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Matrix Biology Highlights

1). Modifying TGF-β: recessive dystrophic epidermolysis bullosa (RDEB) is modified by decorin

Reference | Odorisio, T., Di Salvio, M., Orecchia, A., Di Zenzo, G., Piccinni, E., Cianfarani, F., Travaglione A., Uva, P., Bellei, B., Conti, A., Zambruno, G., Castiglia, D., 2014. Monozygotic twins discordant for recessive dystrophic epidermolysis bullosa phenotype highlight the role of TGF-β signalling in modifying disease severity. *Hum. Mol. Genet.* 23(15):3907-3922. http://www.ncbi.nlm.nih.gov/pubmed/24599399

In a recently published manuscript by Odorisio *et al* in *Human Molecular Genetics,* a monozygotic (MZ) twin pair discordant for RDEB clinical manifestations (Fig. 1, *left panels)* was utilized to identify differences in the transcriptome of twin primary dermal fibroblasts. Since MZ twins are perfectly matched for most genetic (e.g. single nucleotide polymorphisms) and non-genetic traits, the identified differences can be directly linked to the observable phenotype. Intriguingly, dermal fibroblasts derived from the more affected twin express significantly higher levels of TGF-β and; correspondingly, elevated levels of TGF-β-inducible proinflammatory cytokines. Biologically, increased TGF-β signaling manifests as a profibrotic myofibroblast phenotype with increased expression of a-SMA, plasminogen activator inhibitor 1, collagen I release, and collagen lattice contraction. These functional phenotypes paralleled the underlying basal activation of TGF-β canonical (Smad2) and non-canonical (MAPKs) transduction pathways. Conversely, fibroblasts and skin from the less affected twin express significantly increased levels of TGF-β inhibitors, in particular the small leucine-rich proteoglycan decorin (Fig. 1, *right panels)*. Decorin sequesters TGF-β within the physical construct of the ECM, indirectly suppressing TGF-β activity by preventing interaction with TGF-β receptors. Next, the authors demonstrated that exogenously administered or over-expressing decorin core protein reduced contractility of fibroblasts from the more affected twin via reduction of phosphorylated Smad-2. Therefore, via the suppression of TGF-β signaling, decorin may influence the profibrotic and pro-inflammatory phenotype of fibroblasts from RDEB patients, thus mitigating disease clinical manifestations.

2). Cooperation of heparanase and *Ras* drives breast and skin tumorigenesis

Reference | Boyango, I., Barash, U., Naroditsky, I., Li, J.P., Hammond, E., Ilan, N., Vlodavsky, I., 2014. Heparanase cooperates with *Ras* to drive breast and skin tumorigenesis. *Cancer Res.* 74(16):4504-4514. http://www.ncbi.nlm.nih.gov/pubmed/24970482

