CME

Hypertrophic Response and Keloid Diathesis: Two Very Different Forms of Scar

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Learning Objectives: After studying this article, the participant should be able to: 1. Have a greater appreciation of the extent of differences and similarities between keloid and hypertrophic scarring. 2. Have a greater appreciation of the significance of the stage of maturation of a keloid or hypertrophic scar with regard to its morphologic, biochemical, and molecular profile. 3. More critically review basic science research that is based on poorly characterized scar tissue. 4. More critically review clinical studies that are based on poorly characterized scar tissue.

Background: Hypertrophic and keloid scars remain extremely challenging, particularly in their variable response to treatment. The understanding of hypertrophic and keloid scarring is evolving from a position where they were regarded as different stages of the same process to the contemporary perspective of two separate entities. This article reviews the differences in the two forms of scarring and discusses the implications for future research.

Methods: The authors conducted a MEDLINE search of all English language reviews linking key words "hypertrophic," "keloid," and "scarring."

Results: Over the past four decades, there has been considerable clinical and experimental research looking at the biological nature and therapeutic response of keloid and hypertrophic scarring. As more differences are emerging regarding the fundamental biology of the scars, investigators are giving more detailed characterization of their source material. It is evident that even within the broad categories of hypertrophic and keloid scarring there is a heterogenous distribution of pathologic con-nective tissue matrix biology.

Conclusion: Considerable advances have been made in our understanding of the fundamental biology of scarring. As research methodology becomes even more sophisticated, it will be even more crucial to extensively characterize source material, recognizing major differences not only between keloid and hypertrophic scar but also between scars of varying stages of maturation and histomorphological, biochemical, and molecular variations within individual scars. (*Plast. Reconstr. Surg.* 116: 150e, 2005.)

After a dermal injury, a cascade of events is initiated that results in the deposition of a collagen-rich repair matrix. Over a period of several months, this matrix accumulates and in a normal scar is seen clinically as tissue that increases in height, firmness, and redness (vascularity). The scar then stabilizes for a variable length of time, typically 6 to 9 months, before it begins to flatten, soften, and become paler. This is the phase of maturation. The mature scar will never return to the high degree of organization of normal dermal architecture. Hypertrophic scarring is rather different. In this case, after an initiating injury, the wound-

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healing process begins as with normal scarring, but the accumulation of repair matrix follows a more protracted course, with increasing morphologic and biochemical abnormality. Although the hypertrophic scar follows the same cycle as the normal scar, the time course is considerably prolonged and the adverse effects of the scar on form and function, particularly caused by contraction, are significantly worse than those of normal scars. Keloid scarring does not follow the same pattern of evolution, stabilization, and involution of the normal or hypertrophic scar. It may develop directly after an initiating event or some years later, arising from a mature scar. Keloids also can occur as spontaneous lesions. Figure 1 is a diagrammatic representation of qualitative differences among these three forms of scarring. This review considers our growing understanding of the differences between hypertrophic and keloid scars and discusses the implication of these differences in treatment and future research.

LITERATURE REVIEWS

A MEDLINE search to access published reviews in the English language that relate the key words "keloid," "hypertrophic," and "scarring" indicated 22 such articles published from 1966 to June of 2004. The first of these articles was published in the *African Journal of Medicine and Medical Sciences* in 1976.[1] In the abstract, the author observes that "There is abundant evidence in the literature that keloids and hypertrophic scars are different stages of the same process." Rockwell et al. [2] and Muir [3] were more explicitly looking at the differences. McGrouther suggested however that "further attempts to achieve a clinical distinction between hypertrophic and keloid scars seem pointless."[4] This did not stop the reviews, however, and the most comprehensive to date appeared in 1999, with Niessen et al. citing 363 references.[5] There have been a number of reviews that have focused on management[6–8] and recently, after an extensive review of published evidence, an International Advisory Panel on Scar Management published their recommendations on the treatment of hypertrophic scars and keloids.[9] One recurring problem is the lack of precise characterization of the nature of the scar being treated and the interchangeability of the terms hypertrophic and keloid is well illustrated in Alster's article in the *Lancet* titled "Treatment of Keloid Sternotomy Scars. . .," which then

