M1 and M2 MACROPHAGE ACTIVATION
12 August 2009
by Jason Fritz

A tissue macrophage will continuously adjust its expression of surface receptor proteins and secreted products in response to local stimuli, in a manner so similar to the T lymphocytes of the adaptive immune branch that the "Th1 vs. Th2" nomenclature has been adopted to classify macrophage activation as "M1 vs. M2." "M1" activation describes a macrophage performing "classical" anti-microbial functions, while "M2" activation encompasses the "alternative;" quite literally everything else— from helminth defense, to tissue repair in the wake of an oxidative burst, to feed-back regulation of the immune system. As you might expect, "alternative" activation encompasses a vast area of macrophage functionality, and has been more recently subdivided into M2a-c: an IL-4/13 stimulated macrophage (M2a) will express a subtly different array of signaling molecules than an IL-1R + TLR (M2b) or glucocorticoid-activated cell (M2c). This classification scheme is for the "generic" macrophage, i.e. a lung macrophage is fundamentally different from a peritoneal or skin or liver macrophage, and thus may respond differently to the same M2 stimuli. However, even with mounting evidence of increasing layers of variability in macrophage activation, there are some common themes.

M1 is to macrophages as Th1 is to lymphocytes; among other cytokines, Th1 cells can produce high levels of IFN-γ, an extremely potent macrophage chemoattractant, and also one of the most potent endogenous M1 macrophage activation stimuli. LPS (endotoxin) from bacteria can also stimulate M1 (or mixed M1 +M2b) macrophages through TLR4, and is the most well described exogenous M1 stimuli. A macrophage so-stimulated will produce high levels of TNF-α, IL-6 and IL-12, which have a variety of effects on stromal tissue cells but also stimulate Th1 activity and further IFN- γ production. In addition to cytokine production, M1 activation stimulates iNOS activity and phagocytosis, i.e. macrophages become better at consuming and destroying bacteria. Both M1 and M2 macrophages can secrete high levels of IL-lα/β, which can be further increased by LPS stimulation. IL-lα/β can act in an autocrine manner back on the macrophages, inducing production of IL-8 and CCL2, which results in neutrophil and macrophage recruitment, respectively. Interestingly, macrophages can acquire functional neutrophilic granules after those short-lived cells die, and can in turn use the granules to kill phagocytosed bacteria. Thus, once macrophages are recruited and M1-activated by either IFN-γ or LPS, they become fully equipped to attack and destroy.

Similar to the M1 story, M2 is to macrophages as Th2 is to lymphocytes; Th2 cells can produce high levels of IL-4, IL-13 and sometimes IL-10. While all three cytokines can induce M2 activation in macrophages, there are distinct differences in the resultant phenotypes, so we will concern ourselves with the IL-4 mediated M2 activation, which is the one most commonly described. IL-4 greatly stimulates the expression of mannose receptor, which is an opsonin-independent cell surface particle receptor (or pattern-recognition receptor) and is widely accepted as the canonical marker for M2 macrophages. M2 activation also results in increased CD36 expression, which binds to oxidized low density lipoproteins, thrombospondin, and several other molecules. The increased levels of these scavenger receptor proteins in M2 macrophages is consistent with the need to clean out debris in order to successfully resolve, or end, an inflammatory response. Another role for the M2 activated macrophage is to react

against invasion by helminthes or other parasites. Accordingly, IL-4 stimulates the increased expression of several proteases: acidic mammalian chitinase (AMCase), chitinase-3 like proteins, legumain, and various cathepsins. While only AMCase has known chitinase activity (chitinase-3 like proteins do not), and thus can hydrolyze the shells of worm eggs into digestible and MHCII- presentable proteins, the other proteases could aid in presentation of antigens from other invading species. Compared to a M1 macrophage, M2 stimulation decreases phagocytosis, but increases macropinocytosis (the intake of large particles in solution), which augments the ability of the M2 macrophage to sample its environment and more efficiently present antigens. Macrophages are typically M2-activated by tumors, a characteristic of so-called tumor associated macrophages (TAMs). While the specific activation stimuli may involve IL-4 and/or other molecules, the beneficial effects of M2 macrophages for tumorigenesis include increased VEGF and matrix metalloprotease-9 expression, which results in increased neo-angiogenesis and a general breakdown of the basement membrane, facilitating not only tumor growth but metastasis as well. This is likely to be a subversion of a healthy M2 response, as neo-angiogenesis and basement membrane remodeling are both required to repair damage resulting from traumatic injury.

In closing, it is beneficial to point out that macrophages are very plastic cells, and that some of the many signaling molecules mentioned above serve as biofeedback “off” switches. Macrophages can change from M2 to M1 and back any number of times, and this flexibility does not appear to diminish with age of the organism or the cell. As mentioned above M1 macrophages can produce CCL2, which can induce IL-4 expression in lymphocytes, and decrease IL-12 production. Thus the M1 phenotype, which could be extremely destructive due to high ROS/RNS production, can induce its own down-regulation and end up becoming M2.