Nanoparticle-Mediated Drug Delivery and Pulmonary Hypertension

James C. Bonner, Jeffrey W. Card, Darryl C. Zeldin

Nanotechnology offers great potential benefits for drug delivery and therapy of respiratory and systemic diseases. Nanoparticles (NPs) have been of significant interest for some time because they can be designed to simultaneously carry a drug payload, specifically target features of diseased tissues, and carry an imaging molecule to track drug accumulation and clearance in tissues. Moreover, they can be engineered to tailor drug delivery and improve pharmacokinetics. A variety of NPs have been investigated in experimental animal models as tools to improve the delivery and therapeutic efficacy of drugs or genes delivered to the lung or other organ systems.1 The nanotechnology platform for drug delivery contains a number of very different types of nanostructures with widely varying properties. Examples of these NPs include dendrimers, fullerenes, carbon nanotubes, and polymeric NPs.

In this issue of Hypertension, Kimura et al2 report that nuclear factor κB (NF-κB) decoy oligodeoxynucleotides (ODNs) encapsulated in poly-(ethylene glycol)-block-lactide/glycolide copolymer NPs and delivered to the lungs of rats by intratracheal instillation reduced pulmonary arterial hypertension (PAH) induced by monocrotaline (MCT). They showed that NP-encapsulated NF-κB decoy, visualized by fluorescein isothiocyanate labeling, reached the distal regions of the lungs and was present in alveolar macrophages and small pulmonary arteries for ≤14 days after a single instillation. The small pulmonary arteries were also found to be a site of NF-κB activation and NF-κB-dependent inflammatory cytokine production (monocyte chemoattractant protein 1, interleukin 1, and tumor necrosis factor α) in patients with PAH and in rats with MCT-induced PAH. The decoy ODNs, unlike antisense ODNs, which bind specific regions in mRNA, bind directly to the transcription factor and inhibit transcription factor binding to target DNA and initiation of gene transcription (Figure). It was speculated by the authors that cellular uptake of the NPs might slowly release encapsulated decoys into the cytoplasm as the polymeric structure of the NP is hydrolyzed, thereby protecting the encapsulated decoy from intracellular degradation before its arrival to the nuclear target and optimizing the inhibitory activity of the decoy. It is noteworthy that the authors of this study showed that treatment of rats with the NF-κB decoy NPs 3 weeks after MCT injection led to improved survival.2 This finding is more clinically relevant than showing prevention of PAH with decoy NP treatment before MCT exposure and suggests that individuals with established PAH could potentially benefit from this type of therapy.

The NF-κB pathway is one of the most important cellular signal transduction pathways involved in both physiological processes and disease conditions. It plays important roles in the control of immune function, inflammation, stress response, differentiation, apoptosis, and cell survival.3 Moreover, NF-κB is involved in cellular processes critical to the development and progression of cancers. NF-κB is a logical choice as a target to reduce lung inflammation after injury, because a countless number of inflammatory mediators are regulated by NF-κB. Decoy ODNs for NF-κB have been described previously as a possible strategy for the treatment of numerous diseases, including myocardial infarction, glomerulonephritis, arthritis, and cancer.4 The pathology of these diseases is relatively complicated because of the plethora of cytokines (eg, interleukin 1, interleukin 6, interleukin 8, and tumor necrosis factor α) and adhesion molecules (eg, vascular cell adhesion molecule and intercellular adhesion molecule) that drive the associated inflammatory process. However, an underlying feature of these diseases is that the transcriptional regulation of many of these cytokines and adhesion molecules is controlled by NF-κB. Therefore, blocking NF-κB represents a more efficient strategy for reducing inflammation and disease progression than blocking the action of individual downstream mediators that are regulated by NF-κB. It is recognized that many normal physiological functions are regulated by NF-κB, and so the efficacy of this strategy in reducing inflammation could come at a high cost. For example, NF-κB is a key regulator of immune function, and blocking this signaling pathway could reduce immunity and compromise host defense. Therefore, although NF-κB is an attractive target for the treatment and prevention of a wide spectrum of diseases, some caution should be taken to reduce the risk of developing NF-κB inhibitors that might have the deleterious adverse effect of dampening the normal physiological functions of NF-κB.

Targeting NF-κB with an ODN decoy is a relatively novel approach to PAH treatment, especially in the context of combining this therapy with NP-mediated delivery. A previous rat study conducted by Sawada et al5 demonstrated that the NF-κB inhibitor pyrrolidine dithiocarbamate reduced nuclear localization of NF-κB and vascular cell adhesion

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molecule 1 expression on the endothelium of diseased vessels in the lungs and ameliorated MCT-induced PAH. However, pyrrolidine dithiocarbamate is an antioxidant, as well as an NF-κB inhibitor, and the authors of this study acknowledged that the beneficial effects observed could have been attributed to antioxidant properties of pyrrolidine dithiocarbamate. In addition, they mentioned that there is no evidence from genetically modified animals to demonstrate that NF-κB activation itself is necessary for the development of PAH. Although mice with conditional mutations of the NF-κB pathway, including antioxidants, peptides, small RNA/DNA, gens of the National Institutes of Health, National Institute of Environmental Health Sciences (Z01 ES025041), and North Carolina State University College of Agricultural and Life Sciences.

Disclosures

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