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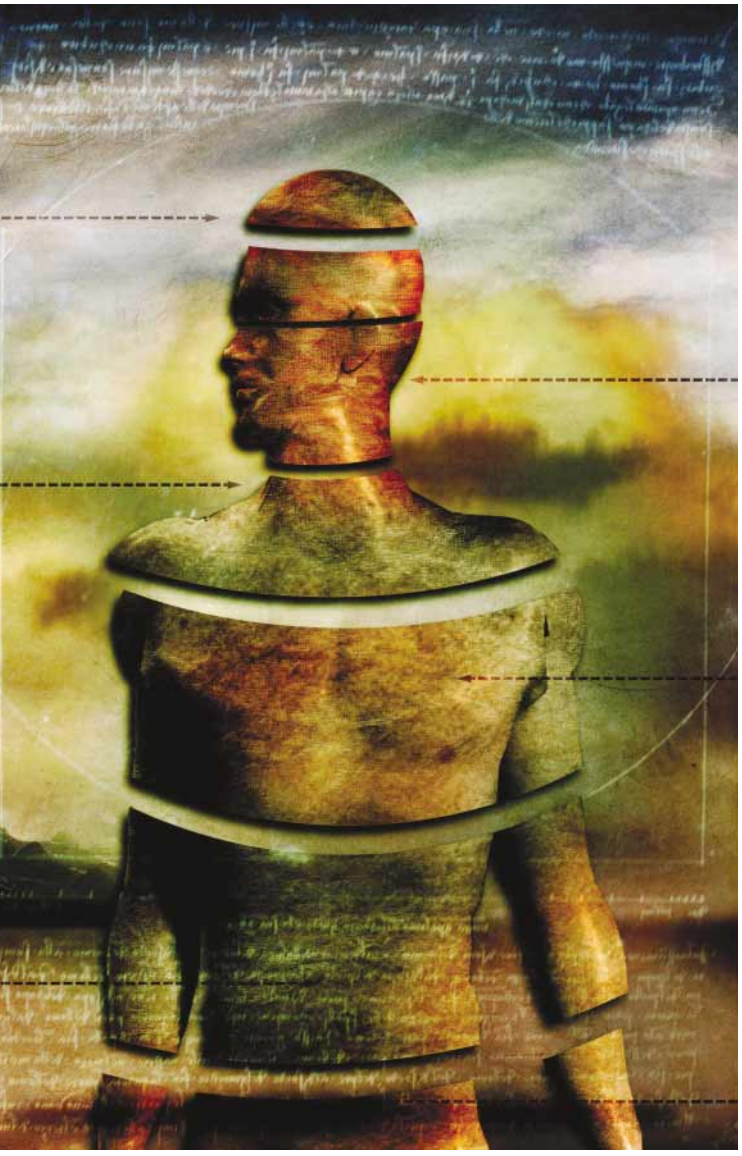
Nonmelanoma Skin Cancers:

Research and Clinical Findings With Immune Response Modifier Therapy



Introduction

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The Histopathology of Nonmelanoma Skin Cancers: Overview of Recent Findings

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The Emerging Potential of Immune Response Modifier Therapy in Superficial Skin Cancers

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The Role of Imiquimod in the Treatment of BCC: Clinical Evidence

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Illuminating the Mode of Action of Immune Response Modifier Therapy in Superficial Skin Cancers

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FACULTY AND UNAPPROVED USE DISCLOSURES

Faculty/authors must disclose any significant financial interest or relationship with proprietary entities that may have a direct relationship to the subject matter. They must also disclose any discussion of investigational or unlabeled uses of products.

Prof Basset-Séguin has nothing to disclose. **Prof Dummer** is a consultant to 3M Pharmaceuticals. He discusses the investigational use of imiquimod in treating mycosis fungoides, cutaneous T-cell lymphomas, and lentigo maligna. **Prof Giannetti** has nothing to disclose. **Prof Kerl** is a consultant to 3M. **Prof Sterry** has received funding for clinical grants from 3M, Coley Pharmaceutical Group, Inc., and Shire Pharmaceuticals Group plc. He is also a consultant to 3M. **Prof Stockfleth** discusses the investigational use of immune response modifiers as oral therapy in patients with hepatitis infections and as an adjuvant for vaccines.

