Research Article

The Yin and Yang of extracellular matrix

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https://doi.org/10.1016/j.mbplus.2021.100075

At a first glance the titles of the articles in our special issue could appear to be deficient of matrix. This is however deliberate. For multicellular organism physiology, the extracellular matrix (ECM) is everything but without cells it is nothing. By the same token, cells are everything but without their microenvironment and ECM they are nothing. Human life, as all multicellular life, depends on a constant, intricate interplay between extracellular and cellular cues. In a way this special issue challenges the boundaries of matrix biology and we believe that in essence all biology can be considered matrix biology – at least when viewed in a relevant translational perspective.

These intricate molecular connections are in balance under normal conditions, and the loss of this equilibrium not only affects disease progression but it can also trigger disease onset as well as aging. This occurs when the tight regulation of ECM deposition is lost or upon impaired modulation of its remodeling due to aberrant activation of proteolytic enzymes.

Starting from the nucleus, Davide Vigetti and colleagues elegantly review how long non-coding RNAs regulate chromatin structure and consequently gene expression of hyaluronan synthases and the appearance of hyaluronan in the ECM [1]. As one of the most abundant ECM components both structural and instructive, hyaluronan is essential for mammalian tissue homeostasis.

Given the complex heterogeneous physical, mechanical, chemical and biological composition of the tissue microenvironment, there is still a scattered understanding of it. This together with the limitation of current methodologies leads to that in general only one or a few of these factors are accounted for in studies. As the microenvironment is the key determinant of cellular physiology and, on the opposite side, cells modify their microenvironment in response to it, careful consideration of substrates and culture configurations are needed to obtain results that withstand the scrutiny of time. Using the most accessible substrates no matter how advanced the models are, can be like study penguin migration on grass – it will generate beautiful images but its wider applicability would be hard to assess.

Jörn Dengjel and coworkers investigate the influence of 2D and 3D cell culture configurations on ECM protein synthesis and composition [2]. By using magnetic 3D bioprinting followed by proteomics, they shows that moving from 2D to 3D induces dramatic changes in the ECM protein production in both primary and transformed cells, resulting in a more tissue-like matrix. Thus, this interesting work points to the vital influence of the spatial organization and stimulation on cells to generate a physiological or pathophysiological applicable ECM. Importantly, this can be achieved in a native state without the use of potentially influencing scaffolds. Thus, 3D scaffold-free cultures should be considered for applications spanning from basic cell biological studies to organ-on-chip models to advance their physiological relevance.

Moving to the interphase of physiology and pathology. Gerhard Sengle, Claire Baldock and colleagues comprehensively review the important, but still yet understudied BMP antagonists and their roles during development and in disease [3]. Remaining at this interphase, one of our contribu-

tions places the spotlight on endothelial ECM protein Multimerin-2 in vessel stability [4]. We show that deposition of Multimerin-2 is phasic during blood vessel formation, with most deposition occurring during vessel maturation. Our investigation reveals that Multimerin-2 is an adhesion substrate for pericytes and furthermore it can regulate cytokine expression by both endothelial cells and pericytes. Thus, Multimerin-2 transmits and facilitates endothelial cell/pericytes crosstalk, a cellular interplay that participates in maintaining vascular stability.

Following the track of growth factor and cytokine regulation, Rui Hua and Jean Jiang elegantly discuss critical functions of the small leucine-rich proteoglycans in bone turnover [5]. They further review how changes in these proteoglycans during aging may impact the hydration status and subsequent bone quality.

To achieve tissue homeostasis regulated renewal of the ECM needs to occur. It is a tissue-dependent process regulated through multiple interconnected events. Deficiency in any of these events or their connections underlies pathologies covering chronic tissue fragility to fibrosis. In neuromuscular diseases, Enrique Brandan and colleagues review the actions of the matricellular protein known as connective tissue growth factor or cellular communication network 2 (CTGF/CNN2) [6]. As a driver of expression of ECM proteins, CCN2 may be a therapeutic target for disease modulation of muscular dystrophies and other neuromuscular diseases with fibrotic aspects.

One hallmark of many types of fibroses is excessive, deregulated deposition of fibrillar collagens. Procollagen C-proteinase enhancer-1 (PCPE1) is an abundant protein in many ECMs. It promotes C terminal processing of fibrillar collagens by enhancing the propensity of processing by BMP-1/Tolloid-like proteinases [6]. In a concise and much-needed review, one of the leaders in the field – Catherine Moali and colleagues discuss the utilization of PCPE1 as a biomarker of fibrosis and its applicability as a potential therapeutic target for various fibrotic indications [7].

BMP-1/tolloid-like proteinases are astacin-like proteinases and act as processors of many ECM proteins leading to more “mature” proteins. This process facilitates the assembly of more stable basement membranes and interstitial matrices. Meprins are also astacin-like proteinases that share some ECM maturing functions with the BMP-1/Tolloid-like proteinases; however they were only recently recognized for these functions. We addressed their roles in skin wound healing and disclose that meprin loss subtly influences wound healing speed, inflammation and the organization of the dermal ECM [8]. The study also provides evidence that meprins have the ability to convert pro-collagen VII to collagen VII, which is essential for the formation of a stable, mechano-resilient skin.

In conclusion, the Yin and Yang of the ECM is intricate and multifaceted, and the altered composition of the ECM and wider tissue microenvironment not only impact on disease onset and progression, but also grants the possibility to develop novel biomarkers and targeted therapies to improve the management of a wide spectrum of diseases. These are aspects that we have aimed to cover by the collected reviews and original research articles in this special issue. We hope that you will enjoy it!

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