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Promoting the pro-inflammatory phenotype in macrophages by blocking the aryl hydrocarbon receptor

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A novel way of regulating the function of immune cells has been discovered and it is mediated by targeting the activation of the aryl hydrocarbon receptor (AhR) [1]. AhR is a ligand-activated transcription factor that responds to various aromatic compounds - exogenous such as plant flavonoids, polyphenolics and indoles and endogenous such as kynurenine [2]. By inhibiting its activation a pro-inflammatory immune response is promoted, whereas its activation exerts an opposite effect [1]. Therefore, we have tested a selection of plant-derived indol derivatives for their AhR-binding activity. According to the inhibition of mRNA expression of Cytochrome P450 Family 1 Subfamily A Member 1 (Cyp1a1), a down-stream effector of AhR activity, a potent AhR antagonist was selected under the code C46. This compound was further tested on mouse peritoneal macrophages for its ability to modulate macrophage function. Macrophages were exposed to the compound C46 *in vitro* in concentrations ranging from 250 to 1000 ng/mL for 48 h. By using flow cytometry we established that C46 significantly and dose-dependently up-regulated the proportion of M1 macrophages ($F4/80^+CD40^+$) and not only that, but it affected only M1 macrophages, while the proportion of M2 ($F4/80^+CD206^+$) remained stable throughout the exposure to different concentrations of C46. In further analysis with DAF-FM staining, it was found that C46 increased the cytocidal function of macrophages, since their content of nitric oxide was increased. With intraperitoneal administration of C46 the results were similar - the proportion of M1 macrophages in the peritoneum was up-regulated, 72 h after the treatment, while the proportion of M2 macrophages remained unaltered. In conclusion, by blocking the AhR signaling pathway with C46, a pro-inflammatory immune response could be achieved by promoting the M1 macrophage phenotype and it may as well be a promising approach for future testing in animal models of cancer.

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