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Induction of ALOX5 during Polarization of M1 Macrophages by Multi-walled Carbon Nanotubes

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Abstract

Fibrogenic carbon nanotubes (CNTs) induce the polarization of M1 and M2 macrophages in mouse lungs. Polarization of the macrophages differentiates the production of proinflammatory and pro-resolving lipid mediators (LMs) to mediate acute inflammation and its resolution in a time-dependent manner. In the present study, we examined the molecular mechanism by which multi-walled CNTs (MWCNTs) induce M1 polarization *in vitro*, with focus on induction of arachidonate 5-lipoxygenase (ALOX5), which is required to produce proinflammatory LMs, such as leukotriene B4 (LTB4). Treatment of J774A.1 macrophages with MWCNTs at a concentration of 2.5 μg/mL increased the expression of ALOX5 mRNA by 2.0-fold at 1-day and 2.5-fold at 3-day post-exposure. At a concentration of 10 μg/mL, MWCNTs increased the ALOX5 mRNA expression by 3.5-fold at 1-day and 5.0-fold at 3-day post-exposure. Immunoblotting shows that MWCNTs significantly increased the ALOX5 protein expression in macrophages. Luciferase reporter assays with the mouse ALOX5 promoter of 2 kilobase upstream of translation start codon demonstrate that the ALOX5 promoter activity increased more than 5-fold over background. This activity was significantly elevated following 5'-deletion analyses of ALOX5 promoter and further enhanced by MWCNT treatment, implicating a transcriptional mechanism in the induction of ALOX5. MWCNTs preferentially induced the expression of CD68, a cell surface marker of M1, by 2.5-fold and induction was persistently high to 3-day post-exposure. Moreover, both the expression and activity of the inducible nitric oxide synthase, an intracellular marker of M1 macrophages, were increased by MWCNTs, indicating induction of M1 polarization. Consistent with this notion, MWCNTs increased the capacity of the macrophages to produce proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-

1β), and proinflammatory LMs, such as LTB4 and prostaglandin E2 (PGE2), as measured by enzyme-linked immunosorbent assays. Taken together, these results support that persistent exposure to MWCNTs polarizes macrophages to M1 cells with induction of ALOX5 and elevated production of proinflammatory LMs to boost the acute inflammatory response to fibrogenic nanoparticles.

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