PERSPECTIVE

HIF and MIF—a nifty way to delay senescence?

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Normal mammalian cells have a finite replicative life span. This rather simple observation, which has profound implications for the biology of aging and cancer, was made several decades ago by Hayflick who found that isolated human fibroblasts grown in culture could not divide indefinitely (Hayflick and Moorhead 1961). After a number of cell divisions (now known as the “Hayflick limit”), cells slowed down their division cycle and acquired a more “flattened” morphology, eventually becoming nondividing, yet viable cells. This process was termed cellular senescence and its many facets, triggers, and consequences for multicellular organisms have only recently begun to be elucidated at the molecular level.

‘Replicative’ and ‘premature’ cellular senescence

We now know that senescence is a phenomenon that is not unique to human diploid fibroblasts but can also be observed in the cell types of other mammals. It is a property of cells of diverse origins and can be elicited by a variety of different stimuli (Campisi 2005). Why did mammalian cells evolve this program of self-restraint that limits their proliferative potential? There is an obvious need for higher organisms to continually replace cells in tissues that undergo attrition. In humans, tissues in the gut, skin, and hematopoietic system turn over trillions of cells on a daily basis. However, since cellular proliferation intrinsically carries a risk of spontaneous or exogenously induced mutations, powerful mechanisms of surveillance against excessive cell division have evolved. The current consensus is that cellular senescence, like apoptosis, is a potent gatekeeper against tumorigenesis that, if unchecked, has detrimental consequences to the organism as a whole (Campisi 2005). However, this tumor suppressing process is not without tradeoff. Senescent cells exit the replicative pool and are unable to participate in tissue regeneration and wound healing; therefore, accelerated or induced senescence is accompanied by a concomitant increase in progressive organ failure (e.g., liver cirrhosis) or aging and, eventu-

ally, death of the organism. Evolutionary pressures appear to have selected for a delicate balance between early tumorigenesis and extended life span (Beausejour and Campisi 2006).

Depending on the nature of the signals that activate it, cellular senescence can be broadly divided into two main categories: “replicative” and “premature.” The former (which is the type of senescence originally observed by Hayflick), is elicited by the shortening of the chromosomal telomeres, which eventually results in telomere erosion and double-strand DNA breaks. Replicative senescence is not believed to occur in fibroblasts from *mus musculus* due to their significantly longer telomeres compared with human cells (Sharpless and DePinho 2004; Campisi 2005). Signals that lead to premature senescence include oncogenic transformation (particularly from the Ras pathway) and oxidative stress and genotoxic insults; e.g., those induced by artificial, nonphysiological in vitro cell culture conditions or by chemotherapeutic agents and ionizing and ultraviolet (UV) radiation (Sharpless and DePinho 2004; Mooi and Peeper 2006). Now, a new study by Welford et al. (2006) in this issue of *Genes & Development* provides compelling evidence that the hypoxia-inducible factor-1 (HIF-1), a well-characterized transcription factor that mediates cellular adaptation to low-oxygen environment and regulates other pathophysiological cellular processes, may also play an important role in attenuating or delaying premature cellular senescence.

What are the known mechanisms and the important players in the pathways leading to replicative and premature senescence? Elegant experiments using cell culture models and knockout mice have revealed that two important tumor suppressor pathways, one mediated by the tumor suppressor gene products p16^{INK4a} and Rb and the other by ARF and p53, are required for the induction and maintenance of the senescent phenotype (Fig. 1; Altorta et al. 1996; Haber 1997). Although there are cases where the stimuli that induce each pathway overlap (Lin et al. 1998), the p16 pathway generally becomes active in response to telomere shortening and oncogenic transformation (particularly by Ras), while the ARF pathway responds to oncogenic stimuli by Myc and E2F and to DNA damage/reactive oxygen species (ROS) (for review on these pathways, see Sharpless and DePinho 2004). It should be noted that the p53 pathway also protects

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Figure 1. Pathways involved in premature senescence in human and rodent cells. The work by Welford et al. (2006) supports a role for HIF-1 α under hypoxic conditions, as well as other physiological stresses and processes in regulating the “premature senescence” in rodent cells. It is not yet known whether this pathway can similarly affect senescence processes in human cells.

against illicit oncogenic transformation by activating a second important anti-tumor process, programmed cell death, or apoptosis. The decision by a cell with extensive DNA damage, oncogenic transformation, or shortened telomeres to undergo senescence versus apoptosis is determined by several factors, including the genetic makeup, microenvironment, and the status of other pro- and anti-apoptotic mechanisms (Chen et al. 2000).

