

Old Cells in Young Airway Smooth Muscle: Does Neonatal Senescence Cause Lifelong Airway Obstruction?

Cellular senescence is emerging as a common feature of many forms of chronic lung disease (1–3). In response to a range of stimuli, individual cells within a tissue can undergo senescence, which is characterized by typically irreversible cell-cycle arrest associated with expression of cell-cycle inhibitors including p16 and p21, expression of cellular markers such as β -galactosidase, and secretion of proinflammatory and profibrotic mediators (4). It is generally accepted that senescent cells play a crucial role in normal repair and in preventing injured cells from developing into cancer (4), but also contribute to establishing abnormal tissue architecture and pathologic cellular phenotypes that perpetuate injury (5, 6). Although the specific mechanisms and pathways that lead to a senescent phenotype in lung cells are only partially understood, a general model has emerged in which diverse cellular injuries (7), including DNA damage and reactive oxygen species toxicity, induce cells to senesce in a stochastic process. Subsequently, as a result of a range of factors that are secreted by senescent cells, collectively termed the senescence-associated secretory phenotype, senescence can lead to paracrine positive feedback that may result in chronic inflammation and tissue dysfunction (8).

Although the term “senescent” connotes an aging-related process, unfortunately, some forms of lung injury occur in the very young and subsequently persist throughout life. Specifically, treatment of respiratory distress in premature infants is associated with life-long obstructive lung disease that can have asthma-like features (9, 10). Thus, in a study reported in this issue of the *Journal*, Parikh and colleagues (pp. 51–60) tested whether senescence occurs in the youngest of patients, namely, neonates exposed to hyperoxia during treatment of respiratory distress (11). They hypothesized that even moderate, clinically relevant hyperoxia may promote the formation of senescent cells in developing airway smooth muscle (ASM), a tissue that is highly relevant to wheezing and other obstructive airway pathologies that develop in survivors of neonatal respiratory distress. To test this hypothesis, the authors cultured fetal ASM cells exposed to 40% O₂ (hyperoxia) and characterized them phenotypically. The authors found that when exposed to hyperoxia in culture, fetal ASM exhibits phenotypic alterations consistent with cellular senescence, including increased expression of p21 and β -galactosidase, and expression/secretion of both proinflammatory (e.g., IL-1A, IL-1B, and IL-6) and profibrotic (e.g., MMP2, MMP12, and collagen 1A1) mediators. Importantly, conditioned media from fetal ASM cells cultured in hyperoxic conditions promoted inflammatory, fibrotic, and contractile responses in naive cells, supporting a model in which senescent cells propagate injury through paracrine

mechanisms in ASM tissue. Moreover, autopsy-derived ASM specimens from neonates who were exposed to hyperoxia during treatment for respiratory distress exhibited senescent cells, whereas control specimens did not. Taken together, these data suggest that even the very young, when exposed to the toxic effects of hyperoxia, can develop cellular senescence associated with secretion of proinflammatory mediators. The correlation between *in vitro* exposures and clinical specimens represents a major strength of this study and strongly supports the notion that ASM senescence contributes to the airway pathology associated with prematurity.

One of the potential clinical implications of defining cellular senescence in association with neonatal exposure to hyperoxia is the availability of so-called senolytic drugs (12), such as dasatinib and quercetin, which are capable of reversing/eliminating senescent phenotypes and reducing the secretion of proinflammatory and profibrotic mediators (13). To determine whether senolytic compounds could reduce the proinflammatory and fibrotic effects of hyperoxia-induced ASM senescence, the authors treated hyperoxia-exposed fetal ASM cells with a combination of dasatinib and quercetin. In comparison with the effects of conditioned medium from untreated hyperoxia-exposed cells, naive fetal ASM exposed to conditioned media from cells cotreated with dasatinib and quercetin exhibited reduced collagen deposition. Because collagen levels can impact ASM contractility (14), which in turn can influence the expression of inflammatory mediators, senolytics may have utility in disrupting paracrine feedback loops that are driven by the senescence-associated secretory phenotype.

Although this study elegantly establishes that hyperoxia induces fetal ASM senescence, and that the senescent phenotype can induce inflammatory and fibrotic responses in naive cells, much work remains to be done to determine the feasibility and potential clinical utility of targeting senescent cells to mitigate the effects of neonatal hyperoxic exposure. Indeed, senescent cells have been shown to be important for normal repair and are also associated with normal developmental processes. Thus, although it may be possible to pharmacologically eliminate or reverse senescent changes in cell culture models, developing a role for such agents in the clinic will require extensive additional translational and clinical investigations. With that noted, the notion that senescent cells participate in a paracrine injury cycle (15), as illustrated in this study, presents potential opportunities for modulating the deleterious effects of these cells selectively by targeting the expression, secretion, signaling, and/or regulation of specific secreted products. The promise of future general and tailored therapies that modulate cellular senescence will need to be carefully

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balanced against the possible salubrious role of senescent cells in repair. ■

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