

# Fragile fugue: p53 in aging, cancer and IGF signaling

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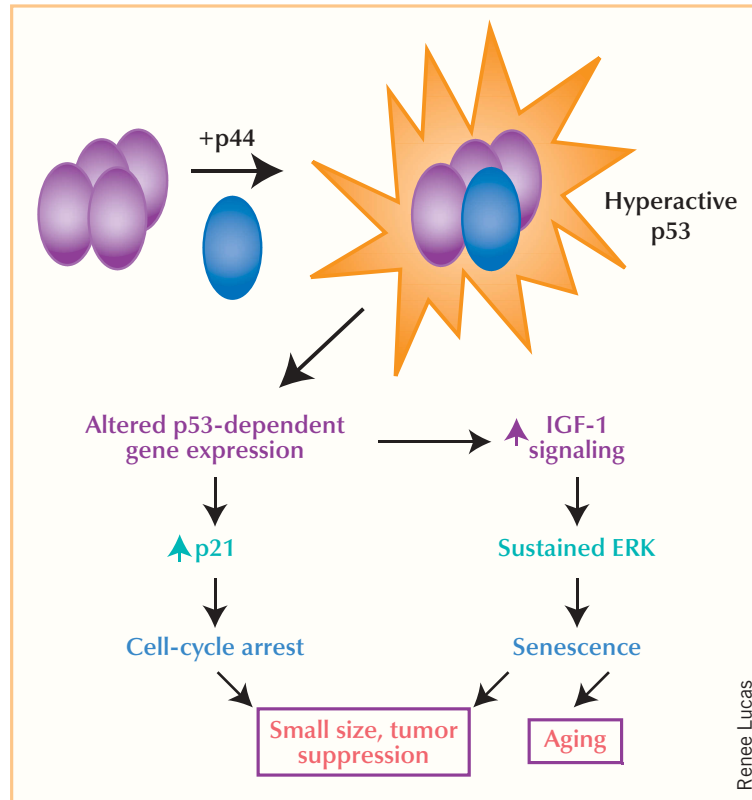
**Aging is driven in part by an evolutionarily conserved hormone signaling pathway. A new study shows that this pathway is controlled by the p53 tumor suppressor, which exquisitely balances the need for cell proliferation against that for tumor suppression.**

There have been remarkable advances—and a few surprises—in understanding basic mechanisms of aging. Among the advances was the discovery of an evolutionarily conserved hormone signaling pathway that drives aging in multicellular organisms. In its rudiments, this pathway resembles mammalian insulin or insulin-like growth factor-1 (IGF-1) signaling<sup>1</sup>. Among the surprises was the finding that the p53 tumor suppressor, when hyperactive, shortens life span and accelerates aging in mice, despite conferring extraordinary protection against cancer<sup>2</sup>. Now, an elegant study by Maier *et al.*<sup>3</sup> directly links p53 to the IGF-1 signaling pathway, shedding new light on tumor suppression and aging in mammals.

p53 regulates transcription and is evolutionarily conserved among metazoans. In simple postmitotic organisms, such as nematodes and flies, p53 homologs resemble a short p53 isoform, p44, which is expressed at low levels in mouse and human cells<sup>4</sup>. The precise function of p44, which lacks an N-terminal region that is present in full-length p53, is not known. But in mammals p44 is thought to interact with p53, altering its ability to modulate gene expression and enhancing its ability to suppress cell proliferation.

Maier *et al.* created transgenic mice that overexpress p44. By four months of age, the p44-transgenic mice showed signs of premature aging; within a year, most of the transgenic animals had died, whereas most of the nontransgenic control mice remained alive and healthy. Interestingly, the p44-transgenic mice were small (one-half the size and weight of their nontransgenic littermates), although they were otherwise normal in appearance.

Does p44 accelerate aging and shorten life span through p53? Apparently so. First, consistent with upregulation of p53 activ-



**Figure 1** Short but mighty. p44 is thought to incorporate into p53 tetramers, thereby hyperactivating the growth-suppressive functions of p53. Activation by p44 alters p53-dependent gene expression. Maier *et al.* show that one consequence of this altered gene expression is increased expression of the cell-cycle inhibitor p21, and subsequent cell-cycle arrest. This cell-cycle arrest may explain the small size and cancer resistance of p44-transgenic mice. Another consequence of the altered gene expression is increased IGF-1 signaling. Persistent IGF-1 signals cause sustained ERK activity, which results in permanent cell-cycle arrest (senescence). The accumulation of senescent cells may also account for the small size and cancer resistance of p44-transgenic mice, as well as their premature aging

ity by p44, p44-transgenic mice had a very low incidence of cancer. Second, p44-transgenic mice in which p53 had been knocked out were normal in size and as tumor-prone as p53 knockout mice with normal p44 levels. That is, p44 overexpression suppressed growth *in vivo*, and the p44-transgenic phenotypes required p53.

Many aspects of the p44-transgenic mice resembled those of the p53-mutant mice created by Tyner *et al.*<sup>2</sup> These animals harbor one mutant p53 allele (resulting in an unnatural N-terminal truncation) and one

wild-type allele. These mice also aged and died prematurely, despite very little cancer, and wild-type p53 was essential for these phenotypes. Thus, the findings of Maier *et al.* support the surprising conclusions of Tyner *et al.*: hyperactivity of p53 can accelerate aging. In addition, because the mutation used by Tyner *et al.* entailed an imprecisely mapped genomic deletion, the new results remove any doubt that p53 is responsible for accelerating aging.

