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Novel acquisitions on the immunoprotective roles of the EGF receptor in the skin

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The EGF receptor (EGFR) and its ligands represent one of the most powerful and complex signaling networks in higher vertebrates. This system exerts an unusually wide spectrum of diverse bioregulatory functions. Numerous indications have been collected in the past decades, essentially based on mouse models, that emphasize its central role in the development and homeostasis of the skin. In particular, the multiple phenotypes of mouse models with distinct dysregulations of the EGFR pathway indicate clearly that this system exerts a major impact on keratinocyte proliferation and differentiation and, eventually, on the process of wound healing, hair follicle morphogenesis and malignant transformation [1]. Notably, despite a long history of robust investigation into the diverse biological outcomes deriving from its possible dysfunctions *in vivo* in the mouse, a novel and, at least in part, unprecedented compendium of the role of EGFR in human skin is now emerging from the widespread use of EGFR inhibitors in the therapy of EGFR-dependent tumors. Currently, a humanized anti-EGFR monoclonal antibody (cetuximab), a fully human monoclonal antibody (panitumumab) and two small-molecule EGFR tyrosine kinase inhibitors (gefitinib and erlotinib) are available for the treatment of four metastatic epithelial cancers: non-small-cell lung cancer, squamous cell carcinoma of the head and neck, colorectal cancer and pancreatic cancer [2]. In patients treated with these drugs, a common adverse effect is a cutaneous inflammatory rash, characterized by papular pustular or acneiform eruption, which can be severe enough to lead to treatment modification or cessation [3]. These skin lesions are frequently pruritic and mostly affect the face and the upper trunk, although they may affect areas such as the dorsal arms and lower legs, and respond to anti-inflammatory drugs. Data from a large number of clinical trials suggest that the presence and severity of this cutaneous toxic effect are the most important positive correlates and predictors of the efficacy of anti-EGFR therapy in terms of progression-free survival [2,3]. Nonetheless, there is a serious need for an improved understanding of this side

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effect to develop adequate staging systems and mechanistically driven therapies, and to ensure quality of life and consistent antineoplastic therapy [3].

Histopathologically, a moderate-to-severe inflammatory reaction dominated by neutrophils, which surround and then invade follicular infundibula, characterizes the eruption. In the epidermis, EGFR is strongly expressed in the basal layer of epidermal keratinocytes and in the outer root sheath of hair follicles. Accordingly, mice with an EGFR dominant negative mutation have curled wiskers and short hair that become progressively sparse. Their hair follicles eventually disappear, accompanied by a macrophage- and multi-nucleated giant cell-driven inflammatory reaction [1]. In addition, focal keratinocyte necrosis due to persistent EGFR inhibition can, *per se*, activate and sustain immune cell recruitment and activation and the consequent folliculitis. In human biopsy specimens taken from affected areas, the stratum corneum is thinner and more compact. Dry skin with diffuse fine scaling can be observed frequently after the onset of the papular pustular rash and, despite the sterile nature of these pustules, secondary bacterial infection with *Staphylococcus aureus* may supervene.

The establishment of a condition of facilitated keratinocyte growth arrest and apoptosis probably contributes to the skin-targeted toxicity of EGFR inhibitors, since it leads to a progressively defective epidermal barrier formation. However, a failure in the mechanisms involved in the regulation of inflammatory reactions of the skin also appears to be implicated. Indeed, a number of recently collected independent observations clearly indicate that EGFR signaling is actively involved in sustaining the innate immune responses of the skin and, on the other hand, in controling its inflammatory events [4,5]. An extensive, up-to-date comment on the crucial role of EGFR in the innate immune defense of the skin is offered by its major contributors in the review entitled ‘EGF receptor: role for innate immunity during wound healing in human skin’ in this issue of the journal. In their review, the authors analyze the crucial effects of EGFR signaling on the innate immune defense of the skin by identifying three major consecutive processes, which include an early recruitment of neutrophils into the wounded site, an increase in the expression levels of antimicrobial proteins by involved tissues and, finally, the re-establishment of the physical barrier. The initial bacterial clearance in the wound is guaranteed by the recruitment of neutrophils, which is essentially driven by keratinocyte release of the chemokine CXCL8/IL-8. Notably, not only are EGFR ligands themselves potent inducers of this chemokine in human keratinocytes, but they also synergize robustly with the leukocyte-derived cytokines TNF-α and IFN-γ in its expression [6]. EGFR activation also leads to up-regulated CXCL8 indirectly, via enhanced expression of the Toll-like receptors (TLRs) 5 and 9 in keratinocytes. Upon stimulation by microbial components, these TLRs sustain the synthesis and release of CXCL8 and a variety of antimicrobial peptides, including defensins and cathelicidins. These small cationic peptides exert a broad range of actions against microorganisms, including Gram-positive and -negative bacteria, fungi and viruses. Importantly, Sørensen *et al.* remark that a variety of antimicrobial peptides highly expressed in human skin during wound healing, which include E-defensin 3, the neutrophil gelatinase-associated lipocalin, secretory leukocyte protease inhibitor, psoriasin, elafin and calgranulins can be induced by ligand-mediated EGFR activation alone in epidermal keratinocytes, even in the absence of any microbial component. The special interplay between the mediators of the innate immunity and EGFR signaling is also witnessed by the observation that the cathelicidin LL-37, abundantly released by infiltrating neutrophils also during the early phase of wound healing, can itself induce EGFR transactivation through a metalloproteinase-dependent release of EGFR ligands [7]. Hence, a specific mediator of the innate immunity triggers the intervention of EGFR-driven regenerative processes and eventually accelerates homeostatic recovery through the improvement of keratinocyte migration and re-epithelialization of the wound, and the final re-establishment of the physical barrier against surrounding microbes.