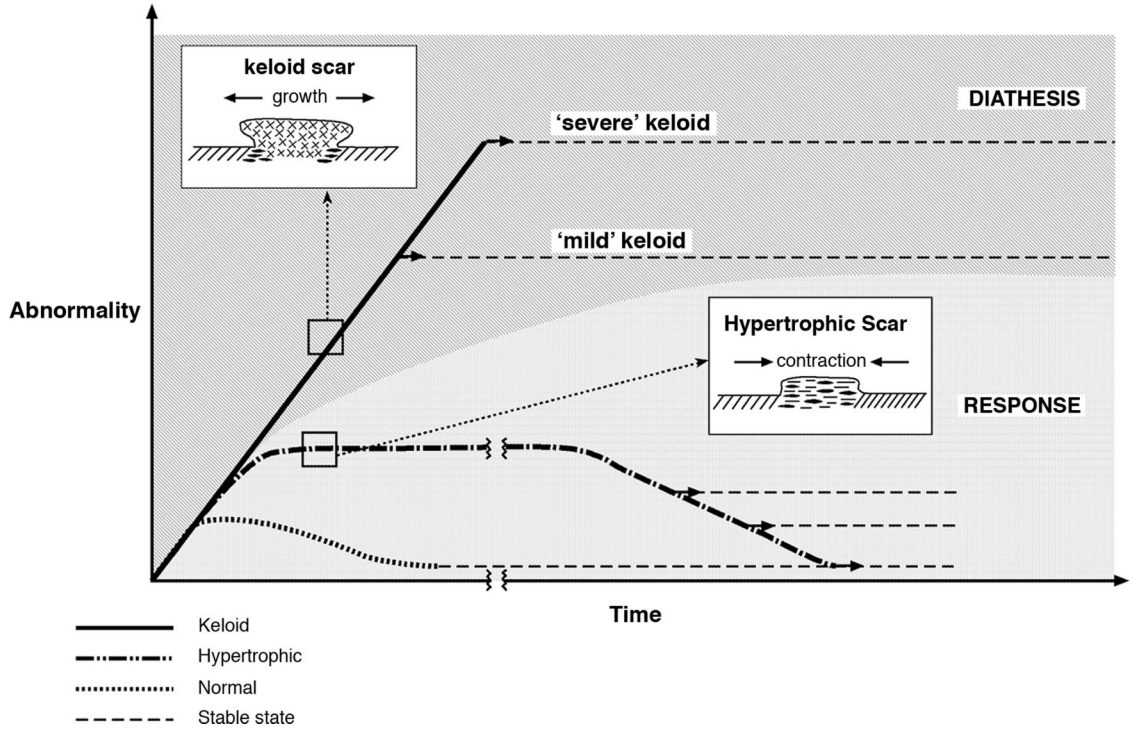

FIG. 1. Normal and hypertrophic scars are similar in terms of their "cycle" of matrix proliferation, stabilization, and maturation. Not all hypertrophic scars will mature to the same degree as a normal scar. Keloid scars rarely "mature," but there are gross morphologic differences between mild and severe keloids. The diagrammatic representations of the hypertrophic and keloid scars demonstrate the different arrangement of cells and matrix in the two forms of scarring together with opposing biological behavior (see text).

proceeds to describe the treatment of hypertrophic scars with the pulsed-dye laser.[10] The multiplicity of treatments and their uniform lack of success in reliably and predictably treating scars does suggest a differences between keloid and hypertrophic scars but also a significant heterogeneity within each category of scar.

Differences

Clinical

Table I shows the typical distinction between hypertrophic and keloid scars based on clinical features.

Biological

Extracellular matrix. In clinical practice, many regard the histopathologist as the final arbiter of diagnosis. This is not the case in scar pathology and indeed the problem illustrated in the histologic analysis of scar tissue illustrates the fundamental flaws in much of the published scientific research into the nature of hypertrophic and keloid scarring. Gertrude Stein's observation on roses does not apply to scars. Scars change with time, but at a point in time, the matrix morphology and cellular function will vary within the scar. Thus, the major problem is sampling and precise characterization of the cell or tissue source. Blackburn and Cosman[11] in their classic article described the difficulty of differentiating between keloid and hypertrophic scarring in the early stages. Later, however, the keloid shows thick, glossy, pale-staining collagen bundles with abundant "mucinous ground substance," few fibroblasts, and no foreign body reaction in contrasts to hypertrophic scar. Kischer and Brody[12] stated that the collagen nodule was a defining structural unit of all hypertrophic and keloid scars that is rich in cells and contains highly organized collagen fibrils. They acknowledge that there are changes as scars mature and suggest that the major histologic difference is the persistence of broad, dull, pink bundles of collagen in keloid scar that are not present in hypertrophic scar. Ehrlich et al.[13] add to the confusion by describing the keloid scar as being characterized by large, thick collagen fibers containing numerous (immature) fibrils closely packed together, in contrast to hypertrophic scars, which exhibit nodular structures in which "fibroblastic cells, small vessels and fine, randomly organized collagen fibres are present." Further studies have looked at evidence of apoptosis in the keloid and hypertrophic scar (see below), and the overall picture is of two scar types that begin with a similar morphology, with the hypertrophic scar phasing through a proliferative to stable state with collagen that is increasingly organized to form bundles parallel with the dermis. In contrast, the keloid scar develops a dense acellular core of collagen with a surrounding concentration of hyperproliferating fibroblasts. The "acellular" core contains thick bands of immature collagen that are poorly vascularized and contain no lymphatics or elastin.

