Dissecting fibroblast heterogeneity in skin cancer

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ABSTRACT

When skin tumours develop from neoplastic epidermal stem cells e.g. through oncogenic epidermal β -catenin activation, these cells not only alter the morphology of the epidermis but also elicit profound changes in the dermal niche by reprogramming the gene signature of adult fibroblasts to a state recapitulating the expression pattern of neonatal dermal cells, and thus their properties. We and others have recently demonstrated that skin fibroblasts arise from two distinct lineages during embryonic development and have unique functions in skin homeostasis. Importantly, the two lineages also play distinct roles in regeneration and fibrotic skin pathologies, suggesting that they also have different functions in skin cancer development and progression. We show that fibroblasts from the two lineages respond to different signals derived from neoplastic cells, and remodel the dermis in a unique manner towards a tumour-prone microenvironment. Moreover, while one fibroblast lineage seems to be important early in cancer development, the other lineage prevails at later stages. Our studies highlight the scope of functional fibroblast heterogeneity in neoplastic skin lesions, and suggest that more focus should be placed on the roles of distinct fibroblast subpopulations in cancer progression, as they might have both tumour-promoting and –suppressing functions at different stages.

INTRODUCTION

Skin & hair follicle development depends on reciprocal mesenchymal-epithelial interactions

Two functionally distinct fibroblast lineages determine the architecture of the dermis

RESULTS

Do papillary & reticular fibroblasts play distinct roles in skin cancer progression?

Epidermal Wnt/β-catenin activation reprograms adult fibroblasts to a neonatal state, thereby inducing fibroblast proliferation and remodelling of the dermis

Epidermal Wnt sequentially induces Hh, TGFβ and FGF signalling in fibroblasts

Effects of pharmacological Hh & TGFβ inhibitors on fibroblast proliferation, ECM remodelling & adipogenesis *in vivo*

Pharmacological Hh and TGFβ inhibitors affect different fibroblast lineages

TGFβ2 controls proliferation & differentiation of the reticular fibroblast lineage

RESULTS

Smoothed deletion selectively in the papillary fibroblast lineage affects EF formation

Distinct fibroblast lineages may play unique roles at different stages of Wnt/β-catenin-mediated hair follicle tumour development

Differential expression of Hh and TGFβ target genes in distinct fibroblast subsets

Papillary and reticular fibroblasts may play unique roles at different stages of squamous cell carcinoma (SCC) development and progression

CONCLUSION

The dermis is comprised of two fibroblast lineages with distinct functions in skin development, homeostasis, regeneration & fibrosis. The dermal response to aberrant epidermal Wnt/β-catenin signalling depends on distinct fibroblast lineages responding to different paracrine signals in an inter-dependent manner. Distinct fibroblast lineages may play unique roles at different stages of skin cancer progression.

REFERENCES
Epidermal β -catenin activation remodels the dermis via paracrine signalling to distinct fibroblast lineages. Lichtenberger B.M., Mastrogiannaki M. and Watt F.M.; *Nat Commun.* 2016 Feb 3;7:10537. doi: 10.1038/ncomms10537.
 β -catenin activation in skin fibroblasts causes fibrotic lesions by preventing adipocyte differentiation of the reticular dermis. Mastrogiannaki M., Lichtenberger B.M., Salmer A., Collins C.A., Ornel R.R. and Watt F.M.; *J Invest Dermatol.* 2016 Feb 19; pii: S0022-202X(16)00489-9. doi: 10.1016/j.jid.2016.01.036.
Distinct fibroblast lineages determine dermal architecture during skin development and regeneration. Drakkel R.R., Lichtenberger B.M., Horta E., Kretschmar K.S., Simons S.D., Charalambous M., Ferron S.R., Herault V., Pavlovic O., Ferguson-Smith A.C. and Watt F.M.; *Nature* 2013 Dec 12;504(7479):277-81.

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