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Induction of Thioredoxin-Interacting Protein and Role in NLRP3 Activation by Carbon Nanotubes in Macrophages

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The NLRP3 (NOD-like receptor family pyrin domain containing 3) inflammasome is an intracellular supramolecular complex that plays an important role in particle sensing and initiation of inflammatory responses to inhaled particles, including nanoparticles, in the lung. The mechanism by which NLRP3 is activated by carbon nanotubes remains unclear. The thioredoxin-interacting protein (TXNIP) is a multi-functional protein of the alpha-arrestin family implicated in redox regulation, glucose uptake, cell proliferation, and activation of NLRP3. Using an *in vitro* model, we investigated the regulation of TXNIP expression in macrophages and explored its role in NLRP3 activation by multi-walled carbon nanotubes (MWCNTs, Mitsui-7). We show that expression of TXNIP in murine macrophages (J774A.1, ATCC) is dependent on the concentration of glucose in the culture media. Expression of TXNIP is barely detectable in unstimulated cells in glucose-free media. Glucose stimulated the expression of TXNIP mRNA and protein in a concentration and time-dependent manner. Treatment of macrophages with MWCNTs stimulated the expression of TXNIP at mRNA and protein levels compared to vehicle control. MWCNTs also induced the interaction and colocalization between TXNIP and NLRP3, and the activation of NLRP3 as assessed by speck formation, caspase 1 activation, and IL-1beta production. Taken together, these findings indicate that TXNIP is a glucose-dependent regulatory protein and is induced in MWCNT-activated macrophages where it may modulate proinflammatory responses through NLRP3-mediated, caspase 1-dependent production of IL-1beta and other proinflammatory mediators.

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