

Dermatology

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Introduction

Dermatology continues to develop at a steady pace. In the past few years there have been exciting advances in our understanding of skin structure and function in health and disease and progress in genetics, epidemiology, immunology, pharmacology and clinical dermatology that have led to new approaches for managing skin diseases. This article will discuss a number of recent advances including treatments that have entered clinical practice recently or are likely to do so soon and have an impact on dermatological practice in years to come. Issues likely to be of interest to a general medical audience are emphasised.

The desmoglein story

Clinical features of most diseases are complex but become easier to understand when underlying molecular mechanisms are clarified. A recent publication¹ beautifully reviews the advances in our understanding of skin structure that have led to elucidation of the mechanisms of blister formation in two well known conditions – pemphigus foliaceus (PF) and staphylococcal scalded skin syndrome (SSSS). In both these diseases the pathological target appears to be the cutaneous desmosome. Desmosomes are the major type of intercellular adhesive junction responsible for holding individual cells together and are distributed widely in the skin and other tissues that experience mechanical stress. Desmosomes contain two essential transmembrane components: desmogleins and desmocollins. Desmoglein 1 is a cadherin type cell-cell adhesion molecule essential for maintaining skin integrity. In PF IgG autoantibodies are developed against desmoglein 1 and inhibit its adhesive function with resultant blister formation in the superficial epidermis. In SSSS, exfoliative toxin is produced by

Staphylococcus aureus present at a distant focus e.g. pharynx, nose, ear or conjunctiva. This toxin enters the circulation and specifically binds and cleaves desmoglein 1. This results in generalised and rapidly progressing skin exfoliation with the split in the skin occurring at the same level as in PF. Bullous impetigo is essentially a localised form of SSSS in which *S aureus* is present in the lesions.

Melanoma aetiology and genetics

During the past several decades there has been a worrying increase in the incidence and number of deaths caused by cutaneous malignant melanoma (CMM) in most Caucasian populations throughout the world. There is convincing epidemiological evidence that the major environmental aetiological risk factor for development of CMM is sun exposure, particularly intermittent sun exposure and sunburn in childhood. It is clear however that sun exposure is not the only factor and other genetic and host factors are involved. The most important host risk factor for CMM in fair-skinned individuals is the presence of common acquired (especially when very numerous) as well as atypical (dysplastic) melanocytic naevi. It is well established that a family history of melanoma also confers increased risk and about 5-12% of patients with melanoma have a family history of CMM in one or more first-degree relatives.² Recent work has shown that in some of these patients the increased risk is due to inheritance of a mutation in highly penetrant melanoma susceptibility genes.³ To date, constitutional mutations have been identified in two melanoma susceptibility genes: CDKN2A (p16), located on chromosome 9 (9p21) and CDK4, located on chromosome 12 (12q13). Penetrance varies with melanoma population incidence rates with estimated penetrance of the CDKN2A mutation by the age of 50 years being 0.5 in the USA, 0.32 in Australia and 0.13 in Europe. Whether this knowledge could in future lead to genetic testing to identify those individuals at particular risk for melanoma remains to be seen.⁴

Pityriasis rosea and human herpesviruses 6 and 7

Pityriasis rosea has long been suspected to have an infective aetiology. Early suspicions about fungi, streptococci and spirochaetes have not been confirmed and most speculation now centres on a viral aetiology. Currently there is debate about the possible role of human herpesvirus 7 (HHV-7) and human

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herpesvirus 6 (HHV-6) in this condition. These two closely related beta-herpesviruses are usually acquired in early childhood (manifesting as exanthema subitum or other febrile illnesses resembling measles and rubella) and subsequently become latent and may reactivate in older children and adults. Although the presence of HHV-7 in skin, plasma and peripheral blood mononuclear cells from patients with pityriasis rosea was first reported in 1997,⁵ some subsequent studies produced conflicting results and it has been argued that the finding of HHV-7 may in any case merely reflect latent or quiescent infection of persisting virus rather than active infection. An important recent study⁶ however, has detected, for the first time by *in situ* hybridization, infiltrating mononuclear cells expressing HHV-7 mRNA and also HHV-6 mRNA in 100% and 75% of pityriasis rosea skin lesions, respectively, compared to only 13% of controls. In addition, HHV-7 and HHV-6 DNA were readily and consistently found in cell-free serum samples obtained from patients with pityriasis rosea. Expression of mRNA in lesional skin and the presence of viral DNA in cell-free serum imply active viral replication suggesting that pityriasis rosea is indeed associated with systemic active infection with both HHV-7 and HHV-6. However it is still unclear as to what exactly triggers its abrupt occurrence in a host harbouring both viruses since early childhood.