The noncollagenous matrix of keloid scars is different from that of hypertrophic scars. Bertheim and Hellstrom[14] described the distribution of hyaluronan in mature scar and hypertrophic and keloid lesions. In mature scar, there was a layer of hyaluronan in the papillary dermis. In hypertrophic scar, hyaluronan was again found in the papillary dermis but in a very thin layer. In keloid tissue, the hyaluronan resembled the bulging reticular dermis. In addition, the keloid epidermis contained more hyaluronan. Hyaluronan is a major component of the early scar, but dur-

TABLE I

Typical Distinction between Hypertrophic and Keloid Scars Based on Clinical Features

	Hypertrophic Scar	Keloid Scar
Overall incidence	More common	Less common
Association with race	No	Increasing association with increasing racially determined pigmentation
Always preceded by injury	Yes	No
Anatomical association	No	Can occur anywhere but areas particularly prone are earlobes, deltoid region, and presternal region
Extent of growth	Confined to area of original injury	Extends into surrounding tissue
Resolves spontaneously	Most will eventually resolve	No
Recurs after surgery	No	Yes
Associated with contracture	Yes	No

*These are subjective and reports are variable (see text).

ing the remodeling process, it is replaced by the sulfated proteoglycans, decorin, biglycan, and versican. Fibroblasts cultured from hypertrophic scar tissue showed a reduced capacity to synthesize decorin,[15] and hypertrophic scar tissue has been shown to have decreased decorin levels.[16] Decorin interacts with collagen by means of its core protein and influences collagen fibrillogenesis, resulting in thinner fibrils. It also interacts with various cytokines including transforming growth factor-β1. As hypertrophic scars begin to mature, decorin levels begin to rise.[17] In contrast, in keloid tissue, the decorin expression remained unaltered compared with normal skin.[18] Versican and biglycan levels are both higher in immature hypertrophic scar compared with normal skin or mature scar.[19] Biglycan is also increased in keloid tissue, particularly in relation to nodular formations.[18] A recent report has indicated differences in the distribution of components of the elastic system (fibrillin-1 and elastin). Fibrillin-1 volume density was significantly higher in normal tissue compared with scar tissue and showed no difference between hypertrophic or keloid scar. In the lower levels of the dermis, elastin levels in keloid tissue were higher than in normal skin or hypertrophic scar.[20]

Microcirculation. Hypertrophic scars and keloid both have an increased microcirculation compared with normal skin and mature scar tissue. Clinically, active lesions are firm and erythematous. In a study looking at blood flow in hypertrophic scars subjected to temperature changes using a laser Doppler flow meter, it was concluded that maturation of the scar was related to microvascular regeneration.[21] Kischer, reporting on a microscopic evaluation of scar tissue, proposed that the genesis of both hypertrophic and keloid scar was hypoxia related to microvascular occlusion from an excess of endothelial cells.[22] This hypothesis fails to explain the spontaneous maturation of the hypertrophic scar. A possible explanation is that vascular endothelial growth factor (VEGF) is expressed at higher levels in keloid tissue, thus perpetuating the drive for endothelial cell production.[23] The profiles of VEGF levels in maturing hypertrophic scar have not been established.

Cell biology. The predominant cell of scar tissue is the fibroblast, which is responsible for producing collagens and other extracellular matrix components, and also for producing enzymes involved in the remodeling process. Considerable attention has focused on the cellular aspects of abnormal scarring, particularly with regard to gene expression and cell-matrix interactions. Cell surface adhesion molecules, integrins influence the cell-matrix interactions, and integrin expression is influenced by cytokines such as transforming growth factor-beta. The remodeling of the matrix is a function of proteolytic degradation and plasmin activator—plasmin and matrix metalloproteinases are two major groups of extracellular matrix degrading enzymes.

As the understanding of the biological complexity of wound healing expands, so does the appreciation that the epidermis plays a very important role in the quantity and quality of dermal repair. The paracrine function of keratinocytes has come under increasing scrutiny.[24] Platelet-derived growth factor, VEGF, heparin-binding epidermal growth factor, granulocyte-macrophage colony-stimulating factor, and transforming growth factor (TGF)-β are all involved in the modulating of diverse cell functions and the production of the extracellular matrix. Antigenic cytokines are also involved in the formation of the extracellular matrix and in turn are related to keratinocyte cytokine production.[25] Another observation is the changes that occur within the keratinocytes during wound healing.

These changes include the roles of adhesion molecules, principally β1 integrin,[26] the resistance of keratinocytes to TGF-β–mediated growth restriction and apoptosis induction,[27] transcription factor activation, in particular activator protein-1,[28] and calcium as a potential central regulator in wound healing.[29] The extracellular matrix is an integral part of the healing tissues and the relationship of reepithelialization and the extracellular matrix[30] and in particular hyaluronic acid[31] has been reviewed. Other studies have looked at the effects of coculture using keratinocytes derived from abnormal scar on fibroblasts. Increased fibroblast proliferation and collagen production was noted[32] and one possible mechanism was thought to be the increased bioavailability of insulin-like growth factor in keloid tissue.[33]

In vitro behavior and in vivo behavior of cells are not necessarily the same. Nevertheless, fibroblasts cultured from keloid tissue have been shown to continue to produce high levels of collagen, elastin, fibronectin, and proteoglycans in culture and to show altered responses when compared with normal fibroblasts when exposed to metabolic modulators such as glu-

cocorticoids, hydrocortisone, growth factors, and phorbol esters. That is to say that keloid fibroblasts have a wide range of abnormality when compared with normal fibroblasts. Fibroblasts cultured from hypertrophic scars also display a moderate elevation in collagen production in vitro, but their response to metabolic modulators is similar to normal fibroblasts. That is to say, they are less abnormal than keloid fibroblasts in terms of metabolism.

Fibroblasts cultured from hypertrophic scars exhibit stronger fibrin clot contraction compared with normal or keloid fibroblasts, and this is thought to be caused by autocrine control with higher levels of TGF-β being secreted. Use of antibody to TGF-β attenuates contraction, but the mechanism of the association of TGF-β to contraction is not clear. TGF-β can induce the expression of the smooth muscle actin which some investigators have reported is present in elevated levels in hypertrophic scar but not in keloid scar.[13] This observation is not consistently reported, however, and Lee et al. have not been able to substantiate this distinction in a study of a Chinese population.[34] Of interest another study in a Caucasian population has demonstrated that smooth muscle actin expression varies considerably with the maturation of the scar both in hypertrophic and keloid scars.[35] TGF-β1 and TGF-β2 have been shown to be expressed in greater levels in keloid fibroblasts compared with those derived from normal skin.[36] In addition, increased expression of TGF-β receptors (types I and II) and increased phosphorylation of Smad 3 (an intracellular TGF-β signaling molecule) are also features of keloids supporting a role for TGF-β in keloid pathogenesis.[37] The experimental evidence suggests that hypertrophic scar fibroblasts may represent a hyperproliferative phenotype that is responding to multiple local stimulatory factors. Keloid fibroblasts, however, represent a unique phenotype that is genetically disposed to changes in extracellular matrix production and plasminogen-activator inhibitor 1 expression. Some stimulatory factor appears to irreversibly switch on this phenotype in susceptible individuals after local wounding.[38] One suggestion for up-regulation of plasminogen-activator inhibitor 1 is hypoxia-mediated signaling in keloids.[39] This experimental evidence contrasts, however, with clinical studies that reflect the polyclonal nature of fibroblasts derived from keloid scars.[40]

Apoptosis

The role of apoptosis in keloid and hypertrophic scarring is of interest. The lack of cells within the keloid tissue has led investigators to postulate the role of apoptosis in pathogenesis. Histologic findings suggested that with increasing maturity, progressive cell degeneration by apoptosis resulted in the typical keloid lesion, with persistence of fibroblast proliferation at the interface of the lesion with normal tissue propagating the fibrosis.[41] It is interesting to note that later investigators have postulated the mechanism of apoptosis being central to hypertrophic scar maturation. In this study interferon-α2b was administered systemically and was associated with a significant increase in apoptotic cells, with a general reduction in fibroblasts and myofibroblasts.[42]

