GENETICS AND GENODERMATOSES

ROLE OF NECTIN-4 DURING SKIN DEVELOPMENT AND TRANSCRIPTIONAL REGULATION.

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Introduction: PVRL4 encodes nectin-4 a cell adhesion molecule relevant for adherens junctions formation. Mutations in PVRL4 cause ectodermal dysplasia with cutaneous syndactyly (EDSS) a syndrome with partial overlap with another ectodermal dysplasia featuring cleft lip/palate caused by mutations in PVRL1, hence the term nectinopathies. Patients with nectinopathies show a failure in hair cycling and renewal (alopecia) that may be correlated to keratinocyte stemness and proliferation defects. Interestingly, clinical overlap exists with patients harboring mutations in p63/IRF6, both involved in skin development. Nectin-4 expression is impaired in keratinocytes derived from p63 mutant keratinocytes and a regulatory feedback loop exists between p63 and IRF6.

Objective: In order to study the role of nectin-4 in skin development, epidermal homeostasis and hair cycling, we investigated possible alterations of stemness, proliferation, and differentiation using EDSS patient's keratinocytes. Furthermore, we studied a possible transcriptional regulation of nectin-4 by IRF6.

Materials and Methods: The clonogenic and prolilferative potential of patient's keratinocyte was evaluated by colony forming efficiency and lifespan assays as compared to age-matched control cells. Clonal characteristic of the cells was analyzed by immunoblotting and immunofluorescence assays using keratinocyte-specific proliferation, senescence and differentiation markers. Nectin-4 expression was analyzed in primary human keratinocytes (hKC) depleted of IRF6 in proliferative and differentiating condition.

Results: We observed a reduction of clonogenic and proliferative potential of primary keratinocytes from patients carrying mutations in PVRL4 gene. Moreover, in hKC depleted of IRF6 nectin-4 expression is reduced, particularly during differentiation.

Conclusions: Preliminary results suggest: i) withdrawal of the keratinocyte staminal compartment in the skin of EDSS patients, that could, at least in part, explain the hair loss

phenotype; ii) transcriptional regulation of nectin-4 by IRF6 in human keratinocytes.