Imiquamod

Imiquamod is an immune response-modifying drug that represents a new approach to the treatment of skin diseases.⁷ Its activity was discovered while screening drugs for anti-herpes virus activity. While imiquamod exhibits no direct antiviral or antiproliferative activity when examined *in vitro* in cell culture systems, it has a potent stimulatory effect on the immune system *in vivo*. It induces local production of interferon-alpha and other cytokines, which in turn stimulate T-cell function, thereby enhancing innate and acquired cellular immunity. The drug is available in a cream base and has been shown to have significant antiviral and antitumour activity. Imiquamod has recently entered clinical practice and is being used to treat viral, especially genital, warts with encouraging results. Viral warts are caused by human papilloma virus (HPV) infection and are often resistant to conventional treatment such as cryotherapy, cautery and wart paints. In one study,⁸ imiquamod 5% cream applied three times per week for up to 16 weeks resulted in complete clearance of genital warts in 50% of patients. Clearance rates are higher in female patients and the treatment is easier to apply than conventional therapy. There is evidence that imiquamod, by stimulating cellular immunity, eliminates HPV itself.⁷ Other conditions for which imiquamod has been used successfully include actinic keratoses, Bowen's disease, basal cell carcinoma and other skin malignancies. Although surgical excision remains the primary management modality for basal cell carcinoma, if these results are confirmed, imiquamod will likely become an accepted option for cases where surgery or

other alternative treatments are not feasible. For the future it is hoped that by manipulating the immune response with imiquamod or similar drugs, it will be possible to treat a number of chronic skin conditions for which present treatments are unsatisfactory.

Biological therapies for psoriasis

Biological therapies modulate basic physiological processes and are being used increasingly in rheumatology and dermatology.^{9,10} The advent in the past few years of biological agents that selectively target components of the psoriatic process has also provided new insights in our understanding of the immune mechanisms underlying this disease.¹¹ The two main approaches for treating psoriasis with biological agents are T-cell targeting and cytokine modulation. Agents like alefacept and efalizumab inhibit T-cell activation via blockade of co-stimulatory molecules. Cytokine modulation is exemplified by strategies that target pro-inflammatory cytokines such as anti-TNF alpha e.g. infliximab and etanercept, or switching what is predominantly a Th1 cytokine disease to a Th2 disease with the use of interleukins 4 or 10. These agents may be combined with established antipsoriatic treatments such as methotrexate. Problems associated with biological therapies include high cost, inconvenience (require administration by injection), and side-effects of immunosuppression and infection. Nevertheless these agents provide new treatment options for severely affected patients and it is likely that their use will become more widespread in future.

Eczema: non-steroid topical immunomodulators

Atopic eczema is common, may be chronic and disabling and is frequently the first manifestation of the atopic predisposition that may progress to the development of asthma and allergic rhinitis - the so-called 'atopic march'.¹² The mainstay of treatment of eczema (and several other inflammatory dermatoses) has been topical steroids since their introduction in the 1950s. Unfortunately, their use may be associated with several hazards, particularly in children, including skin atrophy, hypothalamus-pituitary-adrenal axis suppression and growth retardation due to systemic absorption and cataracts and glaucoma with periocular application. A major advance in the past few years has been the advent of the topical calcineurin inhibitors tacrolimus and pimecrolimus. These promising drugs have been shown to be effective and safe treatments for eczema¹³ and represent a major new class of topical medication that not only complements existing treatment options but also overcomes some of the drawbacks of topical steroid therapy. They do not cause skin atrophy and may prevent disease progression. Their primary mechanism of action, which is distinct from and much more specific than that of topical corticosteroids, is to inhibit inflammatory cytokine transcription in activated T-cells through inhibition of calcineurin.¹⁴ Activity of these drugs has been demonstrated in other inflammatory