The situation, however, has become more confused as further studies emerge. Sayah et al.[43] looked at 64 apoptosis-related genes in keloids and normal scar and found that eight of the 64 were significantly underexpressed in keloid tissue. They hypothesized that keloid fibroblasts failed to undergo programmed cell death and continued to produce and secrete connective tissue beyond the period expected in normal scar formation, thus giving rise to the progressive and hypertrophic nature of keloids. Funayama et al.[44] looked at the interaction between keratinocytes and fibroblasts in coculture models. They found that keloid-derived fibroblasts cultured with keloid-derived keratinocytes exhibited enhanced proliferation and reduced apoptosis when compared with coculture of cells from normal skin. Analysis of these keloid fibroblasts showed significant up-regulation of extracellular signal–regulated kinase, c-Jun N-terminal kinase phosphorylations, expression of Bc1-2 and TGF-β1. Akasaka et al.[45] quantified the expression of caspase-3 and caspase-2 in mature normal, hypertrophic, and keloid scar. They found enhanced expression of caspase-3 (normally activated during apoptosis in vitro) in hypertrophic and keloid scars. Other recent studies have suggested possible therapeutic approaches to keloids by using apoptosis inducers such as sphingosine[46] and imiquimod 5% cream.[47] Two further articles published recently suggest altered cellular kinetics within the fibroblasts within the keloid nodule.[48,49] Both these studies indicated increased proliferation rates for the fibroblasts cultured from the center of keloid lesions, and Luo

et al. again described decreased apoptosis in the keloid-derived fibroblasts.

Genetics

Clinically, the incidence of keloid scarring increases with increased racially determined pigmentation of the skin. It should be noted that keloids have not been reported in albino's of any race, suggesting a potential role of melanin and/or melanocytes in scarring. A genetic association with the keloid diathesis is also supported by the finding of an increased incidence of keloid disease running in families. Bayat et al.[50] looked at the incidence of TGF-β polymorphism in a Caucasian populations with hypertrophic, keloid, and normal scars. The authors recognized the heterogenicity of scarring and subjected their study population to rigorous diagnostic criteria in the recruitment protocol. Nevertheless, they could not demonstrate any significant association with the TGF-β1 gene. Previously, the same group had failed to identify an association with TGF-β2.[51] In a more recent study, the same group has failed to establish any significant association for TGF-β receptor polymorphisms.[52]

Bayat et al., revisiting the genetic link from an epidemiologic perspective, have reported an increased incidence of keloids in families with a positive history of lesions. This was, however, a hospital- rather than a population-based study, and the conclusions are open to question.[53] However, Marneros et al., looking at genome scans from a Japanese and African-American family, have provided evidence for keloid susceptibility loci on chromosomes 2q23 and 7p11.[54]

DISCUSSION

Tables II and III summarize the differences between hypertrophic and keloid scars from the perspective of morphology, immunohistochemistry, and fibroblasts characteristics. In summary, hypertrophic and keloid scar appear to be very different entities, and it would appear useful to talk about a hypertrophic response and a keloid diathesis or disposition. Because they are so different, the treatment strategies should also be different. It is fortunate that some lesions respond to common treatments, but the biological differences are reflected in the very variable response.

The differences between hypertrophic and keloid scarring are such that they could almost be regarded as similar or dissimilar as trauma and tumor. Moreover, within each type of scar, there is a considerable heterogeneity. It is now possible to perform extremely sophisticated analysis of gene expression patterns in hypertrophic scar derived tissue.[55,56] Using microarrays with many thousands of genes, a snapshot of activity can be revealed. Similar studies have looked at keloid tissue using cDNA microarray, but similar criticisms apply. In one study, 402 of 8,400 genes were differently expressed in keloid and normal skin. Two hundred fifty of these, including TGF-β1, were up-regulated and 152 were down-regulated.[57] The problem with these and many of the other laboratory stud-

TABLE II

Morphologic and Immunohistochemical Difference*

	Hypertrophic Scars	Keloids
Connective tissue	Increased	Increased
Collagen structure	Flatter and less distinct bundles, fine fibers	Larger fibers with closely packed fibrils
Orientation of fibers	Wavy, but parallel to epidermis	Random to epidermis
Myofibroblasts	Present	Absent
α-Smooth muscle actin	↑ ↑	↑
Density of blood vessels	Increased (decreasing with maturation)	Decreased
No. of cells	Increased (decreasing with maturation)	Decreased (in nodules); increased (at periphery)

*These are subjective and reports are variable (see text).

TABLE III

Cellular Differences between Fibroblasts Derived from Hypertrophic Scar and Keloid Scar Compared with Fibroblasts in Normal Skin

	HSc Fibroblasts	KSc Fibroblasts
Proliferation rate	Normal	↑ ↑
MMP-2	↑	↑
MMP-9	↓ ↓	↓ ↓
Collagen synthesis	↑	↑ ↑
Decorin synthesis	↓ ↓	Normal
Versican synthesis	↑	↑
Biglycan synthesis	↑	↑
Elastin synthesis	Normal	↑
TGF-β production	↑ ↑	↑ ↑

HSc, hypertrophic scar; KSc, keloid scar; MMP, matrix metalloproteinase.

ies of scars and scar tissue is that the source material has not been sufficiently characterized. Such a characterization would reflect the stage of evolution of the scar but, ideally, also include the resolution of the scar, particularly with reference to response to treatment. As our understanding of the molecular characterization of scar tissue develops, it may well be that treatments will become more focused. It is not inconceivable that in the not-too-distant future a scar biopsy for such molecular characterization (rather that histomorphologic characterization) will become a routine part of scar management.

SUMMARY

Abnormal scar response falls into two main categories: hypertrophic and keloid. Scars within these categories will vary both in their clinical course and in their response to treatment. There will also be variations with single scars at a set time point. This is particularly the case in keloid scars, with distinct cellular and matrix organization at the periphery and center of scars. The implications of these variations becomes more relevant as investigative techniques become even more focused. The continued evolution of the understanding of the underlying biological mechanisms of hypertrophic and keloid scar will require an even more sophisticated characterization of the source material that is being studied. Ideally, this characterization will include clinical data describing the cause and maturation of the scar tissue, the part of the scar biopsied, but also, where possible, the subsequent response of the scar to treatment.

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REFERENCES

1. Adeyemi-Doro, H. O. Keloids: The natural history. *Afr. J. Med. Med. Sci.* 5: 93, 1976.
2. Rockwell, W. B., Cohen, I. K., and Ehrlich, H. P. Keloids and hypertrophic scars: A comprehensive review. *Plast. Reconstr. Surg.* 84: 827, 1989.
3. Muir, I. F. On the nature of keloid and hypertrophic scars. *Br. J. Plast. Surg.* 43: 61, 1990.
4. McGrouther, D. A. Hypertrophic or keloid scars? *Eye* 8: 200, 1994.
5. Niessen, F. B., Spauwen, P. H., Schalkwijk, J., and Kon, M. On the nature of hypertrophic scars and keloids: A review. *Plast. Reconstr. Surg.* 104: 1435, 1999.
6. Alster, T. S., and Tanzi, E. L. Hypertrophic scars and keloids: Etiology and management. *Am. J. Clin. Dermatol.* 4: 235, 2003.
7. Urioste, S. S., Arndt, K. A., and Dover, J. S. Keloids and hypertrophic scars: Review and treatment strategies. *Semin. Cutan. Med. Surg.* 18: 159, 1999.
8. Berman, B., and Flores, F. The treatment of hypertrophic scars and keloids. *Eur. J. Dermatol.* 8: 591, 1998.
9. Mustoe, T. A., Cooter, R. D., Gold, M. H., et al. International clinical recommendations on scar management. *Plast. Reconstr. Surg.* 110: 560, 2002.
10. Alster, T. S., and Williams, C. M. Treatment of keloid sternotomy scars with 585nm flashlamp-pumped pulsed-dye laser. *Lancet* 345: 1198, 1995.
11. Blackburn, W. R., and Cosman, B. Histologic basis of keloid and hypertrophic scar differentiation. *Arch. Pathol.* 82: 65, 1966.
12. Kischer, C. W., and Brody, G. S. Structure of the collagen nodule from hypertrophic scars and keloids. *Scan. Electron Microsc.* Pt. 3: 371, 1981.
13. Ehrlich, H. P., Desmouliere, A., Diegelmann, R. F., et al. Morphological and immunochemical differences between keloid and hypertrophic scar. *Am. J. Pathol.* 145: 105, 1994.
14. Bertheim, U., and Hellstrom, S. The distribution of hyaluronan in human skin and mature, hypertrophic and keloid scars. *Br. J. Plast. Surg.* 47: 483, 1994.
15. Scott, P. G., Dodd, C. M., Ghahary, A., Shen, Y. J., and Tredget, E. E. Fibroblasts from post-burn hypertrophic scar tissue synthesize less decorin than normal dermal fibroblasts. *Clin. Sci.* 94: 541, 1998.
16. Garg, H. G., Siebert, J. W., Garg, A., and Neame, P. J. Inseparable iduronic acid-containing proteoglycan PG (IdoA) preparations of human skin and post-burn scar tissues: Evidence for elevated levels of PG (IdoA)-I in hypertrophic scar by N-terminal sequencing. *Carbohydr. Res.* 284: 223, 1996.
17. Sayani, K., Dodd, C. M., Nedelec, B., et al. Delayed appearance of decorin in healing burn scars. *Histopathology* 36: 262, 2000.
18. Hunzelmann, N., Anders, S., Sollberg, S., Schonherr, E., and Krieg, T. Co-ordinate induction of collagen type I and biglycan expression in keloids. *Br. J. Dermatol.* 135: 394, 1996.
19. Scott, P. G., Dodd, C. M., Tredget, E. E., Ghahary, A., and Rahemtulla, F. Chemical characterization and quantification of proteoglycans in human post-burn hypertrophic and mature scars. *Clin. Sci.* 90: 417, 1996.
20. Amadeu, T. P., Braune, A. S., Porto, L. C., Desmouliere, A., and Costa, A. M. A. Fibrillin-1 and elastin are differentially expressed in hypertrophic scars and keloids. *Wound Repair Regen.* 12: 169, 2004.
21. Clark, J. A., Leung, K. S., Cheng, J. C. Y., and Leung, P. C. The hypertrophic scar and microcirculation properties. *Burns* 22: 447, 1996.
22. Kischer, C. W. The microvessels in hypertrophic scars, keloids and related lesions: A review. *J. Submicrosc. Cytol. Pathol.* 24: 281, 1992.
23. Wu, Y., Zhang, Q., Ann, D. K., et al. Increased vascular endothelial growth factor may account for elevated level of plasminogen activator inhibitor-1 via activating ERK ½ in keloid fibroblasts. *Am. J. Physiol.* 286: C905, 2004.
24. Clark, R. A. F. Epithelial-mesenchymal networks in wounds: A hierarchical view. *J. Invest. Dermatol.* 120: 9, 2003.

