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Epidermal Growth Factor and Epidermal Growth Factor Receptor: The Yin and Yang in the Treatment of Cutaneous Wounds and Cancer

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Abbreviations and Acronyms

AKT = protein kinase B
ECM = extracellular matrix
EGF = epidermal growth factor
EGFR = epidermal growth factor receptor
EGFRi = epidermal growth factor receptor inhibitor
EMT = epithelial–mesenchymal transition
JaK1 = Janus kinase 1
PI3K = phosphoinositol-3 kinase
TKI = tyrosine kinase inhibitor

Significance: Epidermal growth factor (EGF) and EGF receptor (EGFR) play an essential role in wound healing through stimulating epidermal and dermal regeneration. The development of new therapies for enhancing wound healing has included the use of EGF. In addition, EGFR inhibitors (EGFRis) have become a therapeutic option for the treatment of cancer. Thus, therapies targeting EGF/EGFR are useful for the treatment of both cutaneous wounds and cancer.

Recent Advances: Identification of EGFR as a regulator of normal and pathological cell function has allowed for the development of EGFRis for the treatment of cancer and topical administration of EGF to enhance wound healing.

Critical Issues: The use of EGFRi has emerged as an option for metastatic cancers. These drugs induce dermatological toxicity, a papulopustular rash that is pruritic and painful; chronic use may negatively impact wound healing. Currently, there is no standard therapy to alleviate the side effects caused by EGFRi administration except to reduce or eliminate EGFRi usage. Therefore, side effects from these drugs should be taken into consideration on patients prone to develop chronic wounds and with cutaneous injuries.

Future Directions: There is a need for adjunctive treatment to eliminate dermatological toxicity from EGFRi use. The development of new downstream targets of EGFR may be a rational strategy to reduce potential cutaneous side effects and provide a better strategy for the treatment of cancer. Until then, the topical use of EGF could be used to ameliorate dermatological lesions caused by EGFRi.

SCOPE

Epidermal growth factor (EGF) participates in dermal wound healing through stimulation, proliferation, and migration of keratinocyte, endothelial cells, and fibroblast and facilitates dermal regeneration.[1] Early clinical trials showed that topical administration of EGF increased epithelialization and shortened healing time in skin grafts, venous ulcers, and diabetic foot ulcers,[2–5] but the lack of data demonstrating a significant benefit from its application along with data indicating that EGF plays an important role in cancer development[6] significantly hampered further therapeutic use. In addition, clinical studies demonstrating the validity of EGF receptor inhibitor (EGFRi) as an anticancer therapy[7] had made EGF therapy even less desirable. Of late, there has been a resurgence in the use of EGF

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for the treatment of acute and chronic wounds due to new findings indicating that EGF is not an initiating agent of cancer nor does it contribute to malignant transformation.[8] Also, the recent advancements in gel formulation have allowed for an increase in stability, bioactivity, and release of molecules to significantly improve the effectiveness of EGF to promote and enhance chronic wound healing.[9,10] Continued development of polymer therapeutics will allow for novel topical administration of EGF for the treatment of acute and chronic wounds.

TARGET ARTICLES

1. Wong SF, Lindgren A, Mummaneni M, Byun T, Vasko C, Arenos R, *et al.*: A prospective crossover pilot study to evaluate the use of a topical wound gel in patients with cutaneous toxicity caused by epidermal growth factor receptor inhibitors. J Support Oncol 2010; **8:** 202.

2. Peura M, Siltanen A, Saarinen I, Soots A, Bizik J, Vuola J, *et al.*: Paracrine factors from fibroblast aggregates in a fibrin-matrix carrier enhance keratinocyte viability and migration. J Biomed Mater Res A 2010; **95:** 658.

TRANSLATIONAL RELEVANCE

Efficient wound healing is dependent on growth factor and cytokine signals that promote keratinocyte dedifferentiation, and migration for re-epithelialization.[11] EGF is one of the key signaling molecules in stimulating epithelial cell motility, making it a required factor for re-epithelialization.[6] Further, EGF is a major stimulator of fibroblast migration and wound contraction.[9,12] Currently, there is significant increase in the use of EGFRi for the treatment of metastatic cancers resulting in a significant number of serious cutaneous side effects. Fully understanding the down stream signaling molecules of EGFR would allow for the development of more specific targets for the treatment of metastatic cancers without or limited cutaneous side effect or interference in wound healing.