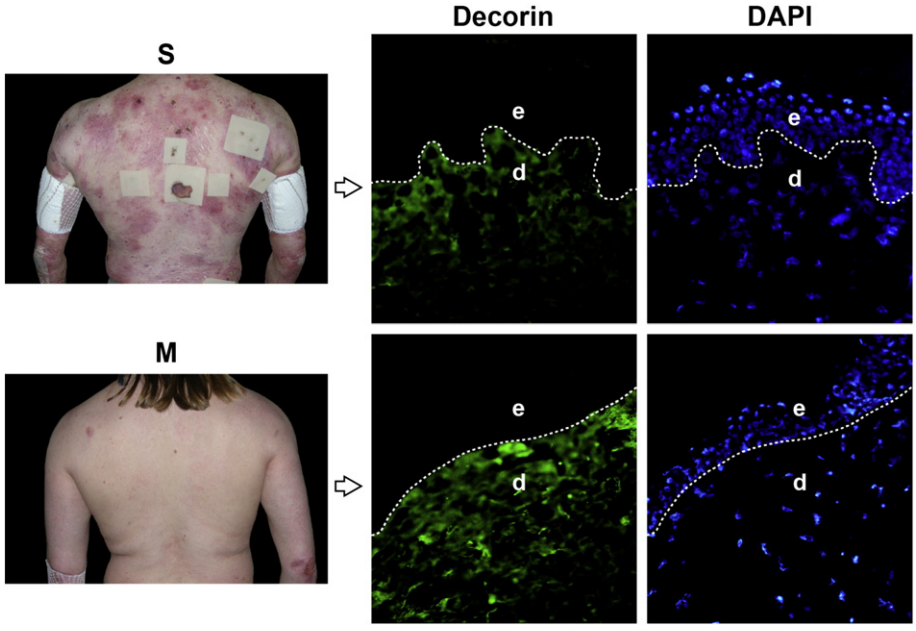

Fig. 1. Decorin is differentially expressed in the skin of a MZ twin pair discordant for the RDEB phenotype. *Left panels:* clinical features of the MZ twins with RDEB. The dorsum of both twins is shown. Twin with the more severe phenotype (S) shows diffuse blisters and erosions, while skin lesions are almost absent in the milder cotwin (M). *Right panels:* decorin immunostaining (green) on skin sections shows a substantial increase in expression within the dermis of the M twin when compared with the dermis of the S twin. Nuclei are stained with DAPI (blue). (e, epidermis; d, dermis). We thank Castiglia, D. for kindly providing the figure.

http://dx.doi.org/10.1016/j.matbio.2014.11.002

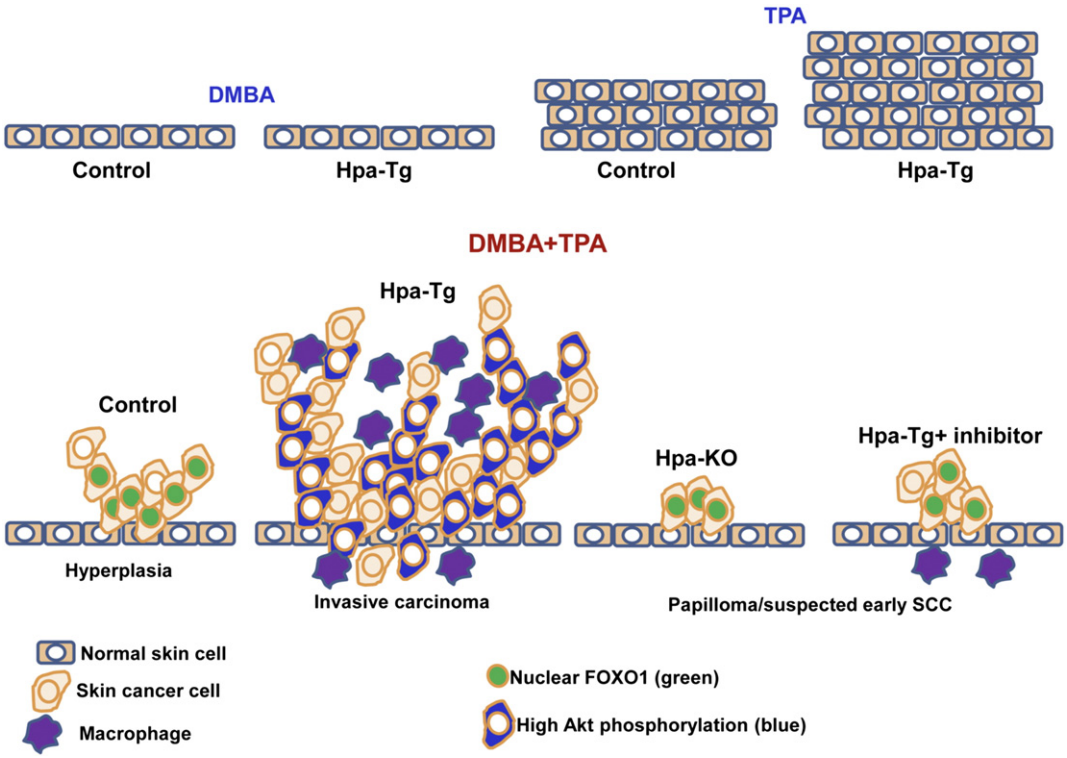

Fig. 2. A schematic representation that depicts the cooperativity occurring between heparanase and Ras in the early steps of breast and skin tumorigenesis and the following consequences of pharmacological inhibition. We thank Ilan, N. for kindly providing the figure.

