REVIEW

Advances in skin grafting and treatment of cutaneous wounds

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The ability of the skin to repair itself after injury is vital to human survival and is disrupted in a spectrum of disorders. The process of cutaneous wound healing is complex, requiring a coordinated response by immune cells, hematopoietic cells, and resident cells of the skin. We review the classic paradigms of wound healing and evaluate how recent discoveries have enriched our understanding of this process. We evaluate current and experimental approaches to treating cutaneous wounds, with an emphasis on cell-based therapies and skin transplantation.

Protection and renewal are among the major functions of epithelial tissues, the sheets of cells that line the surfaces and cavities of the body. The skin, as the body's external epithelium, sustains and repairs injuries throughout a lifetime. This vital role is affected by a wide variety of factors that influence skin wounding and the speed and quality of healing (Table 1). These factors include a number of common diseases and medications, underscoring the broad relevance of cutaneous wound healing to medicine, public health, and the global burden of disease (*1*).

Surgical incisions, thermal burns, and chronic ulcers are among the conditions in which wound healing plays a critical role. More than 70 million surgical procedures are performed in the United States every year (*2*), with more than one-third resulting in hypertrophic scarring or keloid formation. Burn injuries affect >11 million people worldwide annually (*3*). The time to burn wound closure is closely correlated with susceptibility to infection, pain duration, length of hospital stay, and incidence of scarring (*4*). In addition to acute wounds, there has been a steady rise in chronic skin wounds such as pressure ulcers and diabetic foot ulcers, which now affect more than 1% of all people during their lifetime (*5*). The prevalence of diabetes, obesity, and vascular disease in an aging population is fueling a surge in chronic skin wounds, which affect >6 million people in the United States alone at a cost of >$25 billion per year (*2*). Advances in understanding the molecular and cellular basis of cutaneous wound healing will be important for improved wound therapy and prevention.

Enduring paradigms of cutaneous wound healing

Cutaneous wound healing is classically divided into four overlapping stages: hemostasis, inflammation, proliferation, and remodeling. Each stage is characterized by key molecular, cellular, and physiologic events, which are orchestrated in large part by signaling among hematopoietic, immunologic, and resident skin cells. These stages have been reviewed in detail (*6*) and are summarized in Fig. 1.

Immediately after skin injury, multiple physiologic responses are triggered to stop blood loss. Local vascular smooth muscle cells constrict vessels to reduce blood flow. Platelets and coagulation cascade factors form a hemostatic fibrin clot, which serves as a scaffold for the migration of cells, including leukocytes, keratinocytes, and fibroblasts, into the wound (*7*). The inflammatory stage initiates within hours after injury and is fueled by platelet-derived mediators, bacterial by-products, and secreted chemoattractants. Neutrophils infiltrate the injury site first, killing bacteria and degrading damaged matrix proteins (*8*). Monocytes arrive within 24 hours and transform into macrophages to kill microbes, remove tissue debris, destroy remaining neutrophils, and pave the way for angiogenesis and tissue granulation (*9*).

Macrophages also assist in the transition to the proliferation stage, a process whereby newly produced cells fill the wound defect, by releasing a host of growth factors and chemokines including platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), vascular endothelial growth factor (VEGF), and transforming growth factor–α and –β (TGFα and TGFβ), which induce cell migration, cell proliferation, and matrix formation (*10*). Stem cell reservoirs in the hair follicle bulge, isthmus, and interfollicular epidermis release keratinocytes, which proliferate and migrate to achieve wound coverage, then undergo stratification and differentiation to rebuild the epidermal barrier (*11*, *12*). In concert with epidermal repair, angiogenesis begins, stimulated by multiple growth factors including VEGF and FGF-2. The admixture of newly formed blood vessels with fibroblasts, macrophages, and matrix proteins forms "granulation tissue," the soft, pink material that appears at the base of a healing wound. Toward the end of the proliferative stage, fibroblasts differentiate into actin-rich, contractile myofibroblasts (*13*), which pull together the wound edges.

The remodeling phase involves a transition of the dermis from type III to type I collagen predominance, in concert with removal of cells from earlier stages. Collagen remodeling involves matrix metalloproteinases (MMPs) and altered collagen synthesis to produce a scar (*14*). The tensile strength of wounded skin increases during this phase, regaining ~40% of its original strength at 1 month and ~70% by 1 year (*15*). Failure to initiate, terminate, or regulate any particular stage results in pathologic wound healing and manifests in cutaneous entities such as pyogenic granulomas (overgrowth of granulation tissue), hypertrophic scars and keloids (excessive fibrotic response), or chronic ulcers (prolonged inflammation and inability to re-epithelialize).

