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Abandoning M1/M2 for a Network Model of Macrophage Function

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The heart and blood vessels of a healthy individual contain resident immune cells, the majority of which are macrophages that have seeded these organs early in development. In the mouse, ~10% of non-cardiomyocytes are macrophages[1, 2], and humans may have comparable numbers[1]. After myocardial infarction (MI), macrophage numbers increase in the heart through the combined effects of massive recruitment of bone marrow-derived cells and local self-renewal[1, 3]. Likewise, in atherosclerosis, the chronic lipid-driven inflammatory disease that is the underlying cause of MI, macrophage numbers increase in the vessel wall, again because of recruitment and local proliferation[4]. Though many of these insights have been generated in mouse models, compelling evidence from GWAS studies have associated innate immunity mediators with myocardial infarction[5], while prospective human studies have shown that blood monocyte levels can predict cardiovascular events in patients[6].

During the last decade, multiple studies have challenged and, in some cases, dismantled old assumptions about macrophage origins and functions. Many reviews and opinion pieces[7–19] – some of them our own[20–23] – have been written on the subject, as the various communities interested in macrophage biology seek to contextualize the findings into a coherent narrative. We now know that, in the steady state, arterial[24] and cardiac[1, 25–27] macrophages are mostly independent of monocytes but, in response to an inflammatory trigger, such as MI or high-fat diet, monocyte-derived cells accumulate and differentiate to self-renewing macrophages[3, 4, 28, 29]. We also know that macrophage function goes far beyond phagocytosis. Because they reside in nearly every organ, macrophages respond and adapt to their local surroundings, and their non-canonical activities reflect their flexibility. From iron recycling in the spleen[30, 31] and synaptic pruning in the brain[32] to thermoregulation in brown fat[33] and hematopoietic control in the bone marrow and spleen[34], macrophages are remarkably adaptable. Indeed, if transplanted from one organ to another, macrophages adopt their new location's organ-specific transcriptional profiles[35]. Though non-canonical macrophage functions have not yet been observed in cardiovascular organs, newly-available research tools will likely fill in this gap in the next few years.

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Disclosure Section

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A handy and consequently persistent shorthand for understanding macrophage function groups the cells into either M1 or M2 responses. Introduced by Charlie Mills in 2000, the M1/M2 macrophage polarization paradigm[36] was inspired by the Th1 vs. Th2 concept introduced four years earlier by Mosmann and Coffman[37]. Mills' idea was built on the observation that LPS and IFNγ elicit divergent effects on macrophages isolated from different strains of mice. Whereas macrophages isolated from so-called Th1 strains (C57BL/6) produce nitric oxide (NO) in large quantities, the same triggers stimulate arginine metabolism to ornithine in macrophages isolated from Th2 strains (Balb/c). Moreover, Mills explained, the two responses are T cell-independent, and their balance is regulated by TGFβ. Over the years, this paradigm was at times incorrectly fused with the concept of classical vs. alternative macrophage polarization, as proposed by Siamon Gordon in 1992[38]. Gordon showed that IL-4, the prototypical Th2 cytokine, augments expression of the mannose receptor on peritoneal macrophages without inducing TNFα production. In a science version of the game "telephone," during which an original message shifts until it becomes unrecognizable, this "alternative" activation of less inflammatory macrophages became synonymous with "M2" macrophages. Today, M1 macrophages are often thought of as bone marrow-derived cells that are stimulated with LPS and/or IFNγ and depend on STAT1 to produce TNFα, IL-1, and nitric oxide synthase (NOS). In contrast, M2 macrophages are frequently defined as cells that are stimulated by IL-4, rely on STAT6, produce Arginase, and augment Mrc and Ym1. Over the years, this seemingly simple macrophage dichotomy has led to multiple cytokines and surface markers being sorted into one group or the other, the heuristic being that, if a marker is linked to an inflammatory process (CCR2 attracting inflammatory monocytes; proteases participating in catabolism of dead or dying tissue, IL6, IL12, IL23, etc.), then it is an M1 macrophage marker. Conversely, if a marker is linked to resolution of inflammation (IL10, TGFβ, VEGF, CD206, Fizz), then it is a marker of M2 macrophages. With this growing constellation of M1 vs. M2 insignia, it became possible to infer two seemingly distinct macrophage subsets. On occasion, a macrophage elicited from an uncommon environment, or stimulated with something other than LPS, IFNγ, or IL4, augmented expression of a different set of markers and was endowed with its own unique name. Over time, the prevailing model was a macrophage spectrum, with M1 and M2 macrophages at the opposing ends and other groups of macrophages between.

