Discovering skin-rejuvenating matrikines: a new frontier in basic and applied dermatology

Linked Article: Jariwala *et al*. *Br J Dermatol* 2024; **191**:92–106.

https://doi.org/10.1093/bjd/ljae100

The functional homeostasis of living tissues relies upon the proper interactions between cells and their surrounding extracellular matrix (ECM). Crucially, the latter's components and specific architecture mediate the respective mechanical features of tissues and organs rich in type I collagen and elastic fibres, such as the dermis, lungs and large arteries.[1] Physiological and pathological remodelling generates – via the proteolysis of various ECM macromolecules – peptides named 'matrikines', which are endowed with either beneficial or harmful properties. These matrikines can function as growth factors or cytokines, modulating cell proliferation and/or migration, or inflammation and/or apoptosis.[2] Skin's accessibility and the profound age-related and/or pathology-induced (e.g. by ultraviolet radiation exposure) remodelling of its ECM combine to make it a model system ideal for basic and applied studies of the effects of matrikines.

In 2020, Shao *et al*. reported the ECM proteomes (or matrisomes) of multiple human and murine healthy tissues in a searchable database called 'MatrisomeDB'.[3] In their study, published in this issue of the *BJD*, Jariwala *et al*. took advantage of this database to try to identify potentially useful new matrikines via the integration of different methodological approaches into a pipeline.[4,5] Remarkably, the authors sequentially linked artificial intelligence-based *in silico* bioinformatic prediction of the proteolytic cleavage sites of major ECM proteins to the analysis of the effects of the identified potential tetrapeptide matrikines, assessed via the proteomic and transcriptomic activities of cultured human dermal fibroblasts, *in vivo* short-term skin patch testing and a longer-lasting split-face clinical study. This pipeline approach revealed that the combination of two newly identified peptides [i.e. GPKG (glycine–proline–lysine–glycine) and LSVD (leucine–serine–valine–aspartate)] rejuvenated photoaged skin as efficiently as gold-standard all-*trans* retinoic acid did.[4] Furthermore, the authors showed that the same matrikine duo evoked dissimilar responses in different skin types, implying the need to clarify the causes of the divergent skin reactions with a view to personalized precision medicine treatments.[4]

The authors also highlighted that tetrapeptides are a more suitable choice for topical treatments as they penetrate the skin's stratum corneum more easily than do longer peptides, the pathophysiological roles of which need further clarification. They also stressed that, besides studying the actions of mixed peptides formulations, the effects of single peptides should also be elucidated.[4] Moreover, the response to tetrapeptide matrikines of untransformed human keratinocytes, particularly those of the Malpighi proliferating layer, and of melanocytes, should be made clear to gain a fuller understanding of skin's pathophysiology, again with a view to precision medicine applications.

In summary, the integrated pipeline of Jariwala *et al*. fulfils all the requisites for proving that newly discovered tetrapeptide matrikines can be used for research, therapeutic and cosmeceutical purposes.[4] By showing that one can successfully predict and test novel matrikines, these groundbreaking results establish a new frontier for basic and applied dermatology, and the relevance of this exciting contribution overflows dermatology's borders, as the integrated pipeline approach will allow for analysis of the biologic and clinical effects of newly recognized matrikines in a wide spectrum of pathological conditions affecting other ECM-rich tissues and organs, such as heart, muscle, liver and brain.

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Funding sources: This commentary did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of interest: The authors declare no conflicts of interest.

Data availability: Not applicable.

Ethics statement: Not applicable.

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