Evolving concepts in wound healing

Recent discoveries have expanded our understanding of how wound healing stages are regulated. Studies in zebrafish, *Xenopus*, and *Drosophila* reveal that the immediate aftermath of tissue injury results in a burst of damage response signals that are critical to activation of the repair process (*16*), including a hydrogen peroxide gradient that is formed within minutes after injury, which is essential for recruitment of immune cells to the wound (*17*–*19*). In *Drosophila*, the generation of hydrogen peroxide is dependent

Wound-specific variables	Systemic variables	Medications and exposures	Diseases and conditions
Body site	Nutrition	Cancer chemotherapeutic agents	Diabetes
Infection	Age	Nonsteroidal anti inflammatory agents	Autoimmune diseases
Vascular supply	Sex	Glucocorticoids	Venous stasis
Oxygenation	Psychological stress	Radiation therapy	Predisposition to keloids
Mechanical stress	Immobility	Smoking	Some genetic skin diseases
Desiccation		Alcohol and recreational drugs	Immunocompromised state (AIDS, cancer)
Edema			Obesity, vasculitis, neuropathy, some infectious diseases

Table 1. Factors that affect wound healing.

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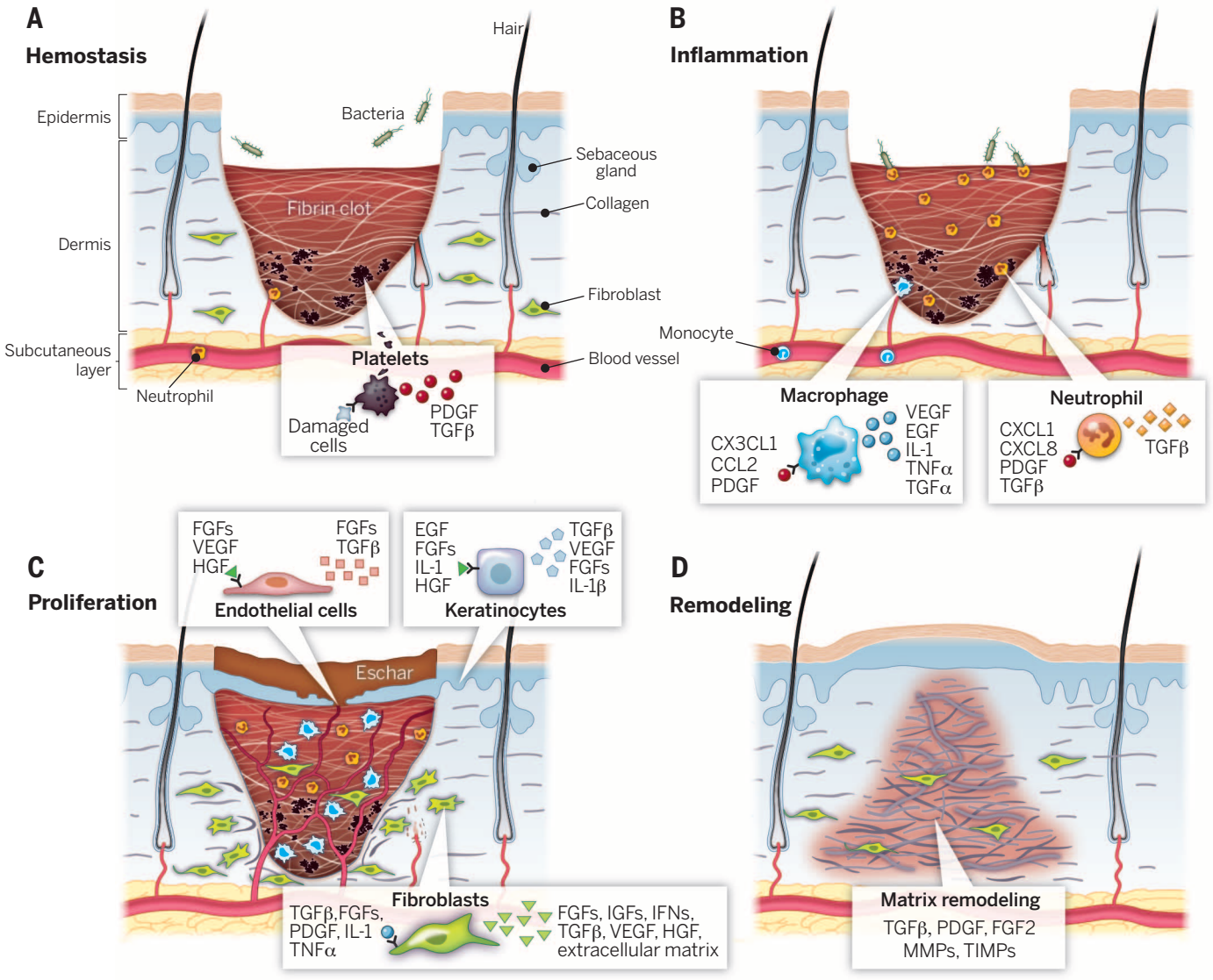

