**////Title: Understanding the Complexity of Epithelia**

**////Stand-first**:

Epithelial tissue is a protective layer of cells bound together into thin sheets that coat the internal and external surfaces of major body organs. The largest is the epidermis – the outer layer of the skin. This sheet-like structure is integral to its function and is maintained by a complex scaffolding network called the extracellular matrix (ECM). Dr Jacopo Di Russo and his colleagues at the Interdisciplinary Centre for Clinical Research of the University Hospital of Aachen, Germany, have recently discussed the diverse nature of the ECM and its hugely unmet potential within bioengineering.

**////Body text:**

Cells are small and flexible, but in multicellular organisms, they come together to form bigger, stronger structures called tissue. Epithelia are sheet-like or complex three-dimensional structures found throughout the body, where they line cavities and free surfaces, forming barriers that serve functions across protection, secretion, and sensory reception.

The epithelium, although mostly consisting of cells, relies on an important, non-cellular structural framework to define its crucial biochemical and mechanical properties. This framework is the ECM and it has many functions across tissue morphogenesis (shape formation), differentiation (function specialisation) and homeostasis (the maintenance of long-term stability).

Simply, a matrix is the material found between cells; it provides mechanical and biochemical support to cells in a tissue, and allows them to fulfil their purpose. Composed of biologically active molecules, understandingthe complexity of the ECM is vital for enabling the engineering of functional biomaterials.

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Biomaterials are at the fascinating interface of medicine and cutting-edge engineering. They are most recognised in common medical applications such as hip joint and heart valve replacements. Accurate ways to model and explain the biochemical complexity of the ECM are of key importance when producing successful interactive materials for these clinical and therapeutic purposes.

Dr Jacopo Di Russo at the Interdisciplinary Centre for Clinical Research of the University Hospital of Aachen, Germany, and his colleagues published a review article that brings together the current knowledge of the ECM, its diverse contents, and its importance in the field of bioengineering. They tell us that the two major forms of the ECM are the basement membrane and the interstitial matrix (IM). Each epithelium is anchored down by the basement membrane, which creates a physical boundary between the cells and the IM or connective tissue. Both ECM components contribute differently to the overall regulation of epithelial functions.

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Importantly, Dr Di Russo and the team point out that the basement membrane is composed of abundant proteins called laminins and collagen (type IV), which play central roles in epithelial functions throughout development and adulthood, such as during wound healing. The necessary cell adhesion required to heal is sustained by these protein components. But while collagen provides the basement membrane with its structural stability, the laminins are more active in orchestrating cell adhesion and interaction. These are not the only differences between these important protein players.

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Laminins are much more diverse due to the many possible protein variants which can be expressed depending on the specific tissue type and location. This protein variety makes the basement membrane the most complex, or heterogeneous matrix in the epithelia. Therefore, it is arguably the most important to study and understand.

Dr Di Russo explains that the basement membrane is thought to be flexible due to its sheet-like organisation, but that developing our knowledge of how physical forces on tissue contribute to cellular changes is currently limited by the experimental techniques available to study this. The available technologies need to be improved to allow the force measurement properties to be better characterised, aiding the design of biomaterials at the interface of synthetic and biological engineering.

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The other distinct layer of the ECM, the IM, is a network of loosely connected fibres containing collagens and elastin, which makes it more flexible. The mechanics of the IM have been more thoroughly characterised and therefore, are better understood. But this flexibility can vary depending on the relative amounts of elastin and collagen present, the type of tissue, and age.

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To engineer functional biomaterials capable of supporting epithelial tissue, it is crucial to understand how cells adhere to the ECM. Dr Di Russo explains that epithelial cells are tightly bound to their basement membrane by specific receptors – which act like a biological glue – to help regulate cell function. Genetic mutations which change the binding of these components can result in epithelial malfunction and loss of tissue integrity. This is seen in some cancers and diseases like epidermolysis bullosa, in which people suffer from blisters on their skin.

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It is important to acknowledge that cells are not always stationary. An example given by Dr Di Russo is that of leukocyte migration, which is when white blood cells move to a site of tissue damage or infection during an immune response. In this scenario, the force-bearing role of the network is less important than its ability to be flexible and allow movement and cell crossing. These differing roles within the ECM contribute to its complexity, but also is useful to scientists working to improve biomaterial design and production. For example, Dr Di Russo and his colleagues share that ECM-derived synthetic peptides can be used to help promote specific cell adhesion to engineered materials.

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Understanding the biochemical and the mechanical properties of epithelia are equally important but must be considered within the context of their specific ECM environments and stage of development. Dr Di Russo uses examples of work in the fruit fly, which has revealed that the ECM in the leg plays a role that is site-specific and centred around the regulation of tension to allow leg development and elongation. This involves a series of detachment, rupture and retraction events, and rearrangements like these lead to a redistribution of forces, which change the mechanical diversity of the whole epithelia – much like a row of dominoes, creating change down the line.

Dr Di Russo and his colleagues explain that this is similar to the case of carcinoma, a type of cancer that starts in cells that make up the skin or the tissue lining organs. During this cancer, mutated cells cooperate with each other and create a local stiffness in regions of tissue. This creates transferrable changes in the interactions with the ECM, and vice versa, with the ECM controlling local tissue mechanics.

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Understanding the complexity of the ECM; its proteins, mechanical forces, and pattern dynamics, and the fine balance that exists between these components in health, is fundamental to the development of functional biomaterials. Without this knowledge, and information on the changes to these structures during ageing and disease, biotechnologies such as those which repair and replace failing biological parts, simply will not work. Therefore, the work of scientists in the bioengineering and biotechnology fields is vital for furthering the development of such therapeutic avenues.

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This SciPod is a summary of the paper ‘Mechanobiology of Epithelia From the Perspective of Extracellular Matrix Heterogeneity’, from Frontiers in Bioengineering and Biotechnology. DOI: <https://doi.org/10.3389/fbioe.2020.596599>.

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