Inflammatory responses to pulmonary application of PEI-based siRNA nanocarriers in mice.

Polymeric non-viral vector systems for pulmonary application of siRNA are promising carriers, but have failed to enter clinical trials because of safety and efficiency problems. Therefore, improving their transfection efficiency, as well as their toxicological profile, is the subject of intensive research efforts. Six different poly(ethylene imine) (PEI)-based nanocarriers, with hydrophilic and hydrophobic PEG modifications, were toxicologically evaluated for pulmonary application in mice. Nanocarriers were intratracheally instilled to determine their toxicological profile, with particular focus on the inflammatory response in the lungs. Nanocarriers from both groups caused an acute inflammatory response in the lungs, albeit with different resolution kinetics and cytotoxicity. Hydrophobic modifications caused a severe inflammatory response with increased epithelial barrier permeability, accompanied by an acute antioxidant response. Hydrophilic modifications, with high PEG-grafting degrees, induced less proinflammatory effects without depleting macrophages and disrupting the epithelial/endothelial barrier in the lungs, while showing only a minor oxidative stress response. For pulmonary applications, local proinflammatory effects should be optimized by further development of nanocarriers with highly grafted PEG-PEI-based carriers or Jeffamine-modified hydrophobic PEI modifications.