Introduction

Important advances continue to be made in understanding the role of topical immune response modifier (IRM) therapy. Interest in this field is high because IRM therapy to date has demonstrated great promise in a wide range of dermatologic diseases.

The first agent developed in this class, imiquimod, currently is approved in Europe for genital warts and small, superficial basal cell carcinomas (BCCs). In the United States, imiquimod is approved by the Food and Drug Administration for the treatment of genital warts, actinic keratoses (AKs), and small, superficial BCCs. It is becoming clear that, as we understand more about imiquimod's mechanism of action, its benefits will extend beyond these indications.

The purpose of this supplement is to provide a review of the current and potential uses of imiquimod in the treatment of superficial skin cancers, to review the mechanism of action of imiquimod and the clinical results in the treatment of superficial BCC and AKs, and to note the emerging potential for immune response modulation in the treatment of other superficial skin cancers. ■

—Professor Alberto Giannetti, MD
Chair
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The Histopathology of Nonmelanoma Skin Cancers: Overview of Recent Findings

Professor Helmut Kerl, MD

Of the three cancerous tumors seen commonly in dermatology, two—basal cell carcinoma (BCC) and actinic keratosis (AK)/squamous cell carcinoma (SCC)—are categorized as nonmelanoma skin cancers (NMSCs). Although attempts have been made to estimate the incidence of NMSC, it is really only possible at this time to state that BCC and AK/SCC are the most frequent malignant tumors in human beings, that NMSC affects millions of individuals, and that AK is undoubtedly the most common among these lesions.

Histopathology of BCC

BCC can be defined as a slow-growing, locally invasive neoplasm of the follicular germinative cells, or trichoblasts, which are found in the human embryo. As such, BCC may also be referred to as a malignant trichoblastic tumor. The histopathologic categories are nodular, superficial (**Figure**), morpheiform, fibroepithelial, and infundibulocystic.

Histopathologically, BCC is determined by the demonstration of aggregations of follicular germinative cells that are columnar and arranged in a palisade. Adjunctive findings include germinative cell necrosis, mitotic figures, altered stromal connective tissues, and clefts between cell aggregations and stroma. Within these basic findings, BCC may show a wide variety of patterns and cytomorphologic features, including a labyrinthine pattern and clear cells, but the palisading arrangement of the cells is still visible.

Included in the differential diagnosis of BCC is its benign counterpart, the trichoblastoma (frequently found in association with epidermal nevi), which also consists of follicular germinative cells. In the past, most cases of trichoblastoma were designated wrongly as BCC. Several important histologic features differentiate BCC from trichoblastoma. Trichoblastoma usually shows no clefts. In addition, trichoblastoma demonstrates hints of papillae formation and a stroma resembling embryonic perifollicular sheath. These are not seen in BCC.

Prognosis and Treatment of BCC

Histologic findings are, of course, important to both treatment and prognosis. The most important prognostic factors are thickness, size, histologic type, and the presence or absence of perineural infiltration.

Patients with superficial BCC—including nodular superficial BCC—are ideal candidates for topical treatment with immunomodulating agents. Those with morpheiform, fibroepithelial, and infundibulocystic tumors require surgical excision of the lesion. Surgical treatment often must be aggressive to be successful. One recent advance—the development of confocal microscopy—

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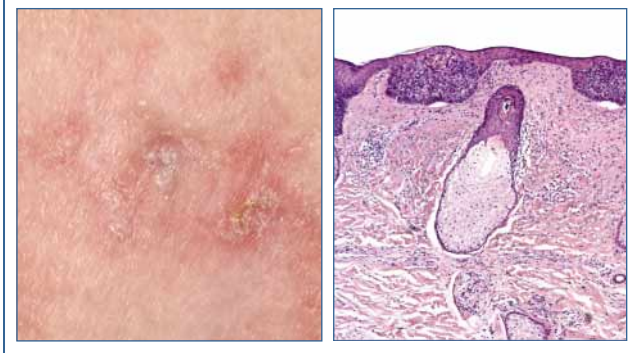
FIGURE. Superficial Basal Cell Carcinoma



Superficial BCC is a low-grade malignancy that makes this patient a candidate for topical immunomodulator therapy.

