Symposium I:
S1-1
Customization of the Basement Membrane during Embryonic Development

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A hallmark of the extracellular matrix (ECM) is its diversity of molecular composition. Individual cell types have their own customized extracellular environment with a distinct molecular composition. Basement membrane is a thin sheet of ECM that underlies epithelial cells and surrounds muscle cells, blood vessels, and peripheral nerves. Basement membrane serves as a physical as well as functional interface of epithelial-mesenchymal interactions, thereby transducing signals in both directions (from the epithelium to the mesenchyme and vice versa) to orchestrate a complex series of organogenetic processes. To better understand the molecular entities of the customized extracellular environment, we set out to comprehensively localize >40 basement membrane proteins in mouse embryos at different embryonic stages [1]. We converted the immunohistochemical data to digital images and compiled them into a database in which individual images can be browsed on the web at desired magnification (http://www.matrixome.com/bm/). Our results are consistent with the concept that ECM composition is regulated developmentally and such customization of ECM composition plays an important role in organogenesis and cell fate determination.


S1-2
Laminin-511 plays a key role in dermal stem cell development and hair formation
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Hair formation requires communication and cooperation between the epithelial and dermal layers of the skin but how this occurs is not fully understood. Here we show that the basement membrane protein laminin-511, located at the interface of epithelial and dermal layers, orchestrates this communication. Initially we found that laminin-511 deficient mice completely lacked hair formation. However, introduction of purified laminin-511 into the skin of these mice dramatically triggered the restoration of fully formed hair. In studying the mechanism of this process, we found laminin-511 induced dramatic changes in the development of the collection of dermal stem cells known as the dermal papilla (DP). DP from laminin-511 null skin showed multiple defects during development, most notably a lack of expression of the key morphogen noggin. This led to a lack of sonic hedgehog (Shh) expression in laminin-511 deficient mouse skin. DP cells from laminin-511 null skin also showed defective formation of primary cilia, which are small microtubule based organelles involved in Shh signaling. We found that addition of exogenous purified laminin-511 restored primary cilia in laminin-511 null DP. We are currently trying to identify key hair morphogenic domains on the large laminin-511 molecule. While deletion of the heparan binding G45 domain on the ε3 chain appears to have no effect on laminin-511's hair promoting activity, the integrin binding G1-3 domain of laminin-511 was absolutely essential. Consistent with this, antibody inhibition or genetic deletion of ε3β1 integrin (laminin-511's receptor) both reduced DP primary cilia and inhibited hair formation. In summary, we have shown that laminin-511 is an early epithelial hair induction signal which binds to ε3β1 integrin on the dermal papilla, stimulates primary cilia development, and sets off a reciprocal noggin-Shh signaling loop between the follicular epithelium and the DP which ultimately leads to hair follicle elongation. Further studies are needed to pinpoint the minimal required sequences for laminin-511's hair promoting activities and to determine whether any forms of alopecia might respond to laminin-511.

References