As mentioned above, cells may also undergo senescence when cultured in the artificial in vitro environment. Routine cell culture in most laboratories is performed at atmospheric air (20% O₂), which is considerably higher than the pO₂ levels encountered by most cell types in living tissues, which can range from 3% to 6% in the brain to 15% in the lung (Hockel and Vaupel 2001). This fact led to the erroneous assumption for many years that mouse embryonic fibroblasts have an inherent replicative senescence limit. However, recent work from several labs showed that if mouse cells were cultured under a more physiological oxygen environment (3% O₂), not only did these cells fail to undergo senescence, but in fact grew better than those cultured under aerobic conditions (Parrinello et al. 2003). Data indicate that rodent cells cultured under 20% O₂ accumulate mutations in their DNA at far higher rates compared with those cultured at 3% O₂, suggesting ROS-dependent activation of senescence; however, this does not preclude a role for alternative or complementary pathways in this process. The study by Welford et al. (2006) provides another mechanistic explanation for these observations by demonstrating that HIF-1, which plays a pivotal role in hypoxic responses (and becomes active at pO₂ levels around 3%), also plays a critical role in delaying the onset of senescence in rodent cells via transcriptional activation of macrophage inhibitory factor (MIF) and inhibition of the p53-mediated pathway. Interestingly, however, the results also suggest an inhibitory role for HIF against premature senescence at nor-

moxic O₂ levels, which raises interesting questions regarding the role of HIF in nonhypoxic pathophysiological conditions.

HIF-1 and its regulation of the hypoxic response of MIF

HIF-1 is a transcription factor consisting of two subunits: an α subunit whose level increases during hypoxia and a β subunit that is constitutively expressed (Semenza 2001). When oxygen is present, prolyl hydroxylases modify HIF-1 α , allowing it to bind to the von Hippel Lindau (VHL) tumor suppressor protein, leading to ubiquitination and, ultimately, degradation of HIF-1 α (Bruick and McKnight 2001; Epstein et al. 2001; Ivan et al. 2001; Jaakkola et al. 2001; Yu et al. 2001). In the absence of oxygen, prolyl hydroxylases are unable to function; hence, HIF-1 α is not hydroxylated, and the protein is stabilized. When stabilized, HIF-1 α heterodimerizes with the β subunit, and the dimer binds to a hypoxia response element (HREs) found in the promoters (or sometimes the intronic regions) of many hypoxia-responsive genes. Dozens of hypoxia-inducible genes have been described, including those that encode vascular endothelial growth factor (VEGF), erythropoietin (EPO), and many of the glycolytic enzymes (Semenza 2001). The HIF-1 response is thought to be part of an adaptive response that improves the chances of surviving the hypoxic insult and/or restores oxygen homeostasis.

Welford et al. (2006) demonstrate that the MIF gene contains an HRE within its promoter. This group (Koong et al. 2000) and others (Bacher et al. 2003; Yao et al. 2005) had previously shown that MIF is induced under hypoxia. In the current study, Welford et al. show by sequence analysis that there are two potential HREs in the 5' untranslated region (UTR) of the mouse MIF promoter—one located at approximately -45 and another at approximately +5 relative to the transcription start site. Deletion of either of these regions significantly decreased the promoter response to hypoxia. However, only the latter seems to be a functional HRE since site-directed mutagenesis within this site led to complete abrogation of hypoxic induction. Both of the regions also contain putative overlapping cyclic AMP response elements (CRE), to which the transcription factor CREB can bind.

Of note, Baugh et al. (2006) independently showed that the human MIF gene also contains an HRE. This site, located at the +25 position, was shown by site-directed mutagenesis to be essential in hypoxic inducibility of the promoter. Baugh et al. also noted that a CRE site was present at the -20-base-pair (bp) region. They provided data supporting a model in which CREB represses HIF-1 under normoxia but is degraded under hypoxia, thus allowing HIF-1 to transactivate the promoter.

