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Mills, Laurel L Lenz, Klaus Ley, 2015-03-23 Macrophages have unique and diverse functions necessary for survival And in humans and other species they are the most abundant leukocytes in tissues The Innate functions of macrophages that are best known are their unusual ability to either Kill or Repair Since killing is a destructive process and repair is a constructive process it was stupefying how one cell could exhibit these 2 polar opposite functions However in the late 1980 s it was shown that macrophages have a unique ability to enzymatically metabolize Arginine to Nitric Oxide NO a gaseous non specific killer molecule or to Ornithine a precursor of polyamines and collagen for repair The dual Arginine metabolic capacity of macrophages provided a functional explanation for their ability to kill or repair Macrophages predominantly producing NO are called M1 and those producing Ornithine are called M2 M1 and M2 dominant responses occur in lower vertebrates and in T cell deficient vertebrates being directly driven by Damage and Pathogen Associated Molecular Patterns DAMP and PAMP Thus M1 and M2 are Innate responses that protect the host without Adaptive Immunity In turn M1 M2 is supplanting previous models in which T cells were necessary to activate or alternatively activate macrophages the Th1 Th2 paradigm M1 and M2 macrophages were named such because of the additional key findings that these macrophages stimulate Th1 and Th2 like responses respectively So in addition to their unique ability to kill or repair macrophages also govern Adaptive Immunity All of the foregoing would be less important if M1 or M2 dominant responses were not observed in disease But they are The best example to date is the predominance of M2 macrophages in human tumors where they act like wound repair macrophages and actively promote growth More generally humans have become M2 dominant because sanitation antibiotics and vaccines have lessened M1 responses And M2 dominance seems the cause of ever increasing allergies in developed countries Obesity represents a new and different circumstance Surfeit energy e g lipoproteins causes monocytes to become M1 dominant in the vessel walls causing plaques Because M1 or M2 dominant responses are clearly causative in many modern diseases there is great potential in developing the means to selectively stimulate or inhibit either M1 or M2 responses to kill or repair or to stimulate Th1 or Th2 responses depending on the circumstance The contributions here are meant to describe diseases of M1 or M2 dominance and promising new methodologies to modulate the fungible metabolic machinery of macrophages for better health

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