CLINICAL RELEVANCE

It is estimated that nearly 6.5 million Americans are afflicted with chronic, nonhealing wounds. This number is rapidly growing due to an aging population and the increased prevalence of obesity and diabetes.[13] Also, the development of new anticancer drugs targeting the EGF receptor has led to the development of a number of adverse cutaneous side effects, which include acneiform eruptions, Paronychia, Xerosis, and Rhagades.[14] Currently, there is no standard of care for the treatment of these cutaneous adverse effects. Thus, there is a significant need to develop new approaches to effectively stimulate tissue repair and regeneration.

There are several options for the treatment of cutaneous wounds, which are grouped into three categories: dressings, topical gels, and engineered skin.[15] Strategies to enhance wound healing have been to incorporate growth factors into current treatments. Cytokines and growth factors play an essential role in modulating cell behavior during wound healing.[11] EGF in particular invokes three important biological actions in tissue repair, cytoprotection, mitogenesis, and migration. Thus, the use of EGF in topical treatments for wound healing has tremendous clinical significance for enhancing wound repair and can be used as an adjuvant for the treatment of cutaneous side effects from EGFRi usage.

EXPERIMENTAL MODELS OR MATERIAL: ADVANTAGES AND LIMITATIONS

Topical gels have been used as a method for delivery of compounds to the skin to enhance wound healing but have only produced moderate results. The development of hydrogel has helped to enhance the ability of topical gels to promote wound closure and improve skin regeneration. Hydrogels are typically a matrix-based gel that serves as a synthetic extracellular matrix (ECM) to fill in the wound and contributes to promoting stromal cell infiltration. The ability to bind to and then release biological materials enhances the ability of the gel to promote wound closure. The current diversity in polymers used to form the gel and the number of variable that can be introduced into the gel dilutes the ability to assess the individual properties necessary for proper wound healing.

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

Growth factors are essential for proper and efficient wound closure and tissue regeneration. The EGF family, in particular EGF and transforming growth factor-alpha (TGF-α), plays a key role in wound healing. EGF is essential for mediating the de-differentiation of keratinocytes to an epithelial linage and to reestablish the epithelial

barrier. EGF binds to the EGFR, a protein tyrosine kinase receptor, expressed on the majority of cells in the skin. Activation of EGFR leads to a number of biological responses, including migration, proliferation, cytoprotection, cellular differentiation, and apoptosis.[8,16] In wound healing EGFR plays an important role in re-epithelialization and dermal maturation.[17] Topical use of recombinant human EGF has been shown to increase re-epithelialization and enhance wound healing.[8] Recent findings have shown that EGFR is overexpressed in solid tumors and is involved in tumor growth and metastasis.[7,18] In addition, clinical studies have demonstrated that the use of EGFRi improved survival rates, making it a valid target for anticancer therapy.[19,20] There are five Federal Drug Administration–approved EGFRi drugs and their increased use has cause the development of a sever skin rash and the formation of pustules on the face, chest, and back of patients. Currently, there is no standardized or effective treatment for the rash and pustule outbreaks.[21] Thus, the development of therapies is necessary for the treatment of these cutaneous side effects.

Hydrogel therapy has become a common treatment for cutaneous wounds in part to their ease of use, physical properties, and ability to deliver bioactive molecules and cells.[22] Hydrogels can be derived from material such as collagen, fibrin, and hyaluronic acid and use of these polymers has become more common since they are components of the ECM. These hydrogels are typically nontoxic to the surrounding tissue and do not promote an immune response.[22] Also, the incorporation and release of biological agents can be easily modulated. Consequently, this has promoted the development of a variety of hydrogel dressing with limited evidence-based research on their efficacy to promote or enhance wound healing. Most studies are based on clinical observations with little understanding of the biological mechanism promoting wound healing. Thus, there is a need to provide scientific evidence to evaluate of the efficacy of hydogels formulations.

The target articles evaluate two different hydrogels for there ability to promote cutaneous wound healing. In the study by Wong *et al.*, the use of Regenecare Wound Gel, used for the local management of painful skin wounds, was evaluated for the treatment of cutaneous side effects from EGFRi use.[23] The gel is an alginate hydrogel composed of collagen, vitamin E, aloe vera, and 2% lidocane and was chosen for its potential use in the management of papulopustular rash, the most common side effect of EGFRi treatment. The results suggest the treatment provided some reduction in pruritus but did not completely alleviate all the symptoms. Even though the study does not provide a defined therapeutic intervention for the management of EGFRi-induced rash, it does demonstrate hydrogel use as a feasible adjunct treatment for cutaneous side effects from EGFRi therapy.[23] Second, the study found that the papulopustular rash spontaneous regressed with continued use of erlotinib, a tyrosine kinase inhibitor (TKI).[23] Erlotinib has been found to inhibit Ras signaling, a downstream signaling molecule of EGFR. This may suggest that targeting specific downstream signaling molecules may reduce or eliminate cutaneous side effects. EGFR signaling has been found to promote cytoprotection (phosphoinositol-3 kinase [PI3K]-AKT pathway) and epithelial–mesenchymal transition (EMT; Janus kinase 1 (Jak1)-signal transducers and activators of transcription 3 (STAT3) pathway). These pathways have been shown to be important in cancer development and metastasis and may be novel targets for the treatment of cancer with limited cutaneous side effects.

