Basement Membrane Zone

# Role of the Basement Membrane Zone in Skin Development

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doi:10.1038/sj.skinbio.6250016

Patterning of the skin during development requires precise reciprocol signaling between adjacent cells. Over the past two decades, several key studies have demonstrated a critical role for basement membrane zone (BMZ) components during epithelial pattern formation. In contrast to a static cellular glue, these papers provide a firm foundation for the notion that the BMZ actively shapes local cellular responses and tissue morphology.

A major component of the BMZ are the integrins, a family of cell-surface receptors that adhere cells to the BMZ and mediate mechanical and chemical signals from it. These signals regulate the activities of growth factor receptors and ion channels, and control remodeling of the intracellular actin cytoskeleton. An early indication of the importance of integrins was in the identification of integrin b4 in the development of junctional epidermolyisis bullosa (Vidal *et al.*, 1995). This suggested that skin integrity critically relied on these adhesion molecules. Later studies demonstrated that the key developmental role that integrins play came from mouse knockout experiments such as those that specifically removed integrin b1 in the skin (Brakebusch *et al.*, 2000). The abnormal BMZ and lack of hair follicle proliferation demonstrated the multiple roles integrin b1 plays during development. Additional studies with other individual integrins such as $a_6$ and $a_v$ have also reinforced the idea that integrins play an instructive role in tissue morphogenesis apart from adhesion, although the precise mechanism of action is still poorly understood.

The trimeric laminin family of proteins that acts as integrin coreceptors also play key roles in adhering cells to the BMZ as well as facilitating integrin signaling. Early reports of the role of laminin 5 (laminin 332) in junctional epidermolysis bullosa suggested it worked in a manner similar to integrin b4 in skin integrity and played an important role in epithelial development (Aberdam *et al.*, 1994). However, additional studies by other groups, including that of Miner and co-workers, suggested the existence of numerous laminin genes and laminin isoforms, and suggested that each may play a key role in the process. Subsequent functional studies have shown the diversity of functions for each of the isoforms during skin development, including laminin 10 (laminin 511) and laminin 1 (laminin 111), in hair follicle morphogenesis.

In addition to integrins and laminins, other components of the BMZ aid in regulating organ development by acting as growth factor co-receptors. For example, long after the morphogen fibroblast growth factor was identified, the key role for BMZ components as a fibroblast growth factor coreceptor was identified (Rapraeger *et al.*, 1991). In this landmark paper, heparin sulfate proteoglycan was shown to be an obligate molecule to allow fibroblast growth factor to bind and activate its cognate receptor. This suggested that the orientation of surface glycosaminoglycans could regulate the activity of a morphogen substance. Since this study, similar types of BMZ coreceptor activities have also been shown for other developmental morphogens that regulate muscle, hair and other appendage development, including Wnt and Sonic hedgehog (Shh) ligands.

Apart from signaling, BMZ components appear to shape the distance and distribution of key morphogens during epithelial development. In one of several landmark papers, The *et al.*, (1999) demonstrated that the product of the tout-velu gene in *Drosophila* controls the distance that hedgehog ligand can travel through cells of the tissue, but not the absolute activity of the ligand on its receptor. The tout-velu gene encodes a heparin sulfate polymerase whose function is to modify glycosaminoglycan moeties of heparin sulfate proteoglycans. Subsequent studies in flies and vertebrate cells have identified other genes that regulate the process of cell-surface glycosylation such as sister of tout-velu, brother of tout velu, dally and dally-like and implicate cellular glycosylation in morphogen movement across a cell. Moreover, the vertebrate homologs of these molecules were also shown to be encoded by the EXT family of tumor suppressor genes, implicating morphogen tissue distribution as a novel tumor mechanism.

## TO CITE THIS ARTICLE

Oro AE (2008) Role of the basement membrane zone in skin development. *J Invest Dermatol* 128: E11–E12

## REFERENCES

Aberdam D, Galliano MF, Vailly J, Pulkkinen L, Bonifas J, Christiano AM *et al.* (1994) Herlitz's junctional epidermolysis bullosa is linked to

mutations in the gene (LAMC2) for the gamma 2 subunit of nicein/kalinin (LAMININ-5). *Nat Genet* 6:299–304

Brakebusch C, Grose R, Quondamatteo F, Ramirez A, Jorcano JL, Pirro A *et al.* (2000) Skin and hair follicle integrity is crucially dependent on beta 1 integrin expression on keratinocytes. *EMBO J* 19:3990–4003

Rapraeger AC, Krufka A, Olwin BB (1991) Requirement of heparan sulfate for bFGF-mediated fibroblast growth and myoblast differentiation. *Science* 252:1705–8

The I, Bellaiche Y, Perrimon N (1999) Hedgehog movement is regulated through tout velu-dependent synthesis of a heparan sulfate proteoglycan. *Mol Cell* 4:633–9

Vidal F, Aberdam D, Miquel C, Christiano AM, Pulkkinen L, Uitto J *et al.* (1995) Integrin beta 4 mutations associated with junctional epidermolysis bullosa with pyloric atresia. *Nat Genet* 10: 229–34