25. Tonnesen, M. G., Feng, X., and Clark, R. A. F. Angiogenesis in wound healing. *J. Invest. Dermatol.* 5: 40, 2000.
26. Grose, R., Hutter, C., Bloch, W., et al. A crucial role of β1 integrins for keratinocyte migration in vitro and during cutaneous wound repair. *Development* 129: 2303, 2002.
27. Amendt, C., Mann, A., Schirmacher, P., and Blessing, M. Resistance of keratinocytes to TGFβ-mediated growth restriction and apoptosis induction accelerates re-epithelialization in skin wounds. *J. Cell Sci.* 115: 2189, 2002.
28. Yates, S., and Rayner, T. E. Transcription factor activation in response to cutaneous injury: Role of AP-1 in reepithelialization. *Wound Repair Regen.* 10: 5, 2002.
29. Lansdown, A. B. G. Calcium: A potential central regulator in wound healing in the skin. *Wound Repair Regen.* 10: 271, 2002.
30. O'Toole, E. A. Extracellular matrix and keratinocyte migration. *Clin. Exp. Dermatol.* 26: 525, 2001.
31. Manuskiatti, W., and Maibach, H. I. Hyaluronic acid and skin: Wound healing and aging. *Int. J. Dermatol.* 35: 539, 1996.
32. Lim, I. J., Phan, T. T., Bay, B. H., et al. Fibroblasts cocultured with keloid keratinocytes: Normal fibroblasts secrete collagen in a keloidlike manner. *Am. J. Physiol.* 283: C212, 2002.
33. Phan, T. T., Lim, I. J., Bay, B. H., et al. Role of IGF system of mitogens in the induction of fibroblast proliferation by keloid-derived keratinocytes in vitro. *Am. J. Physiol.* 284: C860, 2003.
34. Lee, J. Y. Y., Yang, C. C., Chao, S. C., and Wong, T. W. Histopathological differential diagnosis of keloid and hypertrophic scar. *Am. J. Dermatopathol.* 26: 379, 2004.
35. Santucci, M., Borgognoni, L., Reali, U. M., and Gabbiani, G. Keloids and hypertrophic scars of Caucasians show distinctive morphologic and immunophenotypic profiles. *Virchows Arch.* 438: 457, 2001.
36. Lee, T. Y., Chin, G. S., Kim W. J., et al. Expression of transforming growth factor beta 1,2 and 3 proteins in keloids. *Ann. Plast. Surg.* 43: 179, 1999.
37. Chin, G. S., Liu, W., Peled, Z., et al. Differential expression of transforming growth factor-beta receptors I and II and activation of Smad 3 in keloid fibroblasts. *Plast. Reconstr. Surg.* 108: 423, 2001.
38. Tuan, T. L., and Nichter, L. S. The molecular basis of keloid and hypertrophic scar formation. *Mol. Med. Today* 4: 19, 1998.
39. Zhang, Q., Wu, Y., Chau, C. H., Ann, D. K., Bertolami, C. N., and Le, A. D. Crosstalk of hypoxia-mediated signaling pathways in upregulating plasminogen activator inhibitor-1 expression in keloid fibroblasts. *J. Cell. Physiol.* 199: 89, 2004.
40. Chevray, P. M., and Manson, P. N. Keloid scars are formed by polyclonal fibroblasts. *Ann. Plast. Surg.* 52: 605, 2004.
41. Appleton, I., Brown, N. J., and Willoughby, D. A. Short communication: Apoptosis, necrosis, and proliferation. *Am. J. Pathol.* 149: 1441, 1996.
42. Nedelec, B., Shankowsky, H., Scott, P. G., Ghahary, A., and Tredget, E. E. Myofibroblasts and apoptosis in human hypertrophic scars: The effect of interferon-α2b. *Surgery* 130: 798, 2001.