Clinical evidence confirming the role of EGFR as a modulator of skin immune responses arises from the observations that EGFR inhibitors can exacerbate skin lesions in psoriatic patients [8] and, in general, they induce a rash that responds to anti-inflammatory treatments [3]. Very recently, two independent reports presented the cases of patients in which EGFR inhibitor-induced papulopustular eruptions can be provoked by UV exposure [5,9] or by a physical trauma, such as the excision of a skin biopsy [5]. This last effect is typically referred to as the Koebner phenomenon. In susceptible individuals, this phenomenon can be induced by a variety of physical triggers, including pressure, tape stripping, surgical incision and UV light, all of which are responsible for keratinocyte injury and, hence, the initiation of a local inflammatory response [10]. Again, the documentation of the Koebner phenomenon in EGFR inhibitor-induced rash strongly suggests that impairment of EGFR signaling leads to a derangement in the control of inflammatory functions of epidermal keratinocytes. Indeed, we demonstrated that EGFR activation is involved in the control of chemokine expression in human keratinocytes. We observed that EGFR activation potently downregulates the levels of TNF-α- or IFN-γ-induced expression of a cluster of chemokines, which are crucially implicated in the attraction of T lymphocytes, monocytes and neutrophils into the skin, including chemokine (C-X-C motif) ligand (CXCL10)/IL-10, chemokine (C-C motif) ligand (CCL5)/RANTES and CCL2/monocyte chemotactic protein (MCP)-1. By contrast, cultured keratinocytes display a massive upregulation in the levels of these chemokines when EGFR is effectively blocked [11]. The mechanism underlying the upregulation of these chemokines is a dramatic stabilization of their transcripts, which is also detectable when ERK activation alone is selectively blocked. Accordingly, in mouse models of irritant contact dermatitis and allergic contact dermatitis, EGFR or ERK inhibition leads to aggravation of the inflammatory response of the skin, with upregulated chemokine expression and massive skin infiltration by T cells and macrophages. These data strongly suggest that pharmacological abrogation of EGFR/ERK signaling pathway can worsen skin inflammation through the activation of keratinocytes. Of relevance, these mechanisms also operate in the control of skin inflammation in the mouse. Enhanced expression of a cluster of proinflammatory molecules, including T-cell-selective chemoattractants, was also observed in cervical carcinoma epithelial cells treated with small-molecule EGFR inhibitors [12]. More recently, the role of the EGFR signaling in the control of the immune response has been documented in human skin, with the evidence that it also regulates keratinocyte expression of the chemokine CCL27/cutaneous T-cell-attracting chemokine (CTACK) [13]. This chemokine plays a major role in maintaining T-cell-mediated antitumor immune responses in the skin. Precancerous skin tissues, as well as cutaneous carcinomas, show abnormally strong and persistent activation of EGFR. As a consequence, keratinocytes in these tissues lose the capacity to homeostatically express the chemokine CCL27/CTACK and, hence, to maintain proper T-cell-mediated antitumor immune responses. Upregulation of CCL27 expression can be obtained by administration of EGFR inhibitors. This is particularly evident in biopsies of the skin rash induced in patients treated with these drugs [13]. The potentiation of the inflammatory response due to EGFR blockade certainly contributes to induce this rash. However, on the other hand, it may represent an important mechanism for EGFR inhibitor-based epithelial cancer therapy that certainly deserves further investigation.

Clinical and experimental evidence now clearly indicates that EGFR signaling extends its influence to inflammatory and immune functions of the epidermis. In particular, this system enhances the molecular mechanisms underlying the innate protection of the skin against bacterial colonization during wound healing. By contrast, it opposes excessive proinflammatory activation of the epidermal keratinocytes. As a consequence, the inflammatory activation of the epidermis due to EGFR blockade could relevantly contribute to epithelial cancer therapy by boosting the adaptive anti-tumor immune response. These novel acquisitions emphasize the importance of this system in skin pathophysiology and, at the same time, underline the limited knowledge currently available on its complexity.

Biography

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