dermatoses apart from eczema including cutaneous lupus erythematosus, dermatomyositis, flexural psoriasis, bullous autoimmune diseases, chronic actinic dermatitis and polymorphic light eruption. Although topical calcineurin inhibitors are unlikely to replace topical corticosteroids completely, their use is likely to become widespread in dermatological practice in future.

Nuclear hormone receptors

Nuclear hormone receptors (NHRs) are a family of proteins whose function as nuclear transcription factors has become better appreciated in recent years.¹⁵ NHRs are widely expressed in the skin and include glucocorticoid, retinoic acid, vitamin D, thyroxine and peroxisome proliferator-activated receptors. NHR signalling profoundly affects keratinocyte proliferation, differentiation and inflammation in the skin. Animal and human studies have identified specific NHR signalling pathways and characterised the role of NHRs in various skin diseases. Not surprisingly, these proteins are targets of some of the most widely used drugs in dermatology. These include corticosteroids, vitamin D analogues e.g. calcipotriol and tacalcitol and retinoids e.g. tretinoin, isotretinoin and acitretin. These drugs are widely used in the treatment of skin diseases including eczema (corticosteroids), psoriasis (corticosteroids, vitamin D analogues and retinoids) and acne, disorders of keratinisation and photoageing (retinoids). Many of the side-effects of these drugs occur because of expression of NHRs in tissues other than the skin, multiple signalling pathways of individual NHRs and, in the case of retinoid receptors, formation of heterodimers that in turn interact with other NHRs. Further elucidation of these processes will likely lead to development of more specific NHR ligands including selective glucocorticoid receptor agonists and newer generations of retinoids that may prove to be more effective and better tolerated.

Botulinum toxin

Botulinum toxin type A (Botox) has been used successfully for a number of years in a range of neurological conditions including strabismus, blepharospasm, focal dystonias and spasticity associated with juvenile cerebral palsy and adult stroke. It is increasingly being used in aesthetic medicine to correct facial frown lines and wrinkles.¹⁶ Botox blocks the release of the neurotransmitter acetylcholine at the motor end plate with resultant muscle paralysis. The effect is reversible – the motor end plate is eventually reactivated and muscle function is restored. The action of botox usually lasts for a few months but varies between individuals and according to the type of toxin, the dose and the muscle injected. A more recent indication for botox is primary hyperhidrosis.¹⁷ This is a chronic idiopathic disorder that mainly affects the axillae, palms and soles. It may be a major disability and cause significant problems in both private and professional lives. The condition is difficult to manage and the treatments available until now – anticholinergic drugs, iontophoresis, excision/suction curettage of sweat glands

(axillary hyperhidrosis) and transthoracic endoscopic sympathectomy (palmar and axillary hyperhidrosis) are frequently ineffective, time consuming or associated with serious side-effects. When injected intradermally in the hyperhidrotic area botox blocks release of acetylcholine from overactive cholinergic sudomotor nerve fibres that innervate eccrine sweat glands and hence excessive sweating is reduced. Published studies have shown significant reductions in sweating following treatment with botox.¹⁸ Disadvantages of the technique include the high cost of the drug, discomfort of injection (local nerve block anaesthesia required to treat the palms), transient weakness in nearby muscles due to diffusion of the toxin (e.g. in the small hand muscles after treating the palms) and the need to repeat treatment periodically, usually every few months.

