biology driven by tissue culture and animal studies, there have been several recent clinical studies using inhaled nitric oxide (iNO) in preterm infants with persistent pulmonary hypertension, respiratory failure, and severe intraventricular hemorrhage or periventricular leukomalacia.\(^1\) In each of these studies, the premature infants treated with iNO exhibited reduced overall risk of brain injury, decreased risk of cerebral palsy, and improved neurodevelopmental outcomes at 2 years of age. While the underlying mechanisms responsible for these improvements are uncertain at this time, it is tempting to speculate that NO modulation of protease behavior in endothelial cells (and other cell types) is partially responsible. In light of our rapidly increasing understanding of NO as a pleomorphic modulator of a broad range of signaling pathways and continuously emerging targeting technologies, future therapies for a variety of diseases may include “just saying NO.”

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**REFERENCES**

Yang et al previously showed that anti-\(\beta_2\)M mAbs have remarkable tumoricidal activity in hematologic malignancies, both in vitro and in vivo. The current work of Yang and colleagues proposes that it may be possible to inhibit multiple cytokines critical for MM-cell growth and survival by targeting \(\beta_2\)M on the surface of MM cells. They now identify the mechanism of mAb-induced MM-cell death. They demonstrate that \(\beta_2\)M mAbs induce MM-cell apoptosis by recruiting major histocompatibility complex (MHC) class I molecules to lipid rafts, leading to subsequent activation of JNK and inhibition of PI3/Akt and MAPK pathways. Cytokines such as IL-6 and IGF-I, which play a critical role in the growth and survival of MM cells, were not able to rescue the cells from mAb-induced cell death. Yang and colleagues confirmed that binding of the mAb to \(\beta_2\)M resulted in structural reorganization of lipid rafts, excluded IL-6 and IGF-I receptors from the rafts, and blocked subsequent downstream signaling. Because the rafts are active platforms for conducting signals into cells, the modification of lipid-raft structure abrogated all cytokine-mediated JAK/STAT3, PI3K/Akt, and Ras/Raf/MAPK pathway signaling.

Several approaches to induce MM-cell death by neutralizing or blocking cytokines and subsequently disrupting the cytokine-mediated activation of signaling pathways have failed. In contrast, the disorganization of the structural integrity of the cell surface affects cellular functions by blocking cytokine-mediated signaling, and would be an ideal approach for the treatment of MM.

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