Source: Courtesy of Professor Helmut Kerl, MD

The Emerging Potential of Immune Response Modifier Therapy in Superficial Skin Cancers

Professor Reinhard Dummer, MD

Approximately 10 years ago imiquimod, the first drug in the class now known as immune response modifiers (IRMs), was introduced. It had been developed as an antiviral drug and was first approved for use by the US Food and Drug Administration as a topical treatment for genital warts. Its exact mechanism of action was not clearly defined at that time, although it was known that imiquimod was effective in preventing viral replication. Since then, research has shown that the mechanisms by which imiquimod achieves its antiviral effects are very closely tied with those that result in antitumor effects (Table).[1]

Mechanisms of Action: Recent Findings

Imiquimod stimulates the body's immune response by a number of mechanisms, including the induction of α-interferon.[2] In addition, a natural ligand for the receptor that is targeted by imiquimod, toll-like receptor 7, has been identified. This natural target is viral-derived, single-stranded messenger RNA, which is of particular interest because the efficacy that imiquimod has shown in the treatment of epithelial carcinomas lends further support to the previous body of evidence implicating viruses in the induction of dermatologic cancers through infection of tumor-receptive cells. These dermatologic cancers include—in addition to epithelial cancers—T-cell lymphomas and, especially, Kaposi's sarcoma.

Toll-like receptors are the principal receptors of the innate immune response, and interferon certainly is a key molecule, especially if the immune system is coping with viral infections. However, in the adaptive immune response, the antiviral and anticancer effector pathways are the same. For example, cytotoxic T lymphocytes recognize tumor antigens generated in cell cytoplasm, which, after undergoing complicated antigen-processing steps, ultimately are presented as human leukocyte antigen-I surface molecules (otherwise known as "transplantation antigens"). The same is true for viral proteins: with a chronic viral infection, the immune system detects cell activity by the same effector mechanism.

This also is the case with interferon, which was so named because it can bring antiviral activity from one cell to the other—that is, it interferes in the viral replication process. It exerts antiproliferative activity by inducing immune responses that stop cell growth. In addition, interferon monitors and regulates the activity of the principal effector cells of the innate immune response. These are neutrophils that secrete enzymes that can directly kill other cells, including bacteria.[3]

TABLE. Antiviral Strategies Are Antitumor Strategies

Innate immune response
- Neutrophilic cytotoxic reactions
- Interferons
- Natural killer cells

Adaptive immune response
- (Neutralizing) antibodies
- Cytotoxic T cells

Source: Courtesy of Professor Reinhard Dummer, MD

IRM Activity in Actinic Keratoses

The mode of action of IRM therapy offers a clear advantage over ablative treatments for actinic keratoses (AKs) such as cryotherapy, which can treat only clinically evident lesions. In contrast, as Dr Stockfleth discusses in his article (see page 7), IRM therapy permits field therapy for an entire area of damaged skin. Within this area of damaged skin, where future AKs and invasive squamous cell carcinomas (SCCs) can arise, topical treatment may eradicate not only the existing AKs but also subclinical lesions and smaller foci of dyskeratotic clones of cells to prevent recurrence.

In a double-blind, randomized, vehicle-controlled, dose-response pilot study by Stockfleth and colleagues,[4] patients with between 3 and 10 AKs used imiquimod or vehicle three times weekly for 12 weeks. Complete clinical and histologic clearance of AKs was seen in 21 of 25 patients (84%) treated with imiquimod and none of those in the vehicle group. The investigators also reported that after the initial 2 to 4 weeks of therapy, the number of visible lesions in the treated area increased, suggesting that subclinical lesions also were responding to imiquimod applications. After this time, the number of lesions decreased, and, at week 6, there were generally fewer AKs than at baseline.

In two phase III studies,[5] the use of imiquimod was evaluated using either twice-weekly or three-times-weekly applications. Subjects had between four and eight AKs in a 25-cm^2 treatment area. In the group who used imiquimod twice weekly, complete clearance was seen in 45.1% of patients and partial clearance (that is, clearance of more than 75% of lesions but less than 100%) was seen in 59.1%. With the three-times-weekly regimen, 57.1% of patients achieved complete clearance and 72.1% had partial clearance. Efficacy rates were significantly greater than those seen in the vehicle-only groups ($P<0.001$).