Lasers for cutaneous vascular lesions

Laser (light amplification by stimulated emission of radiation) technology for treating cutaneous vascular lesions has progressed rapidly in the past few years.¹⁹ Treatment is based on the principle of selective photothermolysis whereby laser parameters (wavelength, pulse duration and fluence) are tailored for specific cutaneous applications to effect maximum target destruction with minimal collateral thermal damage. The pulsed dye laser has revolutionised the treatment of cutaneous vascular lesions including port-wine stains, spider angiomas and telangiectases and has a low risk profile. Small lesions can usually be totally eliminated after a number of treatment sessions; large port-wine stains respond less completely but in most cases it is possible to produce major cosmetic improvement. Although recent reports suggest that a minority of port-wine stains may recur after successful laser treatment, further laser treatment may still be performed in these cases. Recent developments include lasers with longer wavelengths and pulse durations (1.5-40 milliseconds) and dynamic cooling techniques that deliver a spurt of cryogen to the treated area immediately before each laser pulse to protect the epidermis from thermal injury and reduce discomfort; this allows safe use of higher and more effective laser energy fluences. Thick/raised lesions respond less well because laser light does not penetrate deep enough to cover the whole lesion and the target vessels are too large for effective photothermolysis; response may be enhanced if the lesion is compressed with clear plastic during treatment.²⁰ This simple, recently-described technique presumably reduces the thickness of the lesion, bringing deeper blood vessels closer to the surface and hence within range for laser destruction and reduces the diameter of target blood vessels and vascular spaces to one that is more suitable for photothermolysis.

Antibiotic resistance in dermatology

Increasing resistance to commonly used antibiotics is an unfortunate reality of modern medicine. A recent publication²¹ highlights the problem of antibiotic resistance in dermatological

practice and serves as a useful reminder about the importance of using antibiotics correctly. In this study bacterial isolates from 148 patients with leg ulcers and/or superficial wounds admitted to a tertiary care dermatology inpatient unit in the United States in 2001 were analysed. *Staphylococcus aureus* and *pseudomonas aeruginosa* were the most common bacteria cultured. Seventy-five per cent of *S aureus* isolates cultured from leg ulcers and 44% of those from superficial wounds were methicillin-resistant. Fifty-six per cent of *P aeruginosa* isolates from leg ulcers and 18% of those from superficial wounds were resistant to quinolones. These figures represent a major increase in antibiotic resistance rates when compared to results of a similar survey done in the same unit in 1992. The authors discuss general measures to deal with the problem of antibiotic resistance. These include instituting more effective infection control practices, decreasing nasal colonisation, development of vaccines and development of new or improved antimicrobial agents. Above all the authors emphasise the importance of avoiding indiscriminate use of antibiotics and prescribing them only when strictly indicated and according to local sensitivity data.

The importance of looking beyond the skin. Brachioradial pruritus: a symptom of neuropathy

It is well known that certain skin changes may be associated with or sometimes predate important underlying medical conditions. Recognition of the skin abnormality may be a significant aid to the diagnosis of the associated condition. Brachioradial pruritus, a curious condition characterised by itching localised to the dorsolateral aspect of the arms without any obvious skin eruption, is a case in point. The condition is often considered to be a photodermatosis as, in some patients, it presents or worsens following summer sun exposure. However it may persist throughout the year, the face is not affected and it is rare in childhood, features that have prompted the suspicion that it could be due to compression of cervical nerve roots. In an elegant study published recently,²² seven consecutive patients with brachioradial pruritus underwent detailed electrophysiological studies of the median, ulnar and radial nerves in both upper limbs. Four patients had bilateral delay of the F responses of the median and ulnar nerves, considered diagnostic of cervical radiculopathy. These findings support previous work where clinical examination (pinprick and temperature) detected signs of neuropathy in some patients with brachioradial pruritus. The authors postulate that, whereas cervical nerve root compression commonly causes *pain* radiating from the neck extending to the arms, in some patients it causes *pruritus*. Although the concept of pruritus being a mild variant of pain is not new, there is as yet no satisfactory explanation for the neural differentiation between itch and pain. The authors conclude that in patients with brachioradial

pruritus an underlying neuropathy should be considered and, if detected, further neurological or orthopaedic assessment may be indicated.