Fig. 1. Stages of wound healing. Wound healing is classically divided into four stages: (**A**) hemostasis, (**B**) inflammation, (**C**) proliferation, and (**D**) remodeling. Each stage is characterized by key molecular and cellular events and is coordinated by a host of secreted factors that are recognized and released by the cells of the wounding response. A representative subset of major factors are depicted. PDGF, platelet-derived growth factor; TGF, transforming growth factor; FGFs, fibroblast growth factors; IL-1, interleukin-1; TNF, tumor necrosis factor; KGF, keratinocyte growth factor; IGF, insulin-like growth factor; IFN, interferon; VEGF, vascular endothelial growth factor; HGF, hepatocyte growth factor; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase.

on a burst of calcium that is induced upon wounding (*18*). These findings establish calcium and hydrogen peroxide as the earliest known wound response signals.

The downstream effects of other early damage response signals have been described as well. In *Caenorhabditis elegans*, elevated epidermal calcium concentration produced upon injury fosters actin polymerization and wound contraction (*20*). In mice, apoptotic wound keratinocytes upregulate prostaglandins PGH_2 and PGE_2, which stimulate progenitor cell proliferation (*21*). Together, these discoveries illustrate the multifaceted response that occurs in the first minutes after injury. They also raise the possibility that immediate response signals may serve as future targets for therapeutic intervention in the acute wound.

The relationship between inflammation and scarring has also been an active focus in wound biology. Adult human dermal wounds result in scarring that increases with progressive injury depth. However, it has long been recognized that early-stage human fetuses undergo scarless skin healing (*22*). In addition, wounds of the oral mucosa also heal with much less scarring than cutaneous wounds. One notable difference is a markedly attenuated inflammatory response in fetal and oral mucosal wounds relative to adult skin wounds (*22*, *23*), which suggests that inflammation in adult cutaneous wounds may have evolved as a compromise to combat microbial infection at the expense of scarring. Consistent with this, PU.1-null mice deficient for neutrophils and macrophages heal without scarring (*24*). The relationship between inflammatory cells and scarring, however, is complex. Ablating macrophages at different stages of mouse wound healing demonstrated that macrophages promote scarring during early stages but subsequently promote vascular proliferation and transition to tissue remodeling (*25*), which indicates that inflammatory cells play roles that depend on spatial and temporal contexts (*26*). Understanding these context-specific roles will be essential to deciphering the molecular and cellular relationship between inflammation and healing.

Although studies of the inflammatory wound healing response have tended to focus on the role of neutrophils and macrophages, recent work has identified additional contributors, including γδ T lymphocytes. Human epidermal γδ T cells secrete

soluble factors that promote leukocyte recruitment and keratinocyte proliferation after injury (*27*). In mice, dermal γδ T lymphocytes induce hair follicle neogenesis through Fgf9 release and Wnt pathway induction after wounding (*28*). This discovery has potential implications in human skin regeneration, because adnexal structures such as hair follicles are lost upon healing from deep cutaneous wounds. γδ T lymphocytes are much less abundant in human than in mouse dermis, raising the possibility that human follicular regeneration could be induced by repletion of the proper signaling factors.

