Título: IDENTIFICATION AND FUNCTIONAL CHARACTERIZATION OF MUTATION-INDEPENDENT DISEASE-SEVERITY MODULATORS IN RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA

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Resumen: Genodermatoses are rare inherited skin diseases, mostly monogenic, with a relevant social, economic, and clinical burden. Among them, epidermolysis bullosa (EB) comprises a group of skin fragility disorders, defined by blistering upon minimal trauma, with heterogeneous pathogenesis and clinical manifestations. Recessive dystrophic EB (RDEB) is the most severe form of the disease, caused by mutations in the COL7A1 gene that encodes the main component of the anchoring fibrils that attach the epithelium to the underneath dermal matrix. Patients with RDEB suffer from chronic mucocutaneous blisters driving perpetual cycles of inflammation and fibrosis that support metastatic cutaneous squamous cell carcinomas.
There is currently no cure for the disease, but several approaches are being developed in preclinical and clinical phases. Considering that RDEB involves cutaneous and extracutaneous manifestations it is presumed

necessary the combination of diverse therapies (e.g. cell, gene, and symptom-relief therapies) to improve clinical manifestations and even find a definitive cure. To this end, it is necessary to increase the understanding of the pathomechanisms underlying the primary defect in RDEB, aiming to find new disease modifiers with therapeutic potential.
We used RNA-Seq-based technologies to study altered signaling pathways and gene expression changes that could promote disease progression and carcinogenesis in RDEB and two other cancer-prone genodermatoses with premature aging and chronic inflammation as common hallmarks. Transcriptomic profile of dermal fibroblasts derived from patients with RDEB, Kindler EB (Kindler Syndrome, KS), and Xeroderma pigmentosum C (XPC) was analyzed. Inter-disease comparison pointed to a common activated and synthetic phenotype in all genodermatoses, independent of the primary causal deficient gene. This common signature shares some similarities with that found in myofibroblasts and cancer-associated fibroblasts, characterized by aberrant expression of extracellular matrix proteins, TGF-ß signaling, and oxidative stress. Additionally, the pipeline allowed us to describe and validate in patients¿ serum samples periostin as a novel biomarker in RDEB.
To further investigate modulating factors of the disparate disease course and severity in RDEB, we took advantage of an atypical clinical case of two siblings with equal COL7A1 genotype but discordant phenotypes. Transcriptomic and mechanistic analyses pointed towards oxidative stress, hyper-responsiveness to TGF-ß, and higher fibroblasts' contractile capacity as facilitating players of severe fibrotic features. Furthermore, we disclose a novel and natural TGF-ß inhibitor, PRELP, that could explain, at least in part, the observed differences in skin fragility and fibrosis. Finally, we tested the beneficial therapeutic effects of antioxidants and PRELP in in vitro models, observing a reduction of the pro-fibrotic and contractile phenotype characteristic of RDEB fibroblasts.
This doctoral thesis sheds light on mutation-independent mechanisms that affect severity and progression in RDEB, necessary info to develop reliable biomarkers, and effective symptom-relief or adjuvant therapies to improve patients¿ quality of life. These findings could also have significance for other diseases with similar pathomechanisms, both rare and common disorders (e.g. KS, XPC, fibrosis, and cancer).