SUPPLEMENT

Phenotype diversity of macrophages

Macrophages can reveal markedly different reactive behaviour depending on the stimulating conditions and their environmental context [1]. According to their polarization, and in relation to the nomenclature of Th1 and Th2 types of immune responses (Th as for T helper cell), differentially induced macrophages were referred to as M1 or M2 cells [2]. The first conscious description of macrophage phenotype versatility originated from an 'alternative' activation with the Th2 cytokine interleukin-4 (IL-4) [3]. Macrophages incubated under IL-4 influence (M2 polarization) differ from macrophages 'classically' stimulated (M1 polarization) by the Th1 cytokine interferon-γ (IFNγ) and/or bacterial lipopolysaccharide (LPS), a major cell wall component of Gram-negative bacteria. Alternative activation with IL-4 or IL-13 results in a marked production of IL-10, but little or no IL-12(p70), whereas an inverse ratio is obtained with classically activated cells. Inspired by this seminal observation, numerous non-classical macrophage phenotypes have been described on the basis of transcriptional and non-transcriptional features [1, 2, 4]. Macrophage populations thereby present with distinct expression patterns, and indicative, often reciprocal inductions of key molecules (e.g. IL-10/IL-12/IL-23 or iNOS/arginase, ManR etc.) allow for the identification of the respective phenotype orientation. Nevertheless, the most important aspect is their functional diversity and the resulting consequences for other cells. Macrophages of discrete functional orientation vary in T and B cell interactions, bias for types of immune responses (Th1/Th2), promote or rather resolve inflammation and differ by influences on the extracellular matrix (ECM) structures. By extreme polarization, macrophages direct their activities towards defence or repair. For example, binding of immunoglobulins of various classes/subclasses to their respective Fc receptors can cause completely different responses [5]. Activation by IgG/immune complexes (IC) of the FcγR types linked directly or via FcRγ chain to an intracellular ITAM signalling module (cytoplasmic immunoreceptor tyrosine-based activation motif) can induce toxic macrophage reactions while occupation of FcγRIIB linked to ITIM (immunoreceptor tyrosine-based inhibitory motif which can control ITAM activities) causes opposite effects or prevents killing activities [6-8]. Activities of IgG/IC are further controlled by Fc carbohydrate modification [9]. In addition, cellular responses can drastically shift when pairing IgG/ICs with additional stimuli, such as LPS [10]. Other striking examples for different reactive behaviour relate to tumour-associated macrophages and their support of immune evasion [2, 11] or to the association of inflammatory macrophage subsets with metabolic diseases, such as obesity and atherosclerosis [12-14]. For additional information regarding the features and functions of (especially) microglia in health and disease, development and aging, we refer to recent reviews [15-31].

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