Regardless of how it arose, is there a problem with the current M1/M2 model? For one, the concept is an *in vitro* construction that relies on stimulating macrophages in culture with a defined set of factors. One view posits that, though an oversimplification, this *in vitro* construction nevertheless provides a useful guide for thinking about *in vivo* biology. The problem with this perspective is that macrophages taken out of their native environments and placed in culture change dramatically: after a 7-day incubation period, cultured microglia and peritoneal macrophages completely lose their tissue-specific gene expression programs[39]. To conclude anything from these *in vitro* settings is to ignore the obvious: these are different cells. A second argument in favor of the M1/M2 paradigm acknowledges that it is an *in vitro* construction but insists the macrophage spectrum, with M1 and M2 as its polarized extremes, does exist *in vivo*. If this is true, then knowing something about M1 vs. M2 activity *in vitro* would be useful in the same ways that *in vitro* experiments are useful:

reductionism and standardization. Setting aside the obvious limitations of such utility, relying on the M1/M2 spectrum model remains a perilous proposition. First, as noted above, macrophages placed into culture change dramatically and thus may no longer resemble anything that exists *in vivo*. Second, a "spectrum" is an array ordered according to the magnitudes of certain properties (consider, for example, a spectrum of light). A spectrum requires intermediates that bridge the two extremes. In macrophage biology, we have little evidence for an all-encompassing spectrum.

We do have evidence for a stimulus-dependent activation macrophage *network*. Transcriptional profiling of human macrophages, for example, identified a broad transcriptional repertoire that challenges the M1/M2 paradigm. *In vitro* culture of human monocytes with M-CSF or GM-CSF, followed by activation with diverse stimuli, revealed considerable deviation from the M1/M2 axis, an insight that should be particularly relevant to investigators studying macrophage biology in cardiovascular disease because free fatty acids and high-density lipoprotein (HDL) molecules were among such stimuli[40]. In other words, a macrophage encountering a stimulus relevant to cardiovascular disease produces mediators that lie outside the M1/M2 "spectrum". What needs to be emphasized is that departure from the M1/M2 framework depends on the stimulus. One wonders how many other polarization states, beyond the nine that were identified, exist with additional stimuli or with macrophages isolated from specific organs (i.e., beyond M-CSF- and GM-CSF-generated monocyte-derived macrophages).

Should we abandon the M1/M2 paradigm altogether? Beyond the reasons already mentioned, the reductive M1/M2 model arguably stifles rather than enables discovery. A typical experiment might involve profiling macrophages isolated from the aortas of two different groups of mice with atherosclerosis. The investigators might measure a cassette of transcripts that differ between the groups. Maybe macrophages from one group express more NOS, IL1β and TNFα, while macrophages from another express more Arg1. It is tempting to conclude that the former group enriches for M1 while the latter favors M2 macrophages, but such a conclusion may be myopic at best. More likely, cells augment or attenuate certain markers considered M1 or M2 in parallel (i.e., the same macrophages express NOS and Arg1). In some cases, markers may break from the rule completely (i.e., more CCR2 expression in macrophages otherwise deemed M2). Adherents of the M1/M2 model might either ignore such "outliers" (if they are authors) or review the paper negatively (if they are reviewers). Forcing data onto the M1/M2 spectrum means opportunities for real discovery may be missed. We can avoid this by thinking about macrophage functions as belonging to a network that accommodates for macrophage origins (monocyte- vs. locally-derived tissue residents); environmental stimuli (different organs, different stimuli during steady state and inflammation) and time (development, stages of inflammation, aging).

While it is easy to propose a conceptual shift that adds one or two more dimensions, it is not always obvious how such a shift can be enacted practically. Murray and colleagues proposed naming macrophages according to the stimuli they encounter[19]. Thus, macrophages activated with IL-4 would be called M(IL-4), and macrophages activated with LPS would be called M(LPS). Though such an approach goes beyond the simple duality proposed by the M1/M2 model, it still has limitations. For one, identifying macrophage function according to

a very specific stimulus, often given *in vitro*, does not attend to cell origins, tissue microenvironment, and time. Second, such a nomenclature simply replaces one code for another and therefore requires a deciphering step in between. Calling a macrophage "M(LPS)" is only marginally more informative than "M1" because one still has to dig to understand the function of an LPS-stimulated macrophage. Third, a nomenclature based on stimulus is open-ended enough to become meaningless, because there are a nearly infinite combination of arbitrary stimuli, each yielding a "different" type of macrophage.

To communicate scientific findings we use graphs, gels, charts, plots, tables, and all manner of mathematic and graphic tools. We also use words to convey our ideas and, generally speaking, we seek clarity and accuracy in our scientific language. Why not name macrophages according to what they do in their natural habitats? If they prune neurons, then they are pruning macrophages. If they ingest senescent erythrocytes and recycle iron, then they are iron-recycling macrophages. If they participate in thermoregulation, then they are thermoregulating macrophages. Evocative and lucid description of function can be a scaffold upon which we build the code and its network. By starting with clearly-stated function, we can then consider ontogeny, tissue location, stimulus, timing, and the many transcription factors, receptors, and secondary messengers that contribute to that function. After all, the word "macrophage" is itself a functional definition that has withstood the test of time. Naming macrophages according to their additional functions should be fluid and changeable as functions appear, disapper, and co-exist in the same cell. Just as T cells can be either cytotoxic or helpful – with at least three helper functions now identified – macrophages can be inflammatory, reparative, or something else. Just as human activity extends well beyond a linear spectrum between standing still and sprinting, macrophage activity cannot be confined to a gradient of inflammatory intensity. Let's first understand what these cells do before deciding what they are.

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