MIF

MIF is a proinflammatory cytokine whose level is increased in numerous disease states including acute respiratory distress syndrome, asthma, pulmonary fibrosis,

septic shock, and rheumatoid arthritis (Baugh and Donnelly 2003; Calandra and Roger 2003). MIF can be released by a variety of cell types including monocytes/macrophages, T cells, B cells, endocrine cells, fibroblasts, and epithelial cells. MIF activates or promotes expression of numerous cytokines including TNF- α , IL-2, IL-6, and IFN- γ , and functions to counterbalance the anti-inflammatory and immunosuppressive effects of glucocorticoids. Bacteria, microbial toxins, and cytokines are powerful inducers of MIF secretion by macrophages. The effects of MIF on immunity are complicated. *mif*^{-/-} mice are less capable of controlling infection by *Salmonella typhimurium* (Koebernick et al. 2002); on the other hand, they are resistant to the lethal effects of bacterial lipopolysaccharides (LPS) or *Staphylococcal* enterotoxin (Bozza et al. 1999). MIF also plays an important role in wound healing and regulates many repair/inflammation-associated gene targets (Hardman et al. 2005). Levels of MIF are also increased in many human cancers including those of the prostate, breast, colon, and lung.

What could be the physiological role of hypoxia-induced MIF? For many other HIF targets, the answer is self-evident. For example, if a tissue experiences hypoxia, induction of VEGF helps to increase angiogenesis with the aim of increasing blood flow and oxygenation. EPO helps to increase the red blood cell mass and increase oxygenation at the organismal level in response to systemic hypoxia. The reason why MIF is up-regulated by hypoxia may relate to the fact that there is an intimate relationship between hypoxia and inflammation. During tissue injury, which leads to hypoxia, an essential part of the inflammatory response is the influx of monocytes/macrophages (Karhausen et al. 2005). In fact, using conditional knockout mice, Cramer et al. (2003) showed that activation of HIF-1 α is essential for myeloid cell infiltration and activation. HIF-1 α deletion led to a profound impairment in myeloid cell motility, invasiveness, and bacterial killing. Therefore, HIF-1 α has a direct role in the function of myeloid cells in the inflammatory environment. In this context, it makes sense that HIF-1 would induce MIF to attract inflammatory cells to regions of hypoxia/inflammation. Additionally, some reports have suggested that MIF may have a role in angiogenesis (Bacher et al. 2003; Nishihira et al. 2003), which is another component of the wound healing process.

From a teleologic standpoint, why should HIF-1/MIF prevent senescence? The answer to this is not obvious, but one can speculate. Cells present in sites of inflammation must function in adverse environmental conditions, exposed to low levels of oxygen and glucose and high levels of ROS. Using *hif-1 α* ^{-/-} cells, Walmsley et al. (2005) showed that HIF-1 α prevents neutrophil apoptosis in hypoxia. There is evidence that exposure to ROS can lead to premature senescence (Chen and Ames 1994). Therefore, it is conceivable that HIF-1/MIF have evolved an anti-senescence function in order to protect neutrophils and other cells within regions of inflammation from senescence due to the high levels of ROS that are generated during the inflammatory process. In this respect, a significant finding by Welford et al. (2006) is

the fact that the effects of HIF-1 on MIF expression and senescence occur even at normoxic levels, when HIF-1 α levels are extremely low. This indicates that very low levels of HIF-1 can exert a significant biological effect, but they also suggest that HIF may be playing a physiological role in nonhypoxic conditions.

Another potential reason for an establishment of a HIF-MIF axis against senescence is suggested by the critical role that hypoxia plays during embryogenesis (Giaccia et al. 2004; Covelto et al. 2006; Ramirez-Bergeron et al. 2006). Shortly after gastrulation, diffusion-limited O₂ becomes a factor, and hypoxic responses induced by such oxygen gradients are important for the establishment and maintenance of various progenitor cells and organs (Ramirez-Bergeron et al. 2004). As a major mediator of the hypoxic response, HIF-1 α regulates expression of gene products including EPO, transferrin and its receptor, and VEGF and its receptors that participate in the establishment of early mesoderm and its differentiation into hemangioblasts, and the differentiation and maintenance of the cardiovascular system (Ramirez-Bergeron et al. 2004). It is therefore tempting to speculate that the anti-senescence activity of the HIF-MIF pathway may play a pivotal role in fine-tuning the proper development of these systems.

