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RESEARCH HIGHLIGHT

Master and commander: epigenetic regulation of macrophages

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Macrophages are important innate immune cells with functions in tissue repair and remodeling, induction and resolution of inflammation, as well as elimination of invading pathogens. In a recent study, Schmidt and colleagues describe the open epigenetic landscape of the human inflammatory macrophages, and the transcriptional regulators responsible for their rapid response to environmental signals.

Macrophages are immune myeloid cells that fulfill crucial functions in homeostasis and in disease: they are the main phagocyte population critical for tissue remodeling, debris clearance, as well as elimination of invading pathogens, they are main cytokine producers, and they initiate and modulate both innate immune and adaptive immune responses [1]. Macrophages in tissues have two distinct sources: many of the tissue-resident macrophages (e.g., microglia) originate from the yolk sac, have the capacity of self-renewal in the tissue and are independent of replenishment from the blood compartment [2], while other populations of tissue-resident macrophages (e.g., macrophages in the intestinal mucosa) are dependent on hematopoiesis through a monocyte intermediary in the blood [3]. In contrast to resident macrophages, during infections, adult blood inflammatory monocytes migrate to inflamed tissues and differentiate into monocyte-derived macrophages that can eliminate the pathogen and restore tissue integrity [3].

Macrophage differentiation is crucial for determining cell function, and the regulatory mechanisms controlling it have received much attention. Macrophage differentiation is characterized by integration of epigenetic and transcriptional regulatory signals in which both the microenvironment and the exogenous stimulus play an important role. The finely-tuned integration of epigenetic and transcriptional signals has been described for the monocyte-to-macrophage differentiation in tissues, but much less is known regarding these regulatory networks during differentiation of monocytes into inflammatory macrophages, and the subsequent response to stimulation. In a study published recently in *Cell Research*, Schmidt and colleagues describe the transcriptional regulatory landscape of inflammatory macrophages [4], opening the door for both understanding this important process and aiming at therapeutic approaches to modulate it.

Monocyte-to-macrophage differentiation and activation of macrophages during inflammation, infections or even carcinogenesis has been described in the last decade from the dichotomy between classically-activated M1 macrophages and alternatively-activated M2 macrophages [5]. While M1 macrophages release more proinflammatory cytokines and are important for elimination of infectious pathogens, M2 macrophages have anti-inflammatory properties and are involved in resolution of inflammation and tissue repair. While this concept has proved to be a useful simplification of natural processes, recent studies have argued for a more complex landscape of macrophage differentiation and activation, in which diverse patterns are available during differentiation depending on the microenvironment and stimulus [6]. The study by Schmidt *et al.* [4] gives further weight to this multidimensional model, as specific regulatory landscapes of human monocyte-derived macrophages or inflammatory macrophages are defined, clearly demonstrating that various stimuli (e.g., IFNγ, IL4 or a combination of TNFα + PGE2 + Pam-3Cys) lead to specific epigenetic and transcriptional signatures, rather than a variation of M1 and/or M2 responses. This multidimensional model of macrophage differentiation is supported by studies in murine tissue macrophages [7, 8].

Macrophage differentiation has been recently described to integrate epigenetic and transcriptional cues, leading to well-defined functional programs [9]. The differences in the regulatory networks occurring during differentiation and stimulation by microenvironment or exogenous stimuli were however unknown. In their study, Schmidt and colleagues profiled both gene expression and chromatin landscape of four populations of human inflammatory macrophages activated with distinct stimuli to determine the contribution of transcriptional regulators and histone modifications to macrophage activation. The authors identified both common and specific regulatory elements. Interestingly, while microenvironment signals induce an integration of epigenetic and transcriptional regulation, the stimulation due to exogenous stimuli seems to mainly encompass transcriptional (rather than epigenetic) regulators (Figure 1).

