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Novel Molecular Mechanisms Involved in Macrophage Phenotypic Polarization

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Abstract : Macrophages polarize to proinflammatory M1 or anti-inflammatory M2 states with distinct physiological functions. This transition within the M1 to M2 phenotypes decides the nature, duration, and severity of an inflammatory response. However, inspite of a substantial understanding of the fate of these phenotypes, the underlying molecular mechanisms are not well understood. We have investigated the role of Neuronal nitric oxide synthase (NOS1) mediated regulation of Activator protein 1 (AP-1) transcription factor in macrophages as a critical effector of macrophage phenotypic change. Activator protein 1 (AP-1) is a group of dimeric transcription factors composed of jun, Fos, and ATF family proteins. We determined that NOS1-derived nitric oxide (NO) facilitate Fos and jun interaction which induces IL12 & IL23 expression. Pharmacological inhibition of NOS1 inhibits Fos and jun interaction but increases ATF2 and Fos dimerization. Switching of Fos and jun dimer to ATF2 and jun dimerization switches phenotype from IL–12high IL-23high IL-10low to IL–12low IL-23lowIL-10high phenotype, respectively. Together, these findings highlight a key role of the TLR4-NOS1-AP1 signaling axis in regulating macrophage polarization.

Keywords : inflammation, macrophage, lipopolysaccharide (LPS), proinflammatory cytokines, activator protein 1 (AP-1), neuronal nitric oxide synthase (NOS1)
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