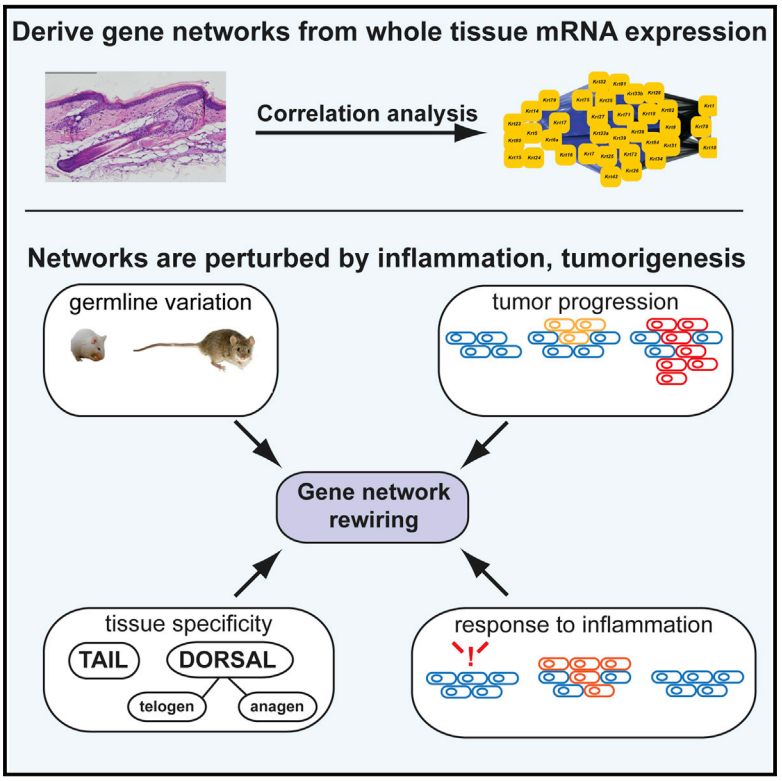
Cell Reports

Resource

Gene Expression Architecture of Mouse Dorsal and Tail Skin Reveals Functional Differences in Inflammation and Cancer

Graphical Abstract



Authors

David A. Quigley, Eve Kandyba, Phillips Huang, ..., Reyno Delrosario, Atul Kumar, Allan Balmain

Correspondence

abalmain@cc.ucsf.edu

In Brief

The demands placed on human skin vary by physical location on the body, producing location specificity in cellular composition, signaling pathways, and response to perturbation, including differential susceptibility to inflammation and disease. Quigley et al. show how skin gene networks respond to perturbation by genetic variation, inflammation, and tumorigenesis.

Highlights

- Gene expression networks reconstruct the cellular composition of a complex tissue
- Genetic influence on gene expression varies by tissue location in the skin
- Smoothened pathway activity is rewired between tail and dorsal skin
- Gene expression networks are rewired in premalignant tumors and again in carcinoma

Accession Numbers

GSE52650

Quigley et al., 2016, Cell Reports *16*, 1153–1165
July 26, 2016
http://dx.doi.org/10.1016/j.celrep.2016.06.061

CellPress

Cell Reports
Resource

Gene Expression Architecture of Mouse Dorsal and Tail Skin Reveals Functional Differences in Inflammation and Cancer

David A. Quigley,[1,2,3,4] Eve Kandyba,[1] Phillips Huang,[1,5] Kyle D. Halliwill,[1] Jonas Sjölund,[1,6] Facundo Pelorosso,[1,7] Christine E. Wong,[8] Gillian L. Hirst,[1] Di Wu,[1] Reyno Delrosario,[1] Atul Kumar,[1] and Allan Balmain[1,9,*]
[1]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA 94158, USA
[2]Department of Genetics, Institute for Cancer Research, Oslo University Hospital, The Norwegian Radium Hospital, Oslo 0310, Norway
[3]K.G. Jebsen Centre for Breast Cancer Research, Institute for Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo 0313, Norway
[4]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA 94158, USA
[5]Genome Institute of Singapore, 60 Biopolis Street, #02-01 Genome Building, Singapore 138672, Singapore
[6]Division of Translational Cancer Research, Department of Laboratory Medicine, Lund University, 22381 Lund, Sweden
[7]Instituto de Farmacología, Facultad de Medicina, Universidad de Buenos Aires, Paraguay 2155, 9th Floor, Ciudad Autónoma de Buenos Aires 1121, Argentina
[8]Institute of Surgical Pathology, University Hospital Zurich, 8091 Zurich, Switzerland
[9]Department of Biochemistry and Biophysics, University of California, San Francisco, San Francisco, CA 94158, USA
*Correspondence: abalmain@cc.ucsf.edu
http://dx.doi.org/10.1016/j.celrep.2016.06.061