Therapeutic approaches to wound healing

Improved understanding of cutaneous healing has guided more sophisticated and targeted approaches to enhancing injury repair. As a foundation to treating all wounds, optimization of controllable healing factors (Table 1) remains a central principle. This can include nutritional support, smoking cessation, blood perfusion and fluid drainage, infection clearance, and mechanical protection. Simple techniques such as maintaining a clean but moist wound environment with occlusive dressings (*29*) help to accelerate re-epithelialization and alter the inflammatory milieu to favor better healing. Mechanical support at sites of high skin tension reduces the development of hypertrophic scars and keloids (*30*). Electric stimulation has proved beneficial by establishing electric fields that guide cells to migrate into the wound (*31*).

In addition to optimizing global and environmental variables, one targeted approach involves applying growth factors to the wound to promote healing. Experimental delivery of factors such as PDGF-BB, endothelial growth factor (EGF), FGF-2, and granulocyte-macrophage colony-stimulating factor (GM-CSF) has shown promise in animal models of wounding. However, clinical efficacy of single-factor therapy in humans has been more limited, with the exception of topical PDGF-BB (becaplermin), which is FDA-approved for treatment of diabetic ulcers and improves healing in clinical trials (*32*), and topical FGF-2, approved for use in China and Japan. One challenge is that these growth factors are administered onto a protease-rich, inflamed wound environment that makes them susceptible to rapid breakdown and clearance. This problem has been addressed by embedding growth factors within an extracellular matrix (ECM), where they can reside and act physiologically. A fibronectin domain–based ECM has been used to deliver PDGF-BB and VEGF-A to a mouse diabetic wound (*33*); the presence of the matrix potentiated the effects of both growth factors on the wound and promoted wound repair. Other approaches to improve delivery include liposomal transfection, particle-mediated transfer, and viral transfer (*34*). However, because wounds and cancer share a number of features (*35*, *36*), application of mitogenic growth factors to wounds may carry some risk. The FDA placed a cancer risk warning on becaplermin in 2008, highlighting a potential drawback of direct growth factor–based therapeutics in wound healing.

The challenge to develop successful wound healing therapies reinforces the complex nature of the process itself, which involves a dynamic interplay of cell types, growth factors, cytokines, and matrix components interacting in an environment in which pH, oxygenation, temperature, and moisture all contribute to the healing wound. This complexity makes the prospect of cell- and graft-based therapies an attractive alternative approach.

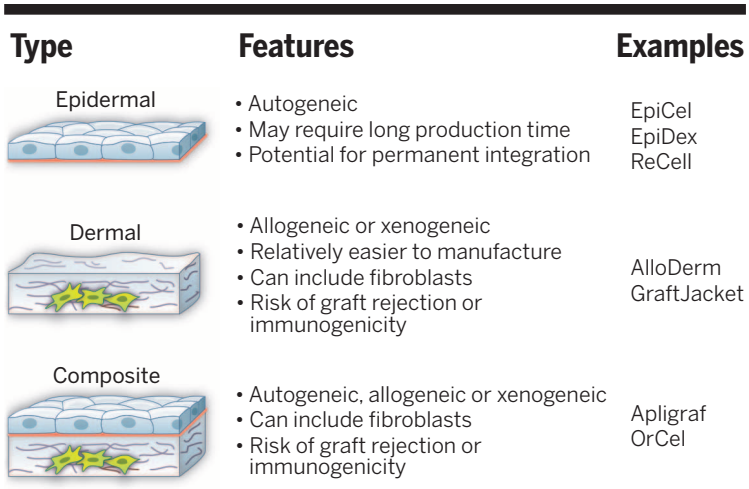

Fig. 2. Bioengineered skin substitutes. Available products can be classified into epidermal, dermal, or composite grafts. Individual products differ according to the source of the cellular material, method of delivery, and presence of supplementary substrates such as fibroblasts or matrix proteins. See table S1 for a comprehensive list of skin substitutes.

Skin grafting: A time-tested approach

The origin of skin grafting, in which skin tissue is removed from one site and transferred to another, is credited to Hindu surgeons circa 800 BCE who described methods of free skin grafts used to repair the nasal mutilations of individuals punished for theft or adultery (*37*). This practice saw a revival in European medicine during the 18th century, and the basic principles of grafting have carried into the modern era. Living skin grafts can be classified as split-thickness skin grafts (STSGs), consisting of the epidermis and part of the dermis, or full-thickness skin grafts (FTSGs), consisting of the epidermis and full-thickness dermis (*38*). STSGs can be meshed for expanded area coverage and are able to survive at graft sites with less vascularity. However, they suffer from contracture during healing. FTSGs require a better vascular bed for survival, but they contract less than STSGs and are preferred for exposed areas of the body, such as the face or neck.