Why does hyperactive p53 promote aging? To answer this question, Maier *et al.*

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focused on IGF-1 signaling. Mutations that blunt an insulin/IGF-1-like pathway in simple, postmitotic organisms markedly increase the adult life span<sup>5</sup>. Recently, genetic manipulations in mice showed that eliminating the insulin receptor in adipose tissue<sup>6</sup> or reducing IGF-1 receptor levels throughout the animal<sup>7</sup> also increase longevity, albeit modestly. Thus, insulin/IGF-1 signals promote aging in nematodes, fruit flies and mice, at least in protected environments such as laboratories. So does p44 overexpression increase such signals in mice? Indeed it does. p44-transgenic mice had higher circulating IGF-1 levels and higher IGF-1 receptor levels in mitotically active tissues. In transfection studies, p44 overexpression stimulated transcription of the gene encoding the IGF-1 receptor, and enhanced IGF-1 signaling by altering levels of regulatory components that act at multiple points in the pathway. Thus, hyperactivity of p53, caused by overexpression of p44, upregulated the IGF-1 signaling axis.

Could this cause premature aging? After all, IGF-1 promotes growth and has been implicated in driving cancer progression<sup>8</sup>. Why, then, are p44-transgenic mice small and resistant to cancer? Maier *et al.* provide two answers (Fig. 1).

First, one of the genes controlled by p53 encodes p21, a potent cell-cycle inhibitor. Active p53 controls many genes, and the effects of p44 on this regulation are complex—depending on the p44 level and target gene, p44 can augment or blunt p53-dependent regulation. In the case of p21, p44 enhanced its expression in mice and cells<sup>3</sup>. Thus, p44 may promote cell cycle arrest through p21, despite robust growth (IGF-1) signals. Indeed, cells from p44-transgenic mice showed reduced proliferation, rather than smaller size, suggesting that p44 augments p53-regulated growth arrest. This augmentation could also explain the cancer resistance of p44-transgenic mice.

The second answer is less straightforward, but intriguing. Maier *et al.* showed that robust IGF-1 signals engage a fail-safe mechanism that shuts down proliferation. This fail-safe mechanism, implemented in part by sustained ERK activity, causes senescence in mouse and human cells<sup>9</sup>. Cellular senescence is an irreversible arrest of proliferation, accompanied by changes in cell function, that suppresses tumorigenesis in mammals<sup>10</sup>. Indeed, cultures from p44-transgenic mice accumulated senescent cells much more readily than non-

transgenic cultures; this accumulation was blocked by an ERK inhibitor. Thus, the small size and tumor resistance of p44-transgenic mice can also be explained by extensive cellular senescence, driven in part by over-robust IGF-1 signaling.

We are still left, then, with the question of why p44-transgenic mice age prematurely. Because senescent cells are dysfunctional and accumulate with age, they have been proposed to cause or contribute to aging in mitotic tissue<sup>10</sup>. Thus, the senescence response may be antagonistically pleiotropic, protecting complex organisms from cancer early in life but contributing to aging late in life. p44-transgenic mice may therefore resist cancer, but age rapidly, because of accelerated accumulation of senescent cells.

The new findings indicate that hyperactive p53 can drive aging, at least in some tissues, by upregulating IGF-1 signals, and offer intriguing explanations for the small size, cancer resistance and accelerated aging of p44-transgenic mice (Fig. 1). They also raise a host of questions. Does active

p53 normally upregulate IGF-1 signaling, or only when p44 is present? Is this upregulation an unappreciated p53/p44 function that promotes tissue (as opposed to DNA) repair? Does p53 drive aging by stimulating apoptosis<sup>2</sup>, senescence, or both? Whatever the case, p53 clearly orchestrates an exquisite equilibrium between competing and counter-regulatory pathways that balance tissue renewal and tumor suppression. Understanding this balance is crucial if we hope to optimize protection from cancer while minimizing aging.

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## Flu strikes the hygiene hypothesis

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**According to the 'hygiene hypothesis', viral infections prevent the development of asthma and other atopic diseases. Influenza virus appears now to enhance, rather than inhibit, the development of asthma and allergic responses.**

As anyone with asthma knows, respiratory viral infections are hazardous to their health. Such infections, which can rapidly precipitate the development of asthma symptoms, cause nearly 80% of asthma exacerbations in children and in adults<sup>1,2</sup>. Infection with viruses such as respiratory syncytial virus, parainfluenza, influenza and rhinovirus are closely associated with the development of wheezing, pulmonary inflammation and airway obstruction. In the March issue of *Nature Immunology*, Dahl *et al.* use a mouse model of asthma to show how influenza virus exacerbates the inflammatory response in the lung, resulting in asthma<sup>3</sup>.

Although influenza and other respiratory viruses unquestionably cause respiratory exacerbations in patients with asthma, Dahl *et al.* point out that influenza virus induces large quantities of IFN- $\gamma$  and a T-helper type 1-polarized immune response, a form of immunity responsible for cell-mediated and cytotoxic reactions. Because type 1 responses can inhibit T-helper type 2 responses, which are associated with humoral immunity and the development of asthma, influenza infection should inhibit allergic asthma. This would be consistent with the hygiene hypothesis, which states that infections in general have the capacity to protect against, rather than exacerbate, the development of asthma and allergies.

This idea that infections protect against the development of asthma and allergies was first suggested by Strachan, who noted

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