Loss of Methylation Modification Marks the Presence of Psoriasis

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The reversibility of epigenetic alterations makes them the attractive targets for therapeutic discovery; however, their potential remains untapped owing to a lack of mechanistic understanding, particularly for inflammatory skin disorders. Here, Li and colleagues begin to fill these gaps by identifying the loss of the DNA hydroxymethylation mark 5-hmC in psoriasis and presenting compelling evidence for its potential contribution to disease manifestations.


Epigenetic regulation affects all the areas of cellular physiology. Therefore, it is not surprising that epigenetic dysregulation is thought to be a key driver of disease (Cavalli and Heard, 2019). Given the reversibility of epigenetic modifications, numerous drugs that target epigenetic writers and erasers are at various stages of development (Shortt et al., 2017). However, while great progress has been made in understanding the biological impact of epigenetic contributions during development and carcinogenesis, less is known about how these changes drive inflammatory diseases. Li et al. (2020) explore these questions in linking a key histopathological feature of psoriasis, namely the expansion of the transit amplifying cells (TACs) observed in the epidermis of psoriatic skin, with altered epigenetics, specifically the changes associated with aberrant DNA methylation dynamics (Figure 1).

DNA methylation and the enzymes that are involved in its regulation play critical roles in the numerous aspects of development, including X-chromosome inactivation, genomic imprinting, and the repression of transposable elements. Furthermore, the dysregulation of DNA methylation is a feature of virtually all cancers (Greenberg and Bourc’his, 2019). DNA methylation is catalyzed by DNMT3A and DNMT3B, which establish and carry out de novo methylation, as well as DNMT1, which performs maintenance methylation. In contrast, TET methylcytosine dioxygenases (TET1, TET2, and TET3) carry out active demethylation by progressively oxidizing 5-methylcytosine to 5-hydroxymethylcytosine (5-hmC), 5-formylcytosine, and 5-carboxycytosine (Figure 1a) (Greenberg and Bourc’his, 2019). Methylation of CpG-rich islands in gene promoters is typically associated with repression. In contrast, methylation over gene bodies is associated with active transcription and may play a critical role in maintaining transcriptional fidelity (Greenberg and Bourc’his, 2019).

Here, by building upon their previous work examining DNA methylation in melanoma (Lian et al., 2012), Li et al. (2020) again identify a reduction of genomic 5-hmC in disease, in this case in psoriasis. Combining human patient sample data with the imiquimod-induced murine model of psoriasis (van der Fits et al., 2009), they propose that the combined reduction of 5-hmC and the TET enzymes results in aberrant transcriptional profiles that are marked by altered retinoid and Wnt/β-catenin signaling that changes keratinocyte stem cell (KSC) dynamics and promotes the conversion of KSCs to TACs. Importantly, the investigators demonstrate that enhancing TET functions through the delivery of ascorbic acid in vitro could reverse some of the psoriatic changes, suggesting that targeting this pathway may have therapeutic efficacy in psoriasis (Figure 1b). These observations support a recent study indicating that ascorbic acid derivatives may have therapeutic efficacy in the models of psoriasis (Kitahata et al., 2018).

In epidermis, DNA methylation has been similarly implicated in key roles during differentiation, aging, and cancer (Köhler and Rodríguez-Paredes, 2020). However, its role in psoriasis and other inflammatory skin disorders is poorly understood. A link between skin disease pathogenesis and DNA methylation is particularly intriguing in light of the expanding data that support DNA methylation signatures as the potential “epigenetic clocks” that are predictive of human aging, even more so than gene expression profiles (Horvath and Raj, 2018). How this may affect risks underlying psoriasis, and whether this may suggest etiological differences between early- and late-onset psoriasis remains to be determined.

New therapies have become available to clinicians for the treatment of psoriasis; however, these therapies involve many risks or side effects. A deeper understanding of epigenetic mechanisms from the keratinocyte and immune cell perspectives might lead to approaches that potentiate the existing treatments or offer safer alternatives. As demonstrated by Li et al.(), there are already numerous compounds that affect epigenetic functions both directly and indirectly (Shortt et al., 2017).
Specifically, the authors propose that ascorbic acid may serve as a potential therapeutic via its ability to promote TET function and reverse deleterious gene expression increases in genes such as NESTIN and FABP5 in vitro. Whether these effects can be recapitulated in vivo to improve psoriasis phenotypes, and how targeting this pathway would affect the immune component of psoriasis are important outstanding questions for future research. These are particularly relevant questions given previous data suggesting that ascorbic acid derivatives may be effective in a mouse model of psoriasis through their ability to repress inflammatory gene expression (Kitahata et al., 2018). It is unclear from this study whether or not inflammatory gene expression was tested in their models.

Some limitations of this work are that it is generally correlative. For example, while the authors observe genome-wide methylation changes in the psoriasis mouse model utilizing hMeDIP-seq (Li et al., 2020), it is unclear if these changes are the primary drivers of disease or secondary events. Furthermore, given the limitations of the imiquimod psoriasis model (Hawkes et al., 2017), future work should involve generating methylation datasets from human patients and additional models, and correlating alterations in the methylation of genome-wide transcriptional changes by RNA-seq. Finally, given the ability of ascorbic acid to enhance the activity of not only TET demethylases but also other Jumonji-C domain-containing histone demethylases (i.e., KDM5C, KDM6A, KDM6B, and so on), future work should rule out other potential off-target effects to define the specificity of any therapeutic benefit.

CONFLICT OF INTEREST
The authors state no conflict of interest.

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