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Forum Editorial

Redox Control of Premature Birth and Newborn Biology

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REDOX REGULATORS OF THE CELL

CELLULAR OXIDATION–REDUCTION (REDOX) STATUS is emerging as an important regulator of various cellular responses, including adaptation to cellular stress (6). To date, the glutathione and thioredoxin pathways are the major cellular redox systems that have been shown to modulate cellular functions, including gene expression, intracellular signaling, and various stress responses (6). Although the cellular environment is predominantly reduced, exposure to oxidants, pathological conditions, or therapeutic administration of high concentrations of oxygen can modulate the cellular redox environment (1, 3, 7, 23). Therefore, cells can react to a shift in redox balance by induction or repression of gene expression or signal transduction (23). This special issue explores how the cellular redox state may influence fetal life or the fetal–neonatal transition. Considering the relatively oxygen-deprived fetal environment, one would expect that newborns would experience a relatively oxidized environment at their very first breath. In addition, higher pO_2 levels at the cell or tissue level would be expected to alter cellular biochemistry and promote tolerance to relatively higher oxygen levels. Furthermore, premature infants who require mechanical ventilation with higher oxygen concentrations are more vulnerable to oxidant-induced cell and tissue damage, which can result in various pathological conditions. Therefore, the roles of redox modulation in the fetal environment, in the transition between fetal and neonatal life, and in various diseases of premature and newborn infants are important areas of investigation. This special forum edition addresses many emerging issues regarding the role of the redox environment in premature infant and newborn physiology.

CELLULAR REDOX IN EMBRYONIC FETAL LIFE

As air-breathing organisms, we all respire under oxygen levels of 20–21%. However, fetal development occurs in an environment that is much more hypoxic; the oxygen concentration *in utero* is <3% (14, 15). Therefore, the fetal redox environment may be critical during embryogenesis and development. The current state of understanding and future research directions in this area have been addressed in this issue (1, 4, 9, 17). As regulation of cellular proliferation is crucial during embryogenesis and fetal development, how the fetal redox environment modulates cell proliferation is an important area of investigation. A review that appears in this issue (9) summarizes the role of redox throughout the embryonic life and the role of oxidant stress and redox-responsive transcription factors in fetal development. The role of thioredoxin in cellular proliferation has been extensively studied. In addition, some studies have examined the role of thioredoxin in implantation, embryogenesis, and development. One review appearing in this issue summarizes our current understanding of the role of thioredoxin in embryogenesis and fetal development (4). Despite these advances, many challenging questions and experimental problems in this field remain to be addressed.

ROLE OF REDOX SIGNALING IN PREMATURE AND NEWBORN DISEASE

Several antioxidant enzymes are up-regulated during the final stages of fetal development to help newborns adapt to life in an environment with a relatively high level of oxygen (10, 16, 22, 24). Thus, premature infants lack sufficient levels of antioxidant enzymes to support life efficiently outside the womb, because this up-regulation of antioxidant enzymes occurs during the third trimester of fetal life. As a result, premature newborns develop various lung diseases, including bronchopulmonary dysplasia (BPD), respiratory distress syndrome, and infection (1, 3, 7). The role of the redox environment in various diseases of premature infants and newborns is the subject of several reports and reviews in this issue (1, 4, 9, 17, 21). Quintos-Alagheband *et al.* have reported the up-regulation of endothelial-monocyte activating polypeptide (EMAP) II, a protein known to inhibit fetal lung neovascularization in premature infant baboons exposed to a higher level of oxygen (21). This study suggests that cellular redox state

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may be causative factor for the expression of this gene. However, further studies are warranted to define the role of lung redox state in EMAP II activation. In addition, the importance of redox modulation of pulmonary surfactant gene expression in hyperoxia is discussed in an article presented in this issue (2). One of the studies described in this issue investigated the role of apoptosis and p53 up-regulation in BPD (8). Furthermore, the modulation of various cell-cycle regulatory proteins in fetal baboons, with or without respiratory distress, has been reported for the first time (5). Other studies in this issue have examined how the response of the antioxidant system functions in neonatal life (1). Exposure to elevated levels of oxygen has been shown to damage DNA (11–13), which can lead to apoptotic cell death involving a p53-dependent or p53-independent pathway (18, 19). However, the extent and magnitude of oxygen-induced DNA damage have not been fully delineated. One report used a cell culture model to address this issue (20). Although many important areas have been covered in this forum, there are still several issues in developmental redox biology that require further research.

FUTURE DIRECTIONS

Although several of the studies in this issue have considerably advanced our understanding of the role of redox status in premature birth and newborn biology, redox regulation of development is not yet fully understood. For example, the embryonic redox state at various stages of development is still unknown. In addition, the shift of redox balance during development has not been well characterized. This information would facilitate understanding how redox signaling mediates gene expression in embryos. It has also not yet been determined how the redox state of the cell may influence the embryonic cell cycle and apoptosis, which plays an important role in fetal development. Finally, our understanding of the role of redox status in the diseases of premature infants and newborns is incomplete. To date, the lung has been the most carefully studied organ in newborn diseases, such as BPD. Clearly, further studies are needed to better understand and eventually develop therapeutic strategies for these diseases.

ABBREVIATIONS

BPD, bronchopulmonary dysplasia; EMAP, endothelial-monocyte activating polypeptide; p53, tumor protein p53 (Li–Fraumeni syndrome).

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