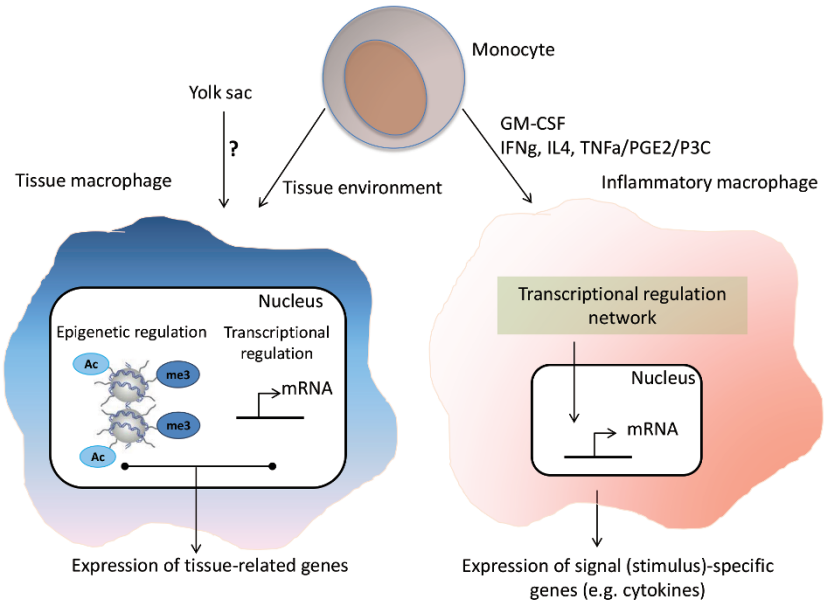

Figure 1 Master and commander: epigenetic versus transcriptional regulation of macrophages. Tissue macrophages originate from either monocyte lineage or the yolk sac, depending on the specific tissues. In contrast, inflammatory macrophages derive from monocytes during migration to the infected tissue, or by using GM-CSF as a model *in vitro*. The function of the resident tissue macrophages is revealed to be dependent on integration of both epigenetic and transcriptional regulators for the expression of tissue-related genes. Of high interest, monocyte-derived inflammatory macrophages are shown to be mainly dependent on a transcriptional regulation network for the expression of signal-specific genes, while epigenetically they are characterized by a broadly open chromatin landscape.

In this respect, the regulatory network of human inflammation-associated macrophage activation is characterized by globally permissive histone. These data indicate that in contrast to differentiated resident macrophages, inflammatory macrophages resulting from acute differentiation during infection or inflammation possess constitutively accessible loci for nearly all central transcriptional regulators. Activated macrophages are thus characterized by accessibility of chromatin loci for transcriptional regulators, and this explains why these cells can rapidly react towards environmental signals. In contrast, tissue macrophages in homeostasis (especially as described until now in the murine system) seem to have a more restricted activation landscape: chromatin is open for transcriptional regulators that are necessary for organ-related functions, but is closed for those important in other tissues or during infection.

While the study by Schmidt and colleagues is important to understand the processes of macrophage differentiation into inflammatory cells, many new questions remain to be answered by future research. One obvious question is whether tissue macrophages can react similarly to the monocyte-derived human macrophages *in vitro*, and whether they would display similar epigenetic and transcriptional pathways. Second, future studies should also address the potential differences between murine and human tissue macrophages: while studies in mice are important as model organisms, increasing energy should be put to investigate human tissue macrophages. A third aspect to be studied in the near future concerns the behavior of tissue macrophages during inflammatory conditions as well as infections *in vivo*. Finally, the findings by Schmidt *et al*. could also provide a model for the study of the context of epigenetic and transcriptional regulation within the monocyte compartment during trained immunity (innate immune memory) [10].

In conclusion, the study by Schmidt *et al*. is an important step towards understanding epigenetic and transcriptional regulation of the function of inflammatory macrophages. This is important not only because it improves our knowledge of an important biological process, but also because it opens new avenues for the identification of novel therapeutic targets in both inflammatory and infectious diseases.

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