Investigation of IRM Use Continues

The mode of action of IRM agents continues to be explored. It is known that topical therapy with imiquimod stimulates responses from macrophages, but it has recently been demonstrated that a response results in plasmacytoid dendritic cells, which carry toll-like receptors 7 and 8 and appear to be potent producers of α-interferon.

As a result, studies with imiquimod have shown promising results in the topical therapy of mycosis fungoides, cutaneous T-cell lymphomas (character-

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The Role of Imiquimod in the Treatment of BCC: Clinical Evidence

Professor Nicole Basset-Séguin, MD, PhD

Basal cell carcinoma (BCC) is the most frequent cancer in adult patients. The estimated incidence of 50,000 new cases every year worldwide is undoubtedly an underestimate because most cases of BCC are not registered. The incidence of BCC is increasing by more than 10% a year. With the aging of the population, BCC is likely to become more of a problem in the future, with a prevalence greater than all other cancers combined.[1]

Treatment Options

The choice of treatment for an individual patient depends on several main factors: site of tumor(s), histologic type, size of the lesion(s), history of previous treatment, patient characteristics (age, Fitzpatrick's skin type, general health), and anticipated cosmetic results.[2] The gold standard of treatment for BCC is surgery: excision, grafts, flaps, and/or Mohs' micrographic surgery. Other options include destructive techniques (cryotherapy, curettage, cautery), photodynamic therapy, radiotherapy, and topical treatment.

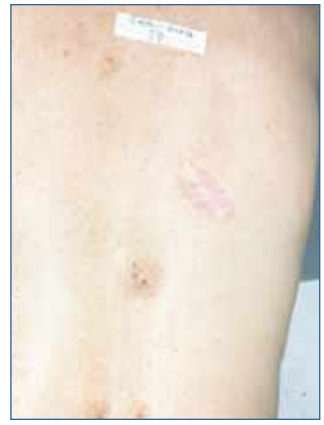
Surgical excision is associated with high cure rates, but it can be painful and can result in scarring—including dystrophic keloid formation—on cosmetically sensitive areas of the body such as the face or, in some cases, over large areas of the skin such as the trunk when multiple lesions are treated **(Figure)**. A poor cosmetic result is a significant consequence of surgery, particularly for superficial lesions that are typically not aggressive and should be considered a low-risk cancer (BCC lesions do not metastasize). The preferred treatment for BCC would yield a high, sustained cure rate, balanced with a good cosmetic outcome, ease of use, and cost-effectiveness.

Rationale for IRM Therapy in BCC

Immune-mediated tumor rejection is a new strategic option under development for the treatment of a number of cancers. For skin cancers, topical therapy may be particularly suitable when treating large areas or in patients with multiple tumors. Immune response modifiers (IRMs), topical agents that modulate the functions of immune cells, are an innovative approach to the treatment of skin cancers.[3,4]

The first agent developed in the IRM class, imiquimod, has a unique mechanism of action that provides the rationale for its use as a topical therapy for BCC. Imiquimod has demonstrated potent antitumor and antiviral activity.[5] In addition, a number of case reports have been published showing that intralesional injection of interferon is effective in difficult cases of BCC, and imiquimod induces innate and cell-mediated immune responses by stimulating the production of a number of cytokines, including interferon and tumor necrosis factor-α.[3]

FIGURE. Scarring After Basal Cell Carcinoma Excision



Cosmetic results must be considered when evaluating treatment options. This patient developed dystrophic scarring following surgical excision of multiple BCCs on her back.

Source: Courtesy of Professor Nicole Basset-Séguin, MD, PhD

Clinical Evidence of IRM Efficacy

A number of phase II dose-response studies were conducted to determine the optimum dosing schedule for imiquimod in patients with BCC. Included among these were a 16-week regimen,[6] 6-week regimens,[7] 12-week regimens,[8] and low-frequency dosing with occlusion.[9] The phase II results showed that imiquimod 5% applied once daily or five times weekly for 6 weeks both provided excellent results with good tolerability.

