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EDITORIAL

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Strain matters: Murine models of BPD

Mouse models of disease have achieved their prominence in part because of the relatively low costs of housing the species and the wide availability of genetically altered strains that can yield mechanistic insights. In this issue, Tiono et al[1] report a comparison of mouse-strain susceptibility to neonatal hyperoxia exposure. The differences they observed in the responses highlight the caution needed when interpreting results using a single congenic strain in disease models. As the authors note in their discussion, the model systems are adjusted to yield a particular morphologic phenotype to best mimic the disease state in question, as recently reviewed in detail by the senior author.[2] Although the high F_iO_2 used by Tiono et al[1] would not be common among patients who develop BPD, it is necessary to produce the interruption in murine alveolarization that is believed to be part of the so-called "new BPD."

However, human BPD is probably more accurately characterized by patchy effects on alveolar development—admittedly inferred in part from studies in nonhuman primates.[3] Our information is surprisingly limited owing to the paucity of pathologic specimens obtained at autopsy. If alveolar development in clinical BPD is nonuniform, then additional stereologic approaches may be needed to quantify less severe effects on rodent alveolar development. Alveolar septal crest density has been used as one such index in hyperoxia-exposed rats[4] that evince both short- and long-term effects on lung development with a less severe exposure to continuous hyperoxia.[5] More detailed morphologic assessments could allow investigators to reduce the F_iO_2 or exposure duration to resemble the pulmonary phenotype observed in primate models that more closely mimic human exposures.

The authors suggested that models using larger, precocial species—sheep, nonhuman primates—might help guide the choice of mouse strain based on the AOE or other responses. Although some information on AOE expression in baboon models has been reported,[6] there is surprisingly little detail about temporo-spatial expression, which might guide such decisions. The problem is to balance a relevant redox stressor with the resistance of the host. To an extent, Tiono et al[1] have addressed part of this problem by providing a very useful menu of choices for mouse strains' morphologic and antioxidant enzyme (AOE) molecular responsiveness, with consistent findings highlighting the vulnerability of the C57BL/6J strain to impaired alveolar development, despite the relatively brisk increases of *Sod3* and *Gss* mRNA and SOD3 protein. Overexpression of *Sod3* targeted to the *Sftpc* expression has been shown to be protective,[7] and its deletion to be detrimental.[8] It is notable that the authors found that the adverse effects of hyperoxia exposure on alveolar development (and AOE expression) in other strains were more variable, although still statistically significant.

A critical issue identified by the authors is how we use small rodent species to screen multiple therapeutic agents for possible intervention. They rightly caution investigators about conflicting conclusions that might be drawn due to differing strain susceptibilities to the exposure (and the intervention). Their suggestion to use outbred mice to partly overcome potentially unrecognized confounding strain effects deserves further emphasis in this context. Pharmacologic interventions that yield apparent benefits (preventive or therapeutic) using an inbred rodent model should be confirmed using outbred strains. Genetic effects on human BPD susceptibility are significant,[9] so it is probably unwise to mask this contribution experimentally by relying solely on congenic strains. This step, as important as the replication of the initial observation, is rarely taken. The author's findings reported here underscore the importance of such a confirmatory approach.

The use of inbred mouse strains to identify possible therapies naturally anticipates translation to prevention or treatment of clinical BPD. Therapeutic trials have been plagued by the imprecise definition of BPD, recently addressed in this journal and elsewhere.[10] This has misled some to conclude that there are no successful approaches for its prevention: this error is inevitable if one defines the disease by its treatment! The wide variation in BPD incidence among tertiary centers[11] and geographic regions[12] shows that some BPD is preventable. But it is increasingly clear that the most prevalent sequelae of BPD, such as impaired lung function[13,14] and cognitive development,[15] may not appear during the neonatal period. Model systems that widen the scope to include longer-term recovery,[5] susceptibility to so-called "second hits,"[16] and extrapulmonary—particularly neurocognitive—outcomes[17] will help to improve the balance between precision and relevance as model systems are further refined.

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