HIF, senescence, and radiation response

Because their findings suggested that loss of HIF-1 α could lead to premature senescence, Welford et al. (2006) determined what effect this would have following radiation, which results in oxidative stress. They found that HIF-1 α -deficient fibroblasts were more likely to undergo senescence after low doses of radiation (0.5 and 2 Gy) compared with wild-type fibroblasts. Likewise, knocking down the level of MIF also predisposed cells to senescing following radiation. Ionizing radiation induces the production of free radicals including H $\cdot$, HO $\cdot$, e_{aq}⁻, and H₂O₂. H₂O₂ is also produced when H $\cdot$ or e_{aq}⁻ reacts with O₂ (von Sonntag 1987). It is estimated that ionizing radiation produces ~2 nM of peroxide free radicals per 10 Gy (Biaglow et al. 1992). This level is not very high compared with the amount of H₂O₂ required to elicit an equitoxic effect (Tuttle et al. 1992). Therefore, the fact that doses as low as 0.5 Gy caused a detectable increase in senescence in the absence of HIF-1 α indicates that this response is extraordinarily sensitive to low levels of free radicals.

Many other groups have examined radiation response in cells as a function of HIF-1 α status (Unruh et al. 2003; Arvold et al. 2005; Moeller et al. 2005; Williams et al. 2005). However, these studies have yielded conflicting results, with some studies showing that HIF-1 α suppression leads to decreased cell survival after radiation, but others showing no change or even increased cell survival. The discrepancies between these studies may be due to cell-type-specific differences in radiation response and/or the method by which they assessed survival (clonogenic assay vs. MTT assay vs. in vivo tumor regrowth). However, none of these studies had suggested

any relationship between HIF-1 and senescence following radiation. A possible reason is that these studies dealt with irradiation of transformed cells in which senescence is a minor component of the radiation response. In contrast, Welford et al. (2006) used nontransformed, nonimmortalized mouse embryo fibroblasts, which allowed them to uncover a senescence phenotype.

Therapeutic implications

The results reported by Welford et al. (2006) have potential clinical implications. Numerous HIF-1 α inhibitors are currently under development (Melillo 2006; Pouyssegur et al. 2006) as anti-angiogenic and anti-tumorigenic compounds. The authors themselves raise the concern that HIF-1 α inhibitors may lead to toxicity in normal tissues when combined with ionizing radiation because of increased cellular senescence. We will have to await normal tissue toxicity data from future studies using HIF-1 α inhibitors with radiation in animal models or humans in clinical trials to settle this question.

Conversely, induction of HIF-1 α may prove beneficial in some circumstances. Based on the observation that senescence is suppressed in hypoxic conditions, stem cell researchers often routinely culture their cells under these conditions. The study by Welford et al. (2006) provides greater rationale as to why this works. There is some evidence to suggest that progressive organ dysfunction following transplantation may be due to cellular senescence, perhaps secondary to oxidative stress generated by ischemia/reperfusion (Chkhotua et al. 2002). If this is the case, and if HIF-1 α can prevent senescence in diverse cell types, then one could speculate that agents that could locally increase the expression of HIF-1 α might counteract this effect and improve organ viability.

In conclusion, the work of Welford et al. (2006) opens up an exciting new chapter in the areas of HIF biology and cellular senescence, but as expected, new important questions regarding this pathway now emerge. How general is this pathway of senescence inhibition? Does it occur in human cells in addition to rodent cells? Does it play a role in epithelial cellular senescence? What is the interplay (if any) between the HIF-MIF-p53 pathway and the p16/Rb-dependent pathway in terms of senescence regulation? HIF-1 is already implicated in the regulation of a vast array of genes that control multiple cellular functions such as angiogenesis, metabolism, invasion/metastasis, and apoptosis that are important in the development and progression of tumors. Is suppression of senescence another function of HIF-1 that helps tumors grow under hypoxic conditions? Undoubtedly these and additional questions will keep researchers in both the hypoxia and senescence fields occupied in the next few years.

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