiener and Brooks-Wilson (2007) also subscribed to this view, suggesting that lamin A deficiency, which renders the nucleus fragile, results in increased cell death. Tissue-specific stem cells that are required to replenish the damaged tissues cannot meet the needs, and the result is an accelerated process of tissue degeneration. Similar to Gotzmann and Foisner (2006), they further argue that the differential effect observed for different tissues is a result of their regenerative potential and/or rate of cell death, and, therefore, HGPS patients do not suffer brain damage, for example. However attractive, these ideas were not experimentally tested or validated until now.

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**Figure 2. A model for mesenchymal stem cell dysfunction in HGPS.** In wild-type mesenchymal stem cells (MSC, left), Notch signaling, which operates through the cleavable and nuclear-penetrating Notch intracellular domain (NICD), is active at basal levels, resulting in basal expression of Notch downstream targets, including Hes1, Hes3, Hes5, Hey1, Hey2, and TLE1. In Hutchinson-Gilford progeria syndrome (HGPS), Notch signaling is increased in mesenchymal stem cells (right), leading to an increase in the expression of Notch pathway genes and to perturbed differentiation, including increased osteogenesis and decreased adipogenesis. INM, inner nuclear membrane.
Scaffidi and Misteli, 2006; Cao et al., 2007) and that lamin A is healthy individuals at low levels and accumulates in old age (Rossi et al., 2007). In addition, recent studies demonstrate impairment in Wnt signaling during aging, affecting the regulation and fate of stem cells in the muscle (Brack et al., 2007), skin, and intestine (Liu et al., 2007).

It remains to be seen why various lamin A mutations have such diverse effects on mesenchymal stem cells and hair follicle stem cells, whether the differentiation capacity of other, non-mesenchymal stem cells is altered in progeria, the role that Notch, Wnt, and other signaling pathways play in other stem cell niches, and whether the observed phenotypes in HGPS are indeed caused by lack of tissue replenishment as a result of stem cell dysfunction. Based on the established link between progeria and stem cell regulation, such questions can now be asked and expectantly answered.

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