A second classification of grafts is based on donor origin. Grafts from one site to another within the same individual are autografts; grafts where the donor and recipient are different individuals of the same species are allografts; and grafts from one species to another are xenografts. Autografts have capacity for full integration into the donor site, whereas allografts and xenografts undergo immunologic rejection with time and thus serve as temporary "biologic dressings." Despite this, several weeks of graft presence can be indispensable in the treatment of burns, ulcers, and difficult wounds, as these temporary biological dressings can limit infections, reduce substrate losses, and improve survival.

Innovations in surgical grafting techniques have advanced the art and science of skin grafting, but living grafts are still imperfect (*39*). Autologous grafts are inherently limited to the size of available donor sites and are insufficient for global burn injuries. Allografts and xenografts, while offering larger amounts of material, are only temporary. An ideal grafting solution would generate unlimited grafting tissue that is well tolerated by the patient, does not suffer from immune rejection, and provides all the therapeutic benefit and function of real skin.

Bioengineered skin equivalents: Are we closer to perfect skin substitutes?

The limitations of living skin grafts have prompted the development of transplantable bioengineered skin of many variations that are now approved for human clinical use (table S1). The ideal bioengineered skin substitute should be safe, have high clinical efficacy, be simple to produce, and be easy to handle and administer. These bioengineered equivalents can be classified into epidermal, dermal, or composite categories according to their structure and the degree of their functional resemblance to normal skin (Fig. 2).

Epidermal substitutes consist classically of a sheet of autologous keratinocytes, isolated from a donor and expanded in vitro. Generating epidermal sheets is time-consuming and costly, and the resulting products have a short shelf life (<24 hours). However, autologous epidermal grafts can be life-saving and have enjoyed numerous innovations at various stages of production, including improvements to cell culture techniques, differentiation techniques, and support/scaffolding assembly (*40*, *41*). Today, autologous epidermal grafts capable of covering the entire surface area of the body can be generated from a 3-cm^2 biopsy (*42*). In contrast, dermal substitute

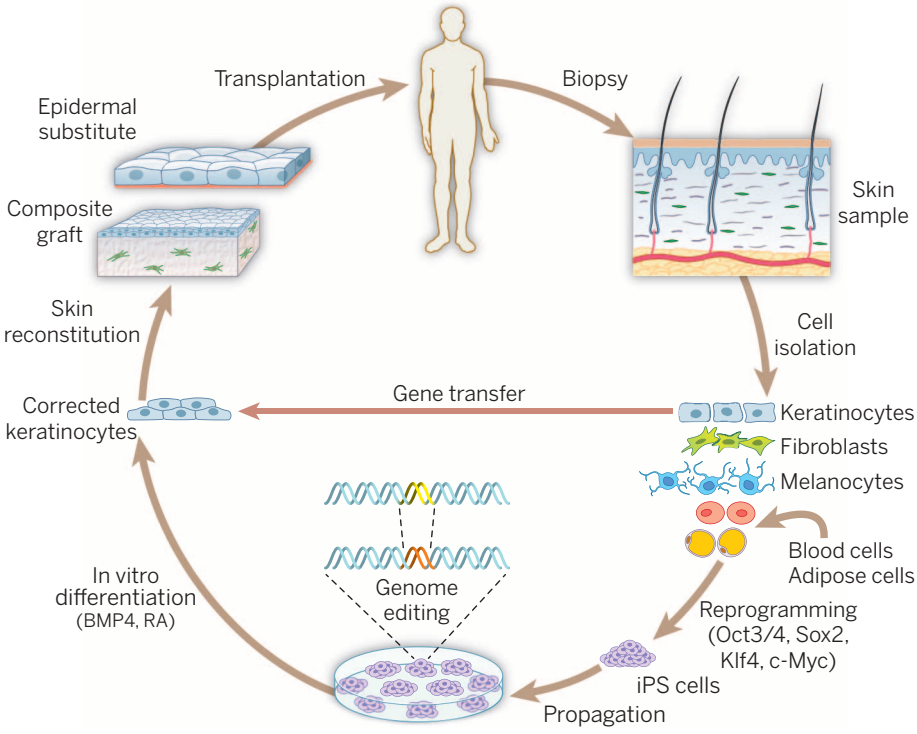

Fig. 3. Genetically engineered skin grafts. Advances in stem cell biology, genome editing capabilities, and grafting techniques have improved the efficacy and applicability of skin grafting in wound healing. Cells of different origins can be harvested from skin or other tissues and either directly altered by gene transfer or reprogrammed into induced pluripotent stem cells (iPS cells) to facilitate genomic editing on larger numbers of cells. The genetically engineered cells are reconstituted into skin tissue as epidermal or composite grafts, then transplanted onto the subject.

