Dermatological discovery: the frontiers between genetics, pharmacology and the patient

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ABSTRACT Advances in the fields of genetics and pharmacology and the understanding of disease mechanisms have occurred apace in recent years in dermatology. As the pathