Commentary

HMGB1: A molecular paradox linking skin injury, inflammation and repair

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High mobility group box 1 (HMGB1), a non-histone DNA-binding protein, behaves distinctly intra- and extra-cellularly. A recent article published in this issue elucidated the HMGB1 governing mechanism in the pathogenesis of cutaneous lupus erythematosus (CLE). This study reveals that UVB exposure to keratinocytes reduces SIRT1 expression, leading to HMGB1-acetylation and subsequent cytoplasmic translocation. This altered HMGB1 state impairs DNA repair, promotes inflammation and leads to exacerbation of lesions of CLE.[1]

HMGB1 normally resides in the nucleus (nHMGB1), facilitating DNA stability and repair. Stress relocates it to the cytoplasm (cHMGB1) and into the extracellular space (eHMGB1), either actively or passively. cHMGB1 induces autophagy and apoptosis, while eHMGB1 acts as an alarmin and regulates inflammation.[2] This functional and locational adaptability is determined by its post-translational modifications (acetylation, deacetylation, methylation, N-glycosylation and phosphorylation). Hyperactive skin disease signalling pathways, including IFN, TNF-alpha, JAK-STAT1 and SIRT1, can implicate such modifications, underlining HMGB1 relevance in dermatological conditions.[2]

Lupus patients with high circulating eHMGB1 levels are more likely to develop skin lesions and UVB exposure amplifies them.[1] However, its systemic levels in CLE patients are not well recorded. Most eHMGB1 comes from cell death. Skin cells, such as keratinocytes, melanocytes, fibroblasts, skin-resident immune and endothelial cells, express HMGB1. Patients with detached or blistering skin conditions are more likely to have high eHMGB1 levels because of injured epidermal cells. In SJS/TEN patients, eHMGB1 levels are higher than in MPE and DRESS patients which rise 7 days before mucocutaneous lesions and stay high during the active phase of the disease.[3] The high level of eHMBG1 may be implicated in differentiating severe from milder phenotypes.

High level of eHMGB1also correlates with psoriasis, acne vulgaris, atopic dermatitis and cutaneous vasculitis disease activity and severity, thus making it a valuable disease evaluating biomarker. Skin and infiltrating-immune cells inherently express HMGB1 sensing receptors such as RAGE, TLR2/3/4/5/7/9, CXCR4, TIM3, IL-1R1, NF-kB and Integrin/Mac1.[2] HMGB1 polarises RAGE-expressing CD8- and CD4-T-cells of psoriatic lesions to produce more IL-17, thereby elevating inflammation.[2] Similarly, in atopic dermatitis, high cHMGB1 reduces filaggrin and loricrin expression by activating NF-kB in keratinocytes. High cHMGB1 levels accelerate vitiligo owing to active SIRT3, Nrf2 and caspase-3 that destroy melanocytes.[2] However, its link to vitiligo disease activity is unclear.

In addition, HMGB1 also demonstrates an unprecedented role in skin disorders. In allergic contact dermatitis (ACD), it reduces IL24 levels (via epigenetically remodelling *IL24*-promotor) and protects since elevated IL24 worsens ACD.[4] Similarly, its high expression stimulates RAGE-expressing endothelial cells to release PGE2 which promotes hair growth and shaft elongation.[2] Furthermore, it also recruits PDGFR-MSCs to wounded sites, enhancing tissue regeneration. In RBEB patients, eHMGB1 levels are 60-fold higher compared to controls and linked to accelerated epithelial regeneration.[2] Given this, it appears that a very high serum concentration is preferable or beneficial as compared to a lower one (i.e. proinflammatory).

Overall, altering HMGB1 expression appears to improve disease outcomes. Drugs like metformin, eritoran, resveratrol and dexmedetomidine are clinically approved and can

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serve this purpose. Anti-HMGB1 mAb is demonstrating encouraging results in various disease mouse models.[5,6] Our comprehension of HMGB1 function, especially in skin diseases, is still evolving. Biologically, HMGB1 appears to uphold tissue homeostasis, either by promoting the clearance of damaged tissue or concurrently protecting surrounding healthy tissue by suppressing inflammation. This remains a topic of active research.

Abbreviations: ***IFN****: Interferon,* ***TNF-alpha****: Tumour necrosis factor-alpha,* ***JAK-STAT****: Janus-kinase/signal-transducers and activators of transcription,* ***SIRT****: Sirtuin,* ***SJS/TEN:*** *Stevens–Johnson syndrome/toxic epidermal necrolysis,* ***MPE****: Maculopapular skin eruptions,* ***DRESS****: Drug reaction with eosinophilia and systemic symptoms,* ***Nrf2****: Nuclear factor erythroid–related factor 2,* ***RAGE****: Receptor-for-advanced-glycation-endproducts,* ***TLR2/3/4/5/7/9****: Toll-like receptors,* ***CXCR-4****: C-X-C-motif-chemokine-receptor,* ***TIM3****: T cell immunoglobulin and mucin-domain containing-3,* ***IL-1R1****:* Interleukin 1 receptor type 1, **NF-kB**: Nuclear-factor-kappa-light-chain-enhancer of activated B-cells, **PGE2**: prostaglandin E2, **PDGFR-MSCs**: Platelet-derived growth factor receptor mesenchymal stem cells.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of Artificial Intelligence (AI)-Assisted Technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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