IL-36γ drives skin toxicity induced by EGFR/MEK inhibition and commensal Cutibacterium acnes

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 4517951
Author(s) Satoh, Takashi K.; Mellett, Mark; Meier-Schiesser, Barbara; Fenini, Gabriele; Otsuka, Atsushi; Beer, Hans-Dietmar; Rordorf, Tamara; Maul, Julia-Tatjana; Hafner, Jürg; Navarini, Alexander A.; Contassot, Emmanuel; French, Lars E.
Author(s) at UniBasel Navarini, Alexander ;
Year 2020
Title IL-36γ drives skin toxicity induced by EGFR/MEK inhibition and commensal Cutibacterium acnes
Journal JCI The Journal of Clinical Investigation
Volume 130
Number 3
Pages / **Article-Number** 1417-1430
Keywords Cytokines; Dermatology; Inflammation; Molecular biology; Skin
Epidermal growth factor receptor (EGFR) and MEK inhibitors (EGFR/MEKi) are beneficial for the treatment of solid cancers but are frequently associated with severe therapy-limiting acneiform skin toxicities. The underlying molecular mechanisms are poorly understood. Using gene expression profiling we identified IL-36γ and IL-8 as candidate drivers of EGFR/MEKi skin toxicity. We provide molecular and translational evidence that EGFR/MEKi in concert with the skin commensal bacterium Cutibacterium acnes act synergistically to induce IL-36γ in keratinocytes and subsequently IL-8, leading to cutaneous neutrophilia. IL-36γ expression was the combined result of C. acnes-induced NF-κB activation and EGFR/MEKi-mediated expression of the transcription factor Krüppel-like factor 4 (KLF4), due to the presence of both NF-κB- and KLF4-binding sites in the human IL-36γ gene promoter. EGFR/MEKi increased KLF4 expression by blockade of the EGFR-MEK-ERK pathway. These results provide an insight into understanding the pathological mechanism of the acneiform skin toxicities induced by EGFR/MEKi and identify IL-36γ and the transcription factor KLF4 as potential therapeutic targets.
Publisher American Society for Clinical Investigation
ISSN/ISBN 0021-9738 ; 1558-8238
edoc-URL https://edoc.unibas.ch/73165/
Full Text on edoc No;
Digital Object Identifier DOI 10.1172/JCI128678
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/31805013
Document type (ISI) Journal Article