The study by Peura *et al.* analyzed the effects of Finectra on improving the ability of a fibrin sealant (Tisseel) to enhance wound healing.[24] Finectra is a conditioned media containing paracrine effectors released from fibroblasts spheroids undergoing nemosis (a process of programmed necrosis in human fibroblasts). The results from this study indicate (1) the ability to induce the secretion of native trophic factors from human fibroblasts, (2) Finectra activity is through activation of EGFR, and (3) a fibrin gel is able to provide a controlled release of incorporated Finectra.[24] This study demonstrates a novel strategy for the delivery of native trophic factor to a wound site to enhance wound healing. Taken together, these studies demonstrate the involvement of EGFR in the activation of keratinocytes, promotion of re-epithelialization, and maintenance of normal skin integraty. The topical administration of EGF may be a useful therapy in ameliorating EGFRi cutaneous side effects without interfering with the systemic antineoplastic effects.

INNOVATION

With the advent of growth factor inhibitors, their increasing use in the treatment of cancer has led to an increased incidence in the development of a number of serious skin reactions. In the article by Wong *et al.*,[23] they investigate the use of a topical wound gel to develop guidelines for the management of incurred skin reactions from continued use of EGFRi. Although the results of the study did not

fully demonstrate the use of Regenecare gel as a regiment for the treatment of EGFRi side effects, it does suggest the use of a topical gel as adjunctive therapy for the management of cutaneous side effects. Second, it found that erlotinib, a TKI, reduced the appearance of skin reactions compared with Cetuximab and Panitumumab (antibody to EGFR). This observation suggests that inhibition of specific downstream signal may be utilized for the treatment of cancer without the incidence of cutaneous side effects.

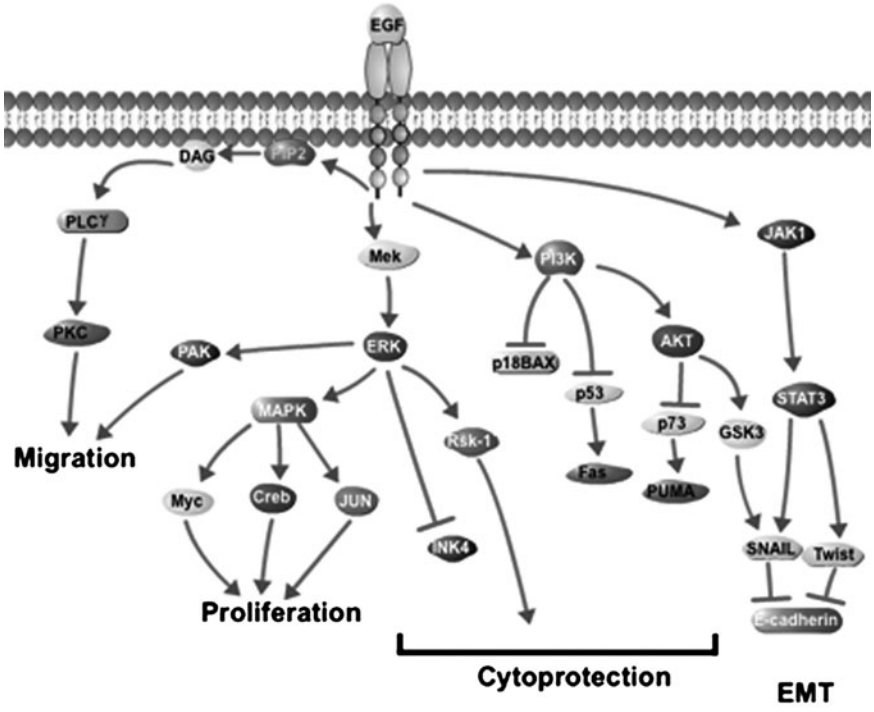
In the article by Peura *et al.*,[24] they developed an allogenic biodegradable topical gel composed of fibrin and Finectra (paracrine effectors from stimulated fibroblasts). The results from this study demonstrated that the fibrin-Finectra gel promoted a significant increase in the adherence, outgrowth, and viability of keratinocytes promoting enhanced re-epithelialization. Further, the study demonstrates that the EGF receptor was the major receptor being activated and a key regulator for enhanced wound healing. Taken together, the use of topical EGF has the potential to be utilized as an adjunct treatment for EGFRi skin toxicities and for the treatment of nonhealing wounds.

