The Role of Extracellular Nuclear Factor-Erythroid Derived Protein 2 (NF-E2) as a Danger Associated Molecular Pattern (DAMP) Released during Acrolein Induced Renal Fibrosis

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Acrolein exposure decreased NF-E2 expression in human proximal renal tubular (HK-11) cells and induced renal cell apoptosis and increased expression of pro-fibrotic proteins. Interestingly, NF-E2 expression increased in HK-11 cell supernatants. Danger associated molecular patterns (DAMPs) are proteins released by dying renal cells and are known to play a role in activating and recruiting inflammatory cells and exacerbating renal injury. Moreover, renal fibrosis is associated with DAMP-mediated inflammation. Therefore, I hypothesized that secreted extracellular NF-E2 acts a DAMP and promotes neutrophil activation, recruitment and survival and regulates renal fibrosis. Neutrophils were exposed to control and acrolein-treated HK-11 cell supernatants and cell lysates were immunoblotted with appropriate antisera. Acrolein-treated cell supernatants stimulated pro-survival ERK phosphorylation (pERK) and promoted neutrophil survival by inhibiting cleavage and activation of pro-apoptotic protein caspase-3. To demonstrate a role for NF-E2 in regulating these effects, acrolein-treated cell supernatants were subjected to anti-NF-E2 immunoprecipitation. Depletion of NF-E2 from acrolein-treated HK-11 supernatants with anti-NF-E2 antibody inhibited pERK, stimulated pro-apoptotic p38 MAPK phosphorylation and promoted human neutrophil apoptosis by promoting caspase-3 cleavage and activation. NF-E2-containing acrolein-treated HK-11 cell supernatants stimulated actin polymerization and chemotaxis in neutrophils. Thus, neutralizing extracellular NF-E2 with anti-NF-E2 antibody therapy may serve as a therapeutic option to reduce inflammation and ameliorate acrolein-induced renal toxicity.

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