products are largely acellular and are prepared from allogeneic, xenogeneic, or synthetic material. Composite substitutes usually consist of allogeneic keratinocytes and fibroblasts, and have the benefit of providing growth factors, cytokines, extracellular matrix, and other elements along with a temporary wound cover. They are easier to manufacture than cell-containing substitutes and readily incorporate into wounds without rejection. However, they do not revascularize well; they have found a role in reconstructive surgery but not as dermal replacement material. Like living dermal composites, they ultimately undergo immune rejection in 3 to 4 weeks (*43*).

Cell-based skin therapies and genetically modified tissue transplantation

A wide variety of experimental approaches have been developed to incorporate stem cell–based therapies in cutaneous wound healing. Stem cells can be delivered in conjunction with skin composites or by various other methods, including direct application. For skin wounds, major efforts have focused on the use of epidermal progenitor cells, mesenchymal stroma/stem cells (MSCs), adipose tissue–derived stem cells (ASCs), and induced pluripotent stem cells (iPS cells).

The robust capacity of epidermal progenitor cells has created new opportunities to improve the performance of autologous epidermal grafts by means of genetically modified keratinocytes expressing factors that promote healing (Fig. 3). This concept closely parallels ongoing efforts using engineered grafts to treat genetic skin disorders such as epidermolysis bullosa (EB), a family of blistering disorders characterized by genetic mutations affecting epidermal-dermal adhesion, which affects 400,000 to 500,000 people worldwide (*44*). Successful skin transplantation of genetically engineered autologous keratinocyte grafts has been achieved in a patient with laminin 332–deficient non–Herlitz junctional EB (*45*). Autologous epidermal keratinocytes were transduced ex vivo with a retrovirus expressing normal laminin cDNA, and cultured epidermal grafts transplanted onto the patient's legs. More than 6 years later, the transgenic epidermis persists, is fully functional, and is virtually indistinguishable from normal epidermis (*46*). For recessive dystrophic epidermolysis bullosa (RDEB), caused by mutations in type VII collagen, a phase I clinical trial is under way using autologous epidermal sheets with wild-type collagen VII delivered by retroviral infection (*47*).

In addition to epidermal progenitors, stem cells including MSCs and ASCs have shown promise in promoting wound healing both by direct transfer onto wounds and by delivery embedded in scaffolds (*48*, *49*). Early studies indicate that both MSCs and ASCs secrete factors that attenuate inflammation, stimulate angiogenesis, and lead to faster wound closure. Both cell types have the potential for harvesting from autologous sites, and ASCs are relatively abundant and easy to obtain. Although clinical translation of MSC- or ASC-based wound therapy is still in the early stages, the potential use of these cells holds great promise.

Finally, advances in iPS cell technology allow patient- and disease-specific stem cells to be used for research and development of therapeutics, including transplantation medicine. iPS cells have been successfully derived from multiple epidermal cell types, including the fibroblasts of a patient with dyskeratosis congenita (*50*), as well as fibroblasts and keratinocytes from individuals with RDEB (*51*). Similar to human embryonic stem cells (hESCs), iPS cells can be reprogrammed to keratinocytes (*52*). Moreover, unlike somatic cells, they have a high proliferation potential, allowing genetic manipulations to be conducted. New therapeutic approaches are emerging that include (i) generation of iPS cells from different sources, including epidermal keratinocytes, fibroblasts, and melanocytes; (ii) insertion of desirable genes or correction of deleterious mutations based on homologous recombination or current genome editing tools such as the CRISPR-Cas9 system; (iii) differentiation of altered iPS cells into desired cell types, including keratinocytes; and (iv) generation of functional skin equivalents using iPS-derived keratinocytes and bioengineered dermal substitutes. A goal of regenerative medicine is to replace or regenerate whole body organs. For skin grafting, this would mean the restoration of all functional components, including hair follicles, sweat glands, and nerves. Although there is no perfect skin substitute currently available, rapid developments in understanding skin development and wound repair, together with advances in stem cell and tissue bioengineering, provide hope that such a product represents a tractable goal in the future.