Two identical phase III controlled studies, conducted in the United States, confirmed these findings.[10] In the phase III studies—which were multicenter, randomized, double-blind, and vehicle-controlled—724 patients with one small, superficial BCC received imiquimod 5% five times weekly, imiquimod 5% once daily (ie, 7 times weekly), or vehicle only for 6 weeks.

The required tumor size was 0.5 to 2.0 cm^2 in diameter, and a biopsy to confirm superficial BCC was performed prior to enrollment. Tumor sites were clinically evaluated at 12 weeks post-treatment, and the area was excised and the specimen submitted to histologic examination. To ensure that no residual tumor would be missed, more than 100 sections per specimen were examined.

The primary efficacy end point was a complete response, both clinically and histologically. The secondary end point was complete histologic response only. Safety was evaluated according to the appearance of local skin reactions, as well as the assessment of skin quality, which included ratings of the skin surface (roughness, dryness, scaling), hyperpigmentation or hypopigmentation, mottled or irregular pigmentation, scarring, and atrophy.

The patients who used imiquimod five times weekly had a clinical and histologic clearance rate of 75% and a complete histologic clearance rate of 82% vs

2% and 3%, respectively, in the vehicle-only group ($P<0.001$). Those who applied imiquimod every day had a clinical and histologic clearance rate of 73% and a complete histologic clearance rate of 79% vs 2% and 3%, respectively, in the vehicle-only group ($P<0.001$).

Treatment discontinuation rates were very low. Rates were almost comparable among the different groups—placebo and the two dosage regimens.

Interestingly, the investigators noted a positive correlation between histologic clearance and the degree of severity of local skin reactions—that is, the more severe the reaction, the better the histologic response. Patients must understand this correlation, and it must be explained that the local reaction is not a side effect but is, instead, an indication that the drug is eliciting a therapeutic response.

Multicenter, phase III, open-label, follow-up studies are currently under way in Europe to assess the long-term benefits of imiquimod in superficial BCC. The enrollment criteria were identical to those of the US phase III studies. The dosage regimen of imiquimod called for applications of imiquimod 5% once daily 5 days per week for 6 weeks. At the 12-week posttreatment follow-up assessment, 90% of subjects had clinical clearance at the tumor site.[11] At the 12-month assessment, 92.7% of those who had had clinical clearance of their tumors at the 12-week evaluation remained clinically clear.

To summarize the recent clinical evidence, imiquimod 5% applied once daily five times weekly for up to 6 weeks is an effective and well-tolerated topical treatment for small, superficial BCCs. The initial clearance rate that should be expected is 90%. Of these, 92% should have a sustained clearance at 1 year. Local skin reactions at the application site should be expected and is, in fact, correlated with a therapeutic benefit. Patients should be informed about the significance of these self-limited responses to imiquimod therapy.

Conclusion

As a treatment for small, superficial BCCs, imiquimod is associated with a high clearance rate and a sustained effect. It is a well-tolerated, noninvasive new treatment option that offers patients a long-term effect with a good cosmetic outcome. ■

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The Emerging Potential of Immune Response Modifier Therapy

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ized by the accumulation of neoplastic T lymphocytes in the skin), and lentigo maligna (an in situ melanocytic neoplasm). Further research in carefully controlled clinical trials is required to determine whether IRM treatment is beneficial in patients with these tumors.

Conclusion

Imiquimod is an effective and well-tolerated topical treatment for AKs that has the advantage of enabling field therapy of large areas of photodamaged skin. The potential of IRM therapy also is being investigated in other dermatologic diseases, including mycosis fungoides, other types of cutaneous T-cell lymphomas, and lentigo maligna. ■

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Illuminating the Mode of Action of Immune Response Modifier Therapy in Superficial Skin Cancers

Professor Dr med Eggert Stockfleth

The new family of drugs, immune response modifiers (IRMs), offers a novel way to treat certain superficial nonmelanoma skin cancers (NMSCs). Until relatively recently, it was not completely understood how IRMs worked in treating NMSCs. However, research has demonstrated several ways in which IRMs work in patients with these tumors.