SUMMARY ILLUSTRATION

EGFR signaling plays an essential role in normal skin integraty and wound healing. Numerous studies have shown that wound healing is enhanced with topical treatment of EGF. On the other hand, inhibition of EGFR signaling is a potent adjuvant in the treatment of cancer. The included figure shows the signaling pathways activated by EGFR, which have been classified into four groups: migration, proliferation, cytoprotection, and EMT. The migration and proliferation pathways have been found to be necessary for normal wound healing.[16] In tumors, cancers cells have been observed to utilize the cytoprotection and EMT pathway for survival.[6,8] Thus, the development of inhibitors to downstream molecules of PI3K and JaK1 may be novel therapies for the treatment of cancer without inhibiting EGFR signaling necessary for proper wound healing. Targeting these pathways may reduce or eliminate the cutaneous side effects generated by drugs targeting the EGF receptor.

CAUTION, CRITICAL REMARKS, AND RECOMMENDATIONS

Topical gels and ointment have been utilized for the treatment of a variety of cutaneous rashes and to enhance wound healing. These gels are composed of a variety of compounds that have been identified to improve wound healing. In many clinical studies the gels have been found to only possess some therapeutic efficacy. The lack of evidence-based studies limits the ability to determine the true efficacy of these gels and the mechanisms responsible for promoting enhanced wound healing. Detailed studies on the physical and biological properties along with the mechanism used to deliver bioactive molecule and/or cells are



necessary to improve the ability of topical gels to be more effective in promoting and enhancing wound healing. The successful use of EGFRi for the treatment of metastatic cancers has lead to a significant increase in cutaneous side effects in patients. Currently, there is no standard treatment of treatment for these side effects and the current methods of treatment have little effect on reducing the papulopustular rash. The continued progression of the rash causes a reduction in EGFRi dosage or administration stoppage. Thus, there is even a greater need for the development of effective therapies for the management of these side effects.

FUTURE DEVELOPMENT OF INTEREST

EGF and EGFR signaling play an important role in wound healing and tissue regeneration and recently observed to play a critical role in oncogenesis and metastasis. EGFRi treatment of metastatic cancers has shown promising results, but has demonstrated significant cutaneous side effects that pose a limit to their long-term use. Considerable focus should be placed on understanding the EGFR signaling in cancer to develop more specific compounds to inhibit cancer progression without affecting EGFR signaling in normal cellular function. The promising results from EGFRi treatment of cancer prompts the need to further investigate downstream signaling molecules of EGFR in particular those associated with oncogenesis (PI3K and JaK1) and EMT (Jak1-STAT3 pathway) as new targets for treatment of metastatic cancers. Until more suitable inhibitors are developed, the use of topical gels containing EGFR ligands could be used as a plausible treatment for EGFRi side effects.

TAKE-HOME MESSAGE

Basic science advance

The extraction of growth factors (EGF and EGFR agonists) from activated fibroblasts provides a novel method for isolating native tropic factors and the development of an acellular active biological matrix by incorporating native paracrine factors into a fibrin gel. The observation that inhibition of tyrosine kinase activation demonstrated a decrease in cutaneous side effects suggests that targeting down stream signaling molecules of EGFR may have a lower incidence of side effects than current EGFRi.

Clinical science advance

The development of a natural biodegradable topical gel infused with cell extracted paracrine effectors, which improves wound closure and healing. The topical gel allows for the delivery of biological relevant stimuli directly to keratinocytes and fibroblast to enhance wound closure and re-epithelialization. This gel has the potential for the management of papulopustular rashes resulting from administration of growth factor-inhibiting drugs and the treatment of nonhealing chronic wounds.

Relevance to clinical care

A delay or disruption in wound healing due to a number of varying risk factors, the development of chronic wound, or wound eruption resulting from growth factor inhibiting drugs requires additional topical therapeutic intervention for the management of these pathologies. In these wounds, administration of additional growth factor enhances re-epithelialization and wound closure to improve wound healing. The paracrine-infused fibrin gel can be used as a safer topical agent for the management of a variety of skin wounds.