References

1. Amagai M. Desmoglein as a target in autoimmunity and infection. *J Am Acad Dermatol* 2003;48:244-52.
2. Goldstein AM, Tucker MA. Genetic epidemiology of cutaneous melanoma. A global perspective. *Arch Dermatol* 2001;137:1493-6.
3. Bishop DT, Demenias F, Goldstein AM *et al*. Geographical variation in the penetrance of CDKN2A mutations for melanoma. *J Natl Cancer Inst* 2002;94:894-903.
4. Kefford RF, Mann GJ. Is there a role for genetic testing in patients with melanoma? *Current Opinion in Oncology* 2003;15:157-61.
5. Drago F, Ranieri E, Malaguti F, Battifoglio ML, Losi E, Rebori A. Human herpesvirus 7 in patients with pityriasis rosea: electron microscopy investigations and polymerase chain reaction in mononuclear cells, plasma and skin. *Dermatology* 1997; 195:374-8.
6. Watanabe T, Kawamura T, Jacob SE, Aquilino EA, Orenstein JM, Black JB, Blauvelt A. Pityriasis rosea is associated with systemic active infection with both human herpesvirus-7 and human herpesvirus-6. *J Invest Dermatol* 2002;119:793-7.
7. Eedy DJ. Imiquimod: a potential role in dermatology? *Br J Dermatol* 2002;147:1-6.
8. Sauder DN, Skinner RB, Fox TL, Owens ML. Topical imiquimod 5% cream as an effective treatment for external genital and perianal warts in different patient populations. *Sex Transm Dis* 2003;30:124-8.
9. Mehlis SL, Gordon KB. The immunology of psoriasis and biologic immunotherapy. *J Am Acad Dermatol* 2003;49(Suppl 2):S44-50.
10. Gordon KB, McCormick TS. Evolution of biologic therapies for the treatment of psoriasis. *Skinmed* 2003;2:286-94.
11. Griffiths CE. The immunological basis of psoriasis. *J Eur Acad Dermatol Venereol* 2003;17 Suppl 2:1-5
12. Leung DY, Bieber T. Atopic dermatitis. *Lancet* 2003;361:151-60.
13. Nghiem P, Pearson G, Langley RG. Tacrolimus and pimecrolimus: from clever prokaryotes to inhibiting calcineurin and treating atopic dermatitis. *J Am Acad Dermatol* 2002;46:228-41.
14. Reynolds NJ, Al-Daraji WI. Calcineurin inhibitors and sirolimus: mechanisms of action and applications in dermatology. *Clin Exp Dermatol* 2002;27:555-61
15. Winterfield L, Cather J, Cather J, Menter A. Changing paradigms in dermatology: nuclear hormone receptors. *Clinics in Dermatology* 2003;21:447-54
16. Said S, Meshkinpour A, Carruthers A, Carruthers J. Botulinum toxin A: its expanding role in dermatology and esthetics. *Am J Clin Dermatol* 2003;4:609-16.
17. Lauchli S, Burg G. Treatment of hyperhidrosis with botulinum toxin A. *Skin Therapy Lett.* 2003;8:1-4.
18. Lowe NJ, Yamauchi PS, Lask GP, Patnaik R, Iyer S. Efficacy and safety of botulinum toxin type a in the treatment of palmar hyperhidrosis: a double-blind, randomized, placebo-controlled study. *Dermatol Surg* 2002;28:822-7.
19. Tanzi EL, Lupton JR, Alster TS. Lasers in dermatology: four decades of progress. *J Am Acad Dermatol* 2003;49:1-31.
20. Boffa MJ. Pulsed dye laser treatment of thick/raised vascular lesions using compression with clear plastic. *J Am Acad Dermatol* 2003;49:879-81
21. Valencia IC, Kirsner RS, Kerdel FA. Microbiologic evaluation of skin wounds: Alarming trend toward antibiotic resistance in an inpatient dermatology service during a 10-year period. *J Am Acad Dermatol* 2004;50:845-9.
22. Cohen AD, Masalha R, Medvedovsky E, Vardy DA. Brachioradial pruritus: a symptom of neuropathy. *J Am Acad Dermatol* 2003;48:825-8