Field Cancerization

One critical area of research has demonstrated an important discovery in skin cancer—that is, the appreciation that actinic keratosis (AK), now recognized as squamous cell carcinoma (SCC) in situ, never occurs as a single tumor. Instead, AKs develop in a sun-damaged area of skin, or "field." As biopsies of such fields have shown, an area that is chronically sun-damaged and that shows any histologic signs of carcinoma in situ will demonstrate these changes at multiple sites in that same field. Thus, the concept of "field cancerization" was proposed and is becoming more widely recognized.

This discovery has led to a new concept of treatment of AKs. Rather than focusing on destroying individual, visible lesions, clinicians are becoming increasingly aware that these lesions represent only an indication of the presence of disease. Instead, the focus is shifting toward field therapy, so that both visible and subclinical lesions can be treated.

Role of the Immune System in AK/SCC

It is now commonly known and understood that a major contributor to the development of AK/SCC is exposure to both ultraviolet (UV)-A and UVB light. Human cells contain several suppressor genes that normally help the body resist malignant changes that can result from UVA and UVB exposure. However, it has long been clear that other factors must be involved in the epithelial changes that result in malignancy, as well as in the prevention of malignancy.

Among the first findings was the discovery of tumor suppressor genes. The most important of these identified to date is the p53 gene, which first appears in the very earliest stage of AK development (stage I). When the p53 gene is functional, it can clear the tumor or initiate the process of programmed cell death, apoptosis (**Figure**).[1] Research to identify other tumor suppressor genes continues, but p53, *ras*, and p16 mutations, along with four other genes, have been identified in stage II and stage III AKs.

How Does IRM Treatment Work?

Experience with populations of immunocompromised patients—particularly those who have undergone organ transplantation—has demonstrated sharp increases in the incidence of both viral diseases and skin tumors.[1] Studies in immunocompromised populations and patients with normal immune function have shown that IRM treatment stimulates both the innate and the adaptive immune responses and stimulates both antiviral and antitumor activity.[2,3]

Stimulation of the innate and adaptive immune responses reverses the UV-induced immunosuppression association with the development and progression of skin cancers. This enables the immune system to recognize and clear skin tumor cells. Stimulation of the cell-mediated immune response is also important in the recognition and destruction of epithelial cells infected with viruses. In addition, cell-mediated immune response activation is associated with immune memory.

Studies with the IRM imiquimod have shown that IRM therapy stimulates the innate immune response through the induction, synthesis, and release of a number of cytokines, including interferon (IFN)-α, interleukin (IL)-1, IL-6, IL-12, and tumor necrosis factor-α. Effects on the cell-mediated adaptive immune response are associated with the induction of T-cell cytokines and activation of Langerhans' cells, the major antigen-presenting cells of the epidermis.

Imiquimod also has been shown to induce apoptosis in certain skin cancer

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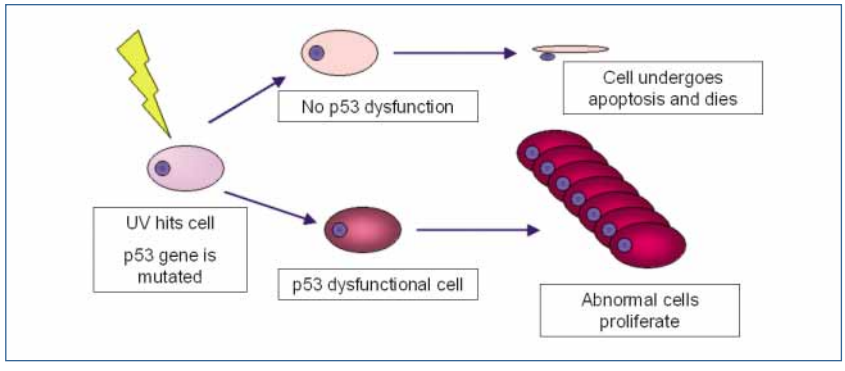
FIGURE. Apoptosis and p53



Functional p53 genes can clear tumors or initiate the process of programmed cell death known as apoptosis. Other tumor suppressor genes also have been identified.

