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Hypoxia and Macrophages Polarization Defecets via Aryl Hydrocarbon Receptor (AHR) Perturbation

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Abstract

Aryl hydrocarbon receptor (AHR) signaling has been introduced to be involved in macrophages polarization. The perturbation of AHR has been reported in hypoxia and related disorders. Here, I would like to highlight the significance of AHR in hypoxia-mediated macrophages polarization and suggest conducting further experiments on related subjects.

Keywords: Aryl Hydrocarbon Receptor; Hypoxia; Macrophages; Polarization

Statement:

Macrophages are particular mononuclear phagocytic cells of the innate immune system, along with the monocytes and dendritic cells and are responsible for the regulation of immune responses and modulation of inflammation (1). Macrophages and their precursors are recognized for their significant phenotypic plasticity and their distinct functional roles which may be assumed to be contradictory; such as the secretion of both pro- and anti-inflammatory cytokines, executing immunogenic and tolerogenic functions, and/or promoting both tissue repair and its injury (2). In response to (micro)environmental stimuli such as pathogens and their metabolites, or the apoptotic or dying cells, macrophages exhibit their functional and phenotypic heterogeneity (2). Accordingly, macrophages will be polarized into classically M1 activated (pro-inflammatory) and/or alternatively M2 activated (anti-inflammatory) subtypes (3). The imbalanced status of polarization in macrophages could be distinctive of some pathological conditions, such as autoimmune disorders (3), malignancies(4) and uncontrolled infectious diseases (5). Several molecules and signaling pathways have been proposed to be involved in macrophage polarization including peroxisome

proliferator-activated receptor gamma (PPAR-gamma) (2), histone deacetylases (HDACs) (3), NF-κB (5), interferon regulatory factors (IRFs) (5) and etc.

Recently, it has been suggested that aryl hydrocarbon receptor (AHR) signaling could be involved in macrophages polarization. In a recent publication by our team, we revealed that I3C-mediated activation of AHR could be associated with the overexpression of M2 and downregulation of M1 markers (enhancing M2 polarization), and exerting immunoregulatory effects on macrophages of SLE patients (6). Similarly, Shinde et al. showed that the activation of AHR by apoptotic/dying cell phagocytes maintains peripheral tolerance and is linked to the polarization of macrophages (7).

AHR is a cytoplasmic receptor and a member of the basic helix–loop–helix–(bHLH) superfamily of atranscription factors, which is normally responsible for metabolizing xenobiotics and is associated with several cellular process and immune responses (7). AHR is extremely responsive to a vast number of environmental and endogenous ligands (6). Hypoxia is a process in which cells are deprived from sufficient oxygen. It is an important determinant in several pathological processes of tumors, autoimmune disorders and fibrotic diseases (8). The imbalance polarization of macrophages is an important feature in most of the abovementioned disorders. It has been reported that hypoxia could interfere with AHR binding to the target gene sequences and that AHR target gene expression could be perturbed in hypoxic environments (9). Interestingly, it is revealed that hypoxia can modify the polarization of macrophages and regulate the inflammatory microenvironment (10). Accordingly, I would like to highlight the significance of AHR signaling in hypoxia-mediated macrophages polarization. Then, AHR could be employed as a helpful target in modulation of inflammation in related disorders such as cancer and autoimmunity and considered as an interesting subject for future research.

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