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REFERENCES

1. Wenczak BA, Lynch JB, and Nanney LB: Epidermal growth factor receptor distribution in burn wounds. Implications for growth factor-mediated repair. J Clin Invest 1992; **90:** 2392.
2. Brown GL, Nanney LB, Griffen J, Cramer AB, Yancey JM, Curtsinger LJ, 3rd, *et al.*: Enhancement of wound healing by topical treatment with epidermal growth factor. N Engl J Med 1989; **321:** 76.
3. Falanga V, Eaglstein WH, Bucalo B, Katz MH, Harris B, and Carson P: Topical use of human recombinant epidermal growth factor (h-EGF) in venous ulcers. J Dermatol Surg Oncol 1992; **18:** 604.
4. Choi JS, Leong KW, and Yoo HS: *In vivo* wound healing of diabetic ulcers using electrospun nanofibers immobilized with human epidermal growth factor (EGF). Biomaterials 2008; **29:** 587.
5. Tanaka A, Nagate T, and Matsuda H: Acceleration of wound healing by gelatin film dressings with

epidermal growth factor. J Vet Med Sci 2005; **67:** 909.

6. Hardwicke J, Schmaljohann D, Boyce D, and Thomas D: Epidermal growth factor therapy and wound healing—past, present and future perspectives. Surgeon 2008; **6:** 172.
7. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, *et al.*: Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004; **351:** 337.
8. Berlanga-Acosta J, Gavilondo-Cowley J, Lopez-Saura P, Gonzalez-Lopez T, Castro-Santana MD, Lopez-Mola E, *et al.*: Epidermal growth factor in clinical practice—a review of its biological actions, clinical indications and safety implications. Int Wound J 2009; **6:** 331.
9. Dogan S, Demirer S, Kepenekci I, Erkek B, Kiziltay A, Hasirci N, *et al.*: Epidermal growth factor-containing wound closure enhances wound healing in non-diabetic and diabetic rats. Int Wound J 2009; **6:** 107.
10. Kondo S and Kuroyanagi Y: Development of a wound dressing composed of hyaluronic acid and collagen sponge with epidermal growth factor. J Biomater Sci Polym Ed 2012; **23:** 629.
11. Werner S and Grose R: Regulation of wound healing by growth factors and cytokines. Physiol Rev 2003; **83:** 835.
12. Fernandez-Montequin JI, Valenzuela-Silva CM, Diaz OG, Savigne W, Sancho-Soutelo N, Rivero-Fernandez F, *et al.*: Intra-lesional injections of recombinant human epidermal growth factor promote granulation and healing in advanced diabetic foot ulcers: multicenter, randomised, placebo-controlled, double-blind study. Int Wound J 2009; **6:** 432.
13. Sen CK, Gordillo GM, Roy S, Kirsner R, Lambert L, Hunt TK, *et al.*: Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen 2009; **17:** 763.
14. Ehmann LM, Ruzicka T, and Wollenberg A: Cutaneous side-effects of EGFR inhibitors and their management. Skin Therapy Lett 2011; **16:** 1.
15. Fan K, Tang J, Escandon J, and Kirsner RS: State of the art in topical wound-healing products. Plast Reconstr Surg 2011; **127 (Suppl 1):** 44S.
16. Wells A: EGF receptor. Int J Biochem Cell Biol 1999; **31:** 637.
17. Tokumaru S, Higashiyama S, Endo T, Nakagawa T, Miyagawa JI, Yamamori K, *et al.*: Ectodomain shedding of epidermal growth factor receptor ligands is required for keratinocyte migration in cutaneous wound healing. J Cell Biol 2000; **151:** 209.
18. Vallbohmer D and Lenz HJ: Epidermal growth factor receptor as a target for chemotherapy. Clin Colorectal Cancer 2005; **5 (Suppl 1):** S19.
19. Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, *et al.*: Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009; **360:** 1408.
20. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, *et al.*: Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006; **354:** 567.
21. Lynch TJ, Jr., Kim ES, Eaby B, Garey J, West DP, and Lacouture ME: Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. Oncologist 2007; **12:** 610.
22. Drury JL and Mooney DJ: Hydrogels for tissue engineering: scaffold design variables and applications. Biomaterials 2003; **24:** 4337.
23. Wong SF, Lindgren A, Mummaneni M, Byun T, Vasko C, Arenos R, *et al.*: A prospective crossover pilot study to evaluate the use of a topical wound gel in patients with cutaneous toxicity caused by epidermal growth factor receptor inhibitors. J Support Oncol 2010; **8:** 202.
24. Peura M, Siltanen A, Saarinen I, Soots A, Bizik J, Vuola J, *et al.*: Paracrine factors from fibroblast aggregates in a fibrin-matrix carrier enhance keratinocyte viability and migration. J Biomed Mater Res A 2010; **95:** 658.