Source: Courtesy of Professor Dr med Eggert Stockfleth

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which allows three-dimensional visualization of excised tissue margins, is proving to be helpful during these procedures.

Classifications of AK/SCC

For several years, the definition of AK as SCC in situ has been gaining recognition. It is now clear that, like invasive SCC, AK is a malignant tumor of keratinocytes, not a "precancerous lesion," as once was believed. As an early development along the spectrum of SCC, AK must be treated. More than 80% of SCC tumors are of the actinic type—that is, arising from AK lesions. Other types of SCC include Bowen's disease (SCC in situ), bowenoid papulosis (induced by human papillomavirus), verrucous SCC (for example, epithelioma cuiculatum), keratoacanthoma (also known as SCC of the infundibular type), and proliferating tricholemmal cyst-type SCC.

Morphologic and histologic evidence has been used to update the classification of AK as SCC in situ. First, clinical observation and histopathologic evidence have shown that SCCs on sun-damaged skin are nearly 100% contiguous with AKs. By implication, SCCs arise from AKs. Further, no conversion or transformation has been demonstrated in the progression of AK to SCC; it is a continuous process. In addition, although the prevailing thinking once was that AKs could spontaneously regress, no compelling evidence exists demonstrating that this is so.

The second line of evidence linking AK and SCC is that AKs fulfill all the histopathologic criteria for SCC, which occurs in three stages. The first stage is characterized by crowding of nuclei, some of which show hyperchromatic features, and occasionally pleomorphic features. Stage II is characterized by pleomorphic features, as well as the appearance of mitotic features. In stage III, the entire epidermis is involved.

Finally, a clonal relationship exists between AK and SCC, demonstrated by frequently shared chromosomal aberrations.

Conclusion

Advances in histopathology research have demonstrated that, in BCC, the most important prognostic factors are thickness, size, histologic type, and the presence or absence of perineural infiltration. Immunomodulating agents are appropriate therapy for patients with superficial (including superficial nodular) BCC. In AK/SCC, research has shown compelling histopathologic evidence that AK lesions are SCC in situ. ■

Immune Response Modifier Therapy

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cells, but not in normal human keratinocytes. These findings suggest that induction of apoptotic processes may be another aspect of imiquimod's mode of action in eliminating virus-infected, dysplastic, or neoplastic epithelial cells. Within hours of application of imiquimod to the skin, cytokines are induced by the Langerhans' cells.[4] Cytokines are responsible for an increase in the T-helper type 1 (T_H1) response.

However, the most important finding in the area of IRM mode of action concerns the discovery, within the past 2 years, that imiquimod binds a special receptor called a "toll-like receptor."[5] These are signal-transducing pattern-recognition receptors located on the surface of effector cells of the innate immunity system. Their function is to identify pathogen-associated molecular patterns (that is, lipopolysaccharides of gram-negative bacteria).

To date, 14 of these toll-like receptors have been identified, and it has been demonstrated that IRMs—imiquimod and resiquimod—are the first and only drugs to date that have been developed that bind to toll-like receptors—specifically, toll-like receptors 7 and 8.[6]

To summarize how imiquimod works, it increases an individual's local immune system through binding toll-like receptors of the antigen-presenting cells. Those antigen-presenting cells are responsible for the expression of cytokines that increase the T_H1 response and, therefore, for increasing the cellular immune response. At the same time, imiquimod stimulates expression of IFN-α from the antigen-presenting cells, thereby blocking the T-helper type 2 cell pathway.

Further research also may demonstrate that imiquimod could directly induce apoptosis through the toll-like receptors, in addition to acting on the classical apoptosis pathways, caspase-3 and caspase-8.

Conclusion

IRMs—as exemplified by imiquimod, the first drug developed in this class—work against both tumor activity and viral infections. The mode of action is an increase in the local cellular immune system, the result of activating both innate and adaptive immunity. Imiquimod combines the very early innate immune response with the adaptive cell-mediated immune response (the so-called "late response").

In the future, IRMs may be shown to be useful oral therapy in patients with hepatitis infections and, because the IRM agent studied to date has been shown to be a very good antigen-presenter, it may prove to be an adjuvant for vaccination. ■

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