The two-faced progeria gene and its implications in aging and metabolism

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Premature aging syndromes have gained much attention, not only because of their devastating symptoms but also because they might hold a key to some of the mechanisms underlying aging. The Hutchinson–Gilford progeria syndrome (HGPS) is caused by a mutation in the *LMNA* gene, which normally produces lamins A and C through alternative splicing. Due to this mutation, HGPS patients express an incompletely processed form of lamin A called progerin. In this issue of *EMBO Reports* [1], the Tazi group demonstrates how mice expressing different *LMNA* isoforms present opposite phenotypes in longevity, fat storage and mitochondrial function.

See also: **IC Lopez-Mejia *et al*** (May 2014)

Increased life expectancy in industrialized societies comes in hand with the development of age-related diseases such as cancer, obesity, and type 2 diabetes. As a consequence, the interest in understanding the biology of aging has grown greatly in the past decades. Several molecular pathways are involved in aging, such as DNA damage, mitochondrial dysfunction, and altered nutrient sensing [2]. Although the mechanistic links between the various aging pathways are only starting to emerge, several of these are in fact intricately connected [3,4].

Studies of age-related pathology involve different model systems, including simple organisms (e.g., worms or flies), mammalian models (e.g., mice or naked mole rats), or even humans. One such human model is the premature aging syndrome Hutchinson–Gilford progeria syndrome (HGPS). This rare disorder is caused by a point mutation in the

LMNA gene. This gene consists of 12 exons in total, but alternative splicing leads to the production of both the lamin A and lamin C proteins, important components of the inner nuclear membrane lamina [5]. Lamin C is encoded by exons 1–10, while lamin A is first produced as a precursor protein, prelamin A, from exons 1–12 and then undergoes four post-translational maturation steps [5]. In the majority of HGPS patients, a single nucleotide substitution in exon 11 activates a cryptic splice site, which causes the removal of 150 nucleotides, and results in a truncated protein that lacks 50 amino acids essential for the last step of lamin A maturation. This incompletely processed prelamin A, named progerin, anchors abnormally to the nuclear membrane and is held responsible for the premature aging in HGPS [5,6]. But how are the other *LMNA* isoforms involved in aging?

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In this issue, Lopez-Mejia and colleagues used mouse models of alternative *LMNA* splicing and provide a link between the development of progeroid premature aging, mitochondrial metabolism, and obesity [1]. Specifically, they studied a mouse model that expresses only lamin C (carrying the so-called *Lmna*^{LCS} allele) and compared it to the short-lived progeria mice carrying the *Lmna*^{G609G} allele [7] (Fig 1). Mouse models expressing only lamin C and lacking lamin A were previously described as healthy, but

were not studied beyond 2 years [7,8]. Therefore, Lopez-Mejia *et al* set out to investigate the lifespan of *Lmna*^{LCS} mice. While progeroid *Lmna*^{G609G} mice were short-lived as reported [7], lifespan of mice expressing only lamin C was approximately 10% longer compared with wild-type mice. Strikingly, these changes in lifespan were associated with opposite metabolic phenotypes: *Lmna*^{LCS} mice store more fat and are insulin-resistant, whereas progerin mice are lean and insulin-sensitive [1] (Fig 1).

The obese and insulin-resistant phenotype of *Lmna*^{LCS} mice seems in apparent contradiction with their enhanced lifespan, but suggests that lamin C expression somehow connects to metabolic pathways. Indeed, indirect calorimetry in these mice showed that *Lmna*^{LCS} mice consumed less energy, though with a marked preference for fat as an energy source. Conversely, the progeria mice displayed higher energy expenditure and burned carbohydrates rather than fat [1]. This observation suggests that the different splice products of *LMNA* alter metabolic energy preferences. But what are the mechanisms underlying the opposite metabolic phenotypes in the two *LMNA* models? Even though *Lmna*^{LCS} mice preferentially use fat as an energy source, adipocytes of these mice have low mitochondrial content and less oxidative capacity, which could lead to decreased energy expenditure and fat accumulation. Conversely, *Lmna*^{G609G} mice have increased mitochondrial number and activity. These opposing effects are reflected at the gene expression level, as the expression of several mitochondrial genes was lower in *Lmna*^{LCS} mice compared with *Lmna*^{G609G} [1], although further mechanistic analyses are needed to establish how *LMNA* isoforms affect mitochondrial gene expression.

Figure 1. Splice variants of the LMNA gene and their proposed contribution to aging, fat accumulation, and mitochondrial metabolism.

(A) The LMNA gene is spliced to produce lamin C (containing exons 1–10) and prelamin A (containing exons 1–12). The latter normally undergoes post-translational processing to produce mature lamin A. In Hutchinson–Gilford progeria syndrome (HGPS) patients, a mutation in exon 11 prevents maturation, leading to an incompletely processed protein called progerin. Wild-type mice express both lamin A and lamin C, while *Lmna*^{LCS} mice express only lamin C. The HGPS model *Lmna*^{G609G} expresses all three isoforms. (B) *Lmna*^{LCS} mice live longer than wild-type mice. Moreover, they are obese and their adipocytes have decreased mitochondrial gene expression. Conversely, *Lmna*^{G609G} mice live shorter, have less fat, and increased mitochondrial gene expression.

In conclusion, the study by Lopez-Mejia and colleagues marks intriguing opposite effects of different LMNA isoforms, and reinforces previous findings that lamin A is dispensable in normal mouse physiology, as long as lamin C is still expressed [7,8]. Additionally, this work suggests a novel connection between the nuclear lamina and mitochondrial metabolism in adipose tissue, adding to the complexity of metabolic longevity networks [3]. Nevertheless, several new questions arise for future elucidation. For

instance, the metabolic phenotype of *Lmna*^{LCS} mice shares more similarities with aged rather than young mice [9]; they have increased fat mass, glucose intolerance and insulin resistance, decreased energy expenditure, and preference for fat as energy source. Still, despite these premature aging features LMNA^{LCS} mice live long, raising the question whether protective, anti-aging pathways are activated. A second question that emerges is how LMNA isoforms affect mitochondrial function in other tissues than white adipose

tissue? While white adipose tissue is particularly important for fat storage, its mitochondrial activity, more specifically fat oxidation capacity, is limited. In contrast, skeletal muscle, heart, and brown adipose tissue rely strongly on fat oxidation. Through the induction and release of myokines and other signaling molecules, these tissues in turn contribute to energy expenditure and whole body physiology. How LMNA affects mitochondrial metabolism and lifespan, for instance through mitonuclear communication [10], and to what extent this contributes to the *Lmna*^{LCS} phenotype in these other tissues, warrants further investigation. Elucidation of these mechanisms may not only have implications for HGPS patients, but could also help to prevent the development of age-related metabolic diseases in otherwise healthy individuals.

Conflict of interest

The authors declare that they have no conflict of interest.

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