Inflammatory Skin Disorders: Monocyte-Derived Cells Take Center Stage

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INTRODUCTION

Current biologics targeting pro-inflammatory cytokines in psoriasis and atopic dermatitis (AD) show excellent clinical efficacy but are not curative, underscoring the need to study the skin immune and non-immune landscape. A recent article published in Science employed single-cell RNA sequencing (scRNA-seq) to generate an atlas of healthy human skin during early prenatal life and adulthood, and further dissect changes occurring in inflammatory skin diseases (1). Developing skin is enriched in innate lymphoid cells and macrophages (Mφ) while healthy adult skin is predominantly populated with T cells, Langerhans cells (LCs), and dendritic cells (DCs). Specifically, adult skin Mφ were subdivided into Mac1 and Mac2 based on distinct molecular signatures. In AD and psoriasis, the percentage of Mac2 is increased resulting in an altered Mac1/Mac2 ratio in lesions. Fibroblasts predominate in fetal non-immune cell compartment while keratinocytes, melanocytes, and endothelial cells represent the major cell types in healthy adult skin. Among the three vascular endothelial (VE) cell subsets identified, only the proportion of VE3 is elevated in adult inflamed skin. Interestingly, Mac2 and VE3 in inflamed skin share a common molecular signature with Mφ and VE in fetal skin. Overall, the authors conclude that skin developmental programs are recalled during inflammatory skin diseases and proposed Mφ as potential targets of treatment. The concept of re-emergence of fetal skin program was recently reported for fetal Tregs that express an effector memory phenotype and closely align with adult Tregs in healthy skin (2). The authors further highlight the advantage of this molecular approach that identified 14 mononuclear phagocyte (MNP) cell states, and state that flow cytometry (FCM) has limitations to uncover diversity of rare cells. However, high dimensional single cell FCM is a complementary approach that has been proven suitable to reveal heterogeneity of skin MNP cell states in blood and skin (3, 4).
NEED FOR CONSENSUS IN MONONUCLEAR PHAGOCYTE NOMENCLATURE

Identification of a phenotypic or transcriptomic signature to precisely define MNP subsets in inflamed tissues has resulted in confounding nomenclature. Monocytes recently recruited to inflamed skin have been referred to as monocyte-derived dendritic cells (Mo-DC), inflammatory DC, inflammatory monocyte-like (Inf Mo-like) cells, inflammatory Mφ (Inf mac), or monocyte-derived Mφ (Monomac) highlighting a need to better define their molecular identities and function (5). Also, circulating conventional DC2 (cDC2) subsets reflect a continuum of activation states which remain unclear in inflamed skin (3). Our recently reported FCM analysis, that utilized nine surface and two cytokine markers with the aim to identify IL-23 or TNFα-expressing MNPs (4), revealed MNP heterogeneity in psoriatic non-lesional (NL) and lesional (L) skin. Another representation of these previously reported data using a different clustering algorithm, FlowSOM, discerned 19 MNP clusters: two Mφ, two Inf Mo-like cells, one inflammatory DC-like (Inf DC-like), three Mo-DC, seven cDC2 and four LC subsets (Figure 1). As depicted in Figures 1B, C, frequencies of Inf Mo-like MNPs which included the IL-23-expressing subset, Inf DC-like and Mo-DCs were augmented while cDC2 and LC subsets were decreased in L skin.

INFLAMMATORY MONOCYTE-LIKE CELLS ARE THE MAJOR MNP SUBSET IN INFLAMED SKIN

It must be emphasized that CD14brightCD64brightCD163- Inf Mo-like cells (MNP_1 and MNP_2) represent the major clusters increased in L skin that were significantly reduced in healed skin.
during treatment with guselkumab (anti-IL-23p19) or secukinumab (anti-IL-17A) (4). In contrast, the two Mø clusters, MNP_3 and MNP_4, like Mac1 and Mac 2 (1), represent relatively minor MNP subpopulations in L skin (4) (Figure 1B). Reynolds et al., in Figure S5, further show that CD1α+Ki-67+ cells expressing Langerin (CD207) infiltrate inflamed skin. In fact, these cells might comprise CD207+CD1α−Inf Mo-like (MNP_1) cells as well as CD207+CD1α− Mo-DC_1 that are distinct from CD1αbrightCD207+ LCs (Figure 1). Interestingly, proportion of LCs, drastically reduced in L skin, was restored during guselkumab or secukinumab treatment (4) supporting their ability to self-renew (8). Alternately, LCs could originate from recruited monocytes in healing tissue (9). Noteworthy, the data from Figure S5 in Reynolds et al. suggesting that a cell state drastically reduced in L skin, was restored during guselkumab or secukinumab treatment (4) supporting their ability to self-renew (8). Alternately, LCs could originate from recruited monocytes in healing tissue (9). Noteworthy, the data from Figure S5 in Reynolds et al. suggesting that a cell state molecu

LONGITUDINAL STUDY OF TISSUE SAMPLES IN A HOMOGENOUS GROUP OF PATIENTS, AS OPPOSED TO SNAPSHOT ANALYSIS IN DIFFERENT COHORTS, helps to identify potential pathogenic and regulatory cells, as well as key targets of treatments. Indeed, following the same psoriasis lesion before and during treatment at different time points strongly suggests that the major Inf Mo-like cells were the target of therapeutic cytokine blockade, underscoring their key role in disease pathogenesis (4).

Finally, further studies on human monocyte cell fate in inflamed and non-inflamed tissue warrant consideration. A consensus in nomenclature that may help to distinguish monocytes in transition to macrophages versus tissue-resident macrophages, distinct from monocytes differentiating into dendritic cells, should encompass the nature and nurture, plasticity, function of these cells and not be simply based on gene expression. This would greatly facilitate advancement/dissemination of scientific knowledge by avoiding calling subsets by different names when reporting a subset with similar phenotypic, molecular and functional signature.

Overall, uncovering the cues for monocyte-derived cell plasticity toward MNP subsets endowed with regulatory, repair or anti-inflammatory functions that restore skin homeostasis might open avenues to develop novel therapeutic strategies for these two common inflammatory skin disorders.

AUTHOR CONTRIBUTIONS

MS and HM wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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**Conflict of Interest:** RB is an employee and shareholder of Innovaderm Research. JA and EJME are/were employees of Janssen Research & Development, a wholly owned subsidiary of Johnson & Johnson. JA and EJME may own stocks in Johnson & Johnson.

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