Functions of epidermal growth factor in human keratinocytes

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Abstract

One of the challenges of OMICS research is the integration of new data into the preexisting, and then re-interpretation of the integrated data. We used readily available meta-analysis computational methods to integrate new data on the transcriptomic effects of EGF in primary human epidermal keratinocytes with the preexisting transcriptomics data in keratinocytes. We separately addressed the consequences of adding EGF to keratinocyte cultures and its reverse, blocking the EGFR kinase with Tyrphostin AG1478.

We first starved primary human epidermal keratinocytes for 24 hrs and next treated them with EGF. Then, we compared the genes expressed in the treated and control cultures in parallel, using Affymetrix microarrays. We find that the addition of EGF promotes keratinocyte proliferation, attachment and motility and, surprisingly, induces DUSPs, the phosphatases that attenuate the EGF signal. Using metaanalysis, we identified overlapping effects of EGF with those of IL-1 and IFNg, both activators of keratinocyte in wound healing and inflammation. We also identified and characterized the genes and pathways which are suppressed by EGF but are induced by agents promoting epidermal differentiation, such as Ephrins and JNK inhibitors.

EGFR activation is important in many malignancies, including cutaneous SCC, lung, colon and other cancers, and targeting the EGFR is currently used to treat such cancers. However, a significant drawback to EGFR targeted therapies is the skin toxicity side effect. This toxicity usually presents as hair and nails abnormalities, papular or pustular folliculitis and pruritic dry skin. These limit the usefulness of EGFR targeting therapies. Surprisingly, the transcriptional effects of EGFR inhibition have not been extensively explored in epidermal keratinocytes. Therefore, we treated primary human epidermal keratinocytes with Tyrphostin AG1478, a specific inhibitor of the EGFR kinase, and compared the treated and control cultures using Affymetrix microarrays. The observed changes were integrated with the preexisting data on transcriptional profiling in epidermal keratinocytes. We find that the inhibition of EGFR suppresses the transcription of genes linked to keratinocyte proliferation, attachment and motility. Interestingly, inhibiting EGFR promotes apoptosis by both induction of proapoptotic and suppression of antiapoptotic genes. Certain transcriptional effects of EGFR inhibition counter the transcriptional effects of retinoids. Surprisingly, EGFR inhibition strongly and specifically induces expression of markers of epidermal differentiation.

Overall, our work defines the yin-yang of EGF signaling in human epidermis, namely both the changes responding to activation of the EGF receptor, and its inhibition. Moreover, this work can serve as a paradigm for integration and analysis of new omics data with the large bodies of data in public repositories.

Biography

Miroslav Blumenberg is an Associate Professor in the R.O. Perelman Department of Dermatology and Department of Biochemistry and Molecular Pharmacology, NYU Langone Medical Center. He has completed his Ph.D. at the Massachusetts Institute of Technology and postdoctoral studies at Stanford University. He has published more than 100 papers in refereed journals, serves on editorial boards of BMC Genomics, Acta Dermatovenerologica APA and World Journal of Biological Chemistry and holds3 patents. Dr. Blumenberg pioneered the use of DNA microarrays in skin biology.