Although hypoxia can cause cell cycle arrest, it may simultaneously suppress a conversion from this arrest to senescence. Furthermore, hypoxia can suppress senescence caused by diverse stimuli, maintaining reversible quiescence instead. Hypoxia activates autophagy and inhibits MTOR, thus also activating autophagy. What is the relationship between autophagy and cellular senescence? Also, can inhibition of MTOR and stimulation of autophagy explain the gerosuppressive effects of hypoxia?

Hypoxia Suppresses Senescence

Hypoxia affects almost all aspects of cellular life. For example, hypoxia stimulates secretion of cytokines, mitogens and modulators of the extracellular matrix. This hyper-secretory phenotype resembles the senescence-messaging secretome or senescence-associated secretory phenotype (SASP), a marker of cellular senescence. Hypoxia can also increase lysosomal content/functions, which (given that senescence-associated- (SA)-β-galactosidase is a lysosomal enzyme) may be manifested as moderate SA-β-Gal-staining. And in some cells, hypoxia can slow down proliferation and even cause cell cycle arrest. Still, this is not senescence. Under hypoxic conditions, cells are relatively small, whereas senescent cells are large (hypertrophic) and flat. Finally, hypoxia-arrested cells can resume proliferation, when placed under normoxia. Recently, my co-authors and I demonstrated that hypoxia can actually suppress senescence caused by diverse stimuli. For example, CDKN1A (cyclin-dependent kinase inhibitor 1A or p21) and CDKN2A (p16) induce cell cycle arrest, which is at first reversible. Then over several days, cells become hypertrophic (they grow in size without division) and acquire SA-β-Gal staining. At that point the arrest becomes irreversible. Cells cannot proliferate, when they are released from cell cycle arrest by removing CDKN1A (p21) and CDKN2A (p16) or by washing out DNA damaging drugs and CDK inhibitors. In contrast, when cells are induced to senesce by CDKN1A under hypoxia (0.2–1% oxygen), they are less hypertrophic and less β-Gal-positive (than cells arrested by CDKN1A under normoxia), and most importantly partially retain replicative potential. In other words, hypoxia shifts senescence into quiescence or, precisely speaking, suppresses conversion from arrest into senescence. Of course, hypoxia does not abrogate the cell cycle arrest induced by CDK inhibitors and DNA damaging agents (it even deepens the arrest) but it makes the arrest reversible. In brief, freshly arrested cells, are not senescent to start with. They become senescent over time in the process named gerogenic conversion or geroconversion. Moreover, hypoxia decelerates geroconversion.

Gerogenic Conversion (Geroconversion)

In proliferating cells, growth-promoting pathways, including those regulated by MTOR (mechanistic target of rapamycin), are activated. Cellular mass growth is balanced by cell division. When the cell cycle is arrested (by telomere shortening,
Is Activation of Autophagy/Lysosomes Compensatory?

So why does a senescent cell, despite an active MTOR, activate the autophagy/lysosomal pathway? One answer is that this ensures SASP, making the cell “malignant.” Yet, another answer is that it happens (seemingly paradoxically) exactly because of active MTOR during cell cycle arrest. In 2003, I speculated that when the cell cycle is blocked and GF- and mitogen-activated pathways are still active the cells would undergo senescence. At first, such a cell grows in size almost exponentially. But a cell cannot and does not grow in size indefinitely. Something should limit its growth: either MTOR should be switched off or catabolism via lysosomes should be increased to limit growth. Inactivation of MTOR may occur due to exhaustion of cell medium, however, this is really an artifact of cell culture. In other conditions, MTOR activity remains high. Compensatory activation of lysosomes counteracts growth. Noteworthy, MTOR activates lysosomal biogenesis. Growth and degradation reach an active equilibrium. Both lysosomal activation and SASP are examples of numerous (and often tissue-specific) hyperfunctions of senescent cells.

Further Questions and Implications

So what one would expect when MTOR is inhibited by hypoxia during geroconversion? There will be a lesser need in compensatory autophagy. Could this explain the paradoxical decrease of SA-β-Gal staining by hypoxia during geroconversion of arrested cells, even though hypoxia
can slightly increase β-Gal in proliferating cells? Hypoxia is a normal condition in tissues in vivo. Furthermore, stem cell niches are commonly hypoxic. Given that hypoxia can suppress gerogenic conversion, this may contribute to the prevention of senescence of stem cells during lifetime, and perhaps, slow aging of postmitotic cells in the organism compared with cell culture.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.