SUMMARY

Inherited germline polymorphisms can cause gene expression levels in normal tissues to differ substantially between individuals. We present an analysis of the genetic architecture of normal adult skin from 470 genetically unique mice, demonstrating the effect of germline variants, skin tissue location, and perturbation by exogenous inflammation or tumorigenesis on gene signaling pathways. Gene networks related to specific cell types and signaling pathways, including sonic hedgehog (*Shh*), *Wnt*, *Lgr* family stem cell markers, and keratins, differed at these tissue sites, suggesting mechanisms for the differential susceptibility of dorsal and tail skin to development of skin diseases and tumorigenesis. The *Pten* tumor suppressor gene network is rewired in premalignant tumors compared to normal tissue, but this response to perturbation is lost during malignant progression. We present a software package for expression quantitative trait loci (eQTL) network analysis and demonstrate how network analysis of whole tissues provides insights into interactions between cell compartments and signaling molecules.

INTRODUCTION

The skin is the largest human organ, forming an essential barrier against environmental insults, including physical and chemical exposures. Skin is the tissue of origin of the commonest form of cancer in white populations (Diepgen and Mahler, 2002) as well as a host of other diseases ranging from relatively common inflammatory conditions, such as atopic dermatitis, to rare life-threatening conditions, such as the skin fragility syndrome epidermolysis bullosa. Studies both in mice and in humans have uncovered the underlying genetic basis of many skin diseases and have led to pioneering discoveries in tissue transplantation, regeneration, and stem cell biology (Blanpain and Fuchs, 2006). Keratinocytes, the most common cell type in skin, produce several closely related families of proteins with distinctive locations and functions (Fuchs, 1995; Schneider et al., 2009). Keratins were initially characterized as structural proteins that form the cytoskeletal architecture (Steinert et al., 1985), but they can also function in signaling pathways in skin in response to tissue perturbation (Arwert et al., 2012; Gu and Coulombe, 2007; Paramio and Jorcano, 2002).

Skin morphology, function, and tumor susceptibility vary in different parts of the body (Rinn et al., 2008). To withstand physical stress, the soles of human feet, mouse paws, and mouse tails have thicker and tougher epidermal layers than dorsal skin. Mouse dorsal skin, but not tail skin, is highly sensitized to squamous papilloma development induced by chemical initiators and promoters of carcinogenesis (Schweizer and Marks, 1977b). Exposing *Ptch1*$^{+/-}$ mice to ionizing radiation produces basal cell carcinomas (BCCs) in dorsal skin (Wang et al., 2011). In contrast, activation of the hedgehog pathway by oncogenic smoothened (*Smo*) driven by widely expressed *Krt14*-Cre results in development of BCCs preferentially in mouse tail skin (Youssef et al., 2012). Similarly, overexpression of *Gli2* using a *Krt5* promoter also led to development of BCCs in the tail skin (Grachtchouk et al., 2000). The underlying basis of these site-specific phenotypes is not presently understood.

In this study, we identify significant differences in the network architecture of signaling pathways between mouse dorsal and tail skin using gene expression quantitative trait loci (eQTL) and differential correlation analysis. We performed this analysis in a cohort of 470 genetically distinct animals produced by crossing FVB/N and *Mus spretus* mice, two highly divergent strains. We analyzed differential gene expression networks after stimulation of inflammation and epithelial proliferation using the tumor