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SUPPLEMENTARY MATERIALS

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Table S1

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REVIEW

The melanoma revolution: From UV carcinogenesis to a new era in therapeutics

Jennifer A. Lo and David E. Fisher*

Melanoma, the deadliest form of skin cancer, is an aggressive disease that is rising in incidence. Although melanoma is a historically treatment-resistant malignancy, in recent years unprecedented breakthroughs in targeted therapies and immunotherapies have revolutionized the standard of care for patients with advanced disease. Here, we provide an overview of recent developments in our understanding of melanoma risk factors, genomics, and molecular pathogenesis and how these insights have driven advances in melanoma treatment. In addition, we review benefits and limitations of current therapies and look ahead to continued progress in melanoma prevention and therapy. Remarkable achievements in the field have already produced a paradigm shift in melanoma treatment: Metastatic melanoma, once considered incurable, can now be treated with potentially curative rather than palliative intent.

Melanoma is among the most aggressive and treatment-resistant human cancers. In 2014, an estimated 76,100 new cases and 9710 deaths are expected in the United States, with melanoma accounting for 75% of all skin cancer deaths (*1*). Although these stark numbers highlight the need for improved prevention strategies and treatments, the explosion of discovery and concrete clinical advances in the melanoma field have brought great optimism in recent years. From identification of cancer genes to successes of new drugs in clinical trials, progress in understanding melanoma is now leading the way for other malignancies.

Cells of origin: Melanocytes

Melanomas arise from malignant transformation of melanocytes, the melanin-producing cells of the skin, eye, mucosal epithelia, and meninges that are responsible for pigmentation and photoprotection. Several common subtypes of melanoma are shown in Fig. 1. Melanocytes are derived from neural crest progenitors, and their development is modulated by the receptor tyrosine kinase (RTK) c-KIT and microphthalmia-associated transcription factor (MITF) (*2*).

Melanocytes produce two main types of pigment: brown/black eumelanin and red pheomelanin. Eumelanin is the photoprotective pigment that provides ultraviolet radiation (UVR) attenuation. Pigment synthesis is stimulated by binding of α-melanocyte–stimulating hormone (α-MSH) to melanocortin 1 receptor (MC1R) on melanocytes (Fig. 2). MC1R activates cyclic adenosine monophosphate (cAMP) production and cAMP response element–binding protein (CREB)–mediated transcriptional activation of MITF. MITF in turn promotes transcription of pigment synthesis genes and melanin production. MC1R is a major determinant of pigmentation, and loss-of-function polymorphisms result in impaired eumelanin production, with the most severe loss-of-function alleles producing red hair and fair skin (*2*). In addition to basal pigmentation, acquired pigmentation can be elicited by stimuli such as UVR (Fig. 4) (*3*).

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Melanoma risk factors

The strongest melanoma risk factors are family history, multiple moles, fair skin, immunosuppression, and UVR. Epidemiologic studies have implicated intense intermittent UVR exposure and severe sunburns during childhood in conferring the highest risk (*4*). Indoor artificial tanning devices that deliver UVR to the skin have also been linked to dose-dependent melanoma risk (*5*). UVR has multiple effects on the skin, including genetic changes, induction of reactive oxygen species (ROS), alterations in cutaneous immune function, and production of growth factors [reviewed in (*6*)]. Recent mouse model studies have shown that UVR induces inflammatory responses involving macrophages and neutrophils that can promote melanocytic cell survival, immunoevasion, and perivascular invasion (*7*, *8*).

The red hair/fair skin phenotype, characterized by fair skin, freckling, and inability to tan, is associated with the highest melanoma risk of all pigmentation phototypes (*9*), an observation traditionally attributed to reduced UVR protection. However, a recent study demonstrated that pheomelanin synthesis contributes to melanomagenesis through a UVR-independent mechanism thought to involve elevated ROS (*10*). Thus, high melanoma susceptibility in red hair/fair skin individuals is likely attributable to intrinsic carcinogenic effects of pheomelanin synthesis as well as UVR.

The mutational landscape of melanoma

Over the past two decades, there have been revolutionary changes in the methodologies used

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