43. Sayah, D. N., Soo, C., Shaw, W. W., et al. Downregulation of apoptosis-related genes in keloid tissues. *J. Surg. Res.* 87: 209, 1999.
44. Funayama, E., Chodon, T., Oyama, A., and Sugihara, T. Keratinocytes promote proliferation and inhibit apoptosis of the underlying fibroblasts: An important role in the pathogenesis of keloid. *J. Invest. Dermatol.* 121: 1326, 2003.
45. Akasaka, Y., Ishikawa, Y., Ono, I., et al. Enhanced expression of caspase-3 in hypertrophic scars and keloid: Induction of caspase-3 and apoptosis in keloid fibroblasts in vitro. *Lab. Invest.* 80: 345, 2000.
46. Chang, S. E., Kim, K. J., Ro, K. H., et al. Sphingosine may have cytotoxic effects via apoptosis on the growth of keloid fibroblasts. *J. Dermatol.* 31: 1, 2004.
47. Jacob, S. E., Berman, B., Nassiri, M., and Vincek, V. Topical application of imiquimod 5% cream to keloids alters expression genes associated with apoptosis. *Br. J. Dermatol.* 149: 62, 2003.
48. Giugliano, G., Pasquali, D., Notaro, A., et al. Verapamil inhibits interleukin-6 and vascular endothelial growth factor production in primary cultures of keloid fibroblasts. *Br. J. Plast. Surg.* 56: 804, 2003.
49. Luo, S., Benathan, M., Raffoul, W., Panizzon, R. G., and Egloff, D. V. Abnormal balance between proliferation and apoptotic cell death in fibroblasts derived from keloid lesions. *Plast. Reconstr. Surg.* 107: 87, 2001.
50. Bayat, A., Bock, O., Mrowietz, U., Ollier, W. E. R., and Ferguson, M. W. J. Genetic susceptibility to keloid disease and hypertrophic scarring: Transforming growth factor β1 common polymorphisms and plasma levels. *Plast. Reconstr. Surg.* 111: 535, 2003.
51. Bayat, A., Bock, O., Mrowietz, U., Ollier, W. E., and Ferguson, M. W. Genetic susceptibility to keloid disease and transforming growth factor beta 2 polymorphisms. *Br. J. Plast. Surg.* 55: 283, 2002.
52. Bayat, A., Bock, O., Mrowietz, U., Ollier, W. E., and Ferguson, M. W. Genetic susceptibility to keloid disease: Transforming growth factor beta receptor gene polymorphisms are not associated with keloid disease. *Exp. Dermatol.* 13: 120, 2004.
53. Bayat, A., Arscott, G., Ollier, W. E. R., McGrouther, D. A., and Ferguson, M. W. J. Keloid disease: Clinical relevance of single versus multiple site scars. *Br. J. Plast. Surg.* 58: 28, 2005.
54. Marneros, A. G., Norris, J. E. C., Watanabe, S., Reichenberger, E., and Olsen, B. R. Genome scans provide evidence for keloid susceptibility loci on chromosomes 2q23 and 7p11. *J. Invest. Dermatol.* 122: 1126, 2004.
55. Paddock, H. N., Schultz, G. S., Baker, H. V., et al. Analysis of gene expression patterns in human postburn hypertrophic scars. *J. Burn Care Rehabil.* 24: 371, 2003.
56. Tsou, R., Cole, J. K., Nathens, A. B., et al. Analysis of hypertrophic and normal scar gene expression with cDNA microarrays. *J. Burn Care Rehabil.* 21: 541, 2000.
57. Chen, W., Fu, X., Sun, X., et al. Analysis of differentially expressed genes in keloids and normal skin with cDNA microarray. *J. Surg. Res.* 113: 208, 2003.