A study by Boyango and colleagues, as published in *Cancer Research,* demonstrated the novel genetic cooperativity between heparanase and Ras that is responsible for driving the initial phases of breast and skin tumorigenesis. The authors employed two different mouse models, (Hpa-transgenic, *Hpa-Tg;* and knockout, *Hpa-KO),* for delineating the early pro-tumorigenic contributions and signals made by heparanase. Importantly, over-expression of heparanase resulted in expanded and disorganized acinar structures coincident with increased cell proliferation. Introducing aberrant *H-Ras* exacerbated these cellular phenotypes and culminating with increased invasive growth *in vivo.* Thus, taking advantage of a classical two-step chemical protocol for inducing skin tumorigenesis (vis-a-vis DMBA + TPA), the authors found the *Hpa-Tg* model significantly more sensitive to carcinogen induced tumor formation. Indeed, the *Hpa-Tg* mice experienced an increased in tumor burden

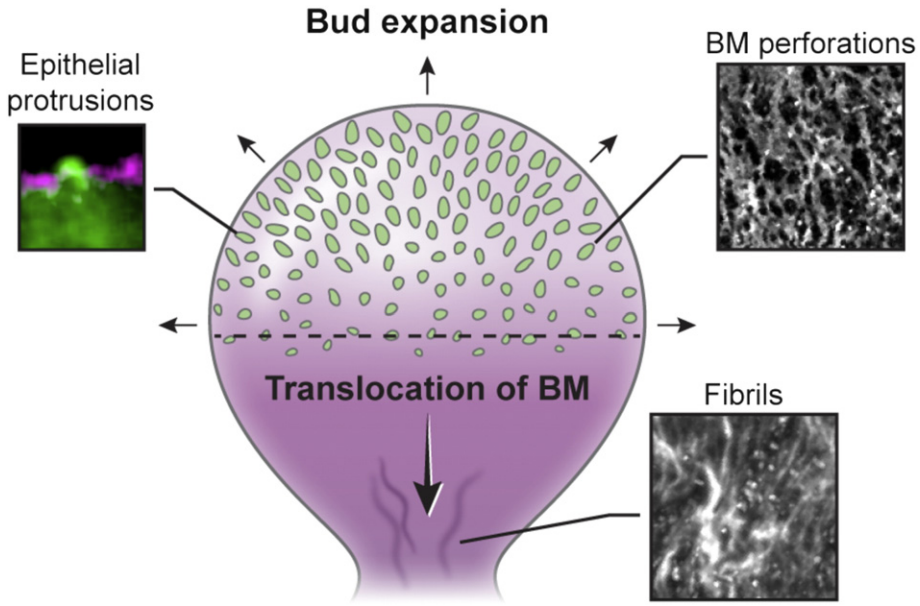

Fig. 3. Dynamics of the salivary gland basement membrane. The basement membrane (BM, depicted in magenta), surrounds expanding salivary gland epithelial end buds. At the expanding tip, the BM becomes perforated with numerous holes that decrease in size and number closer to the middle of the bud. These microperforations appear to be formed by a combination of proteases degrading the BM, epithelial cell protrusions extending through the BM (epithelial protrusions, depicted in green), and myosin II-mediated contraction of the BM. The presence of the micro-perforations increases the distensibility of the BM, allowing for outgrowth of the epithelium, as well as myosin II-mediated rearward translocation and accumulation of the BM around the duct. Figure kindly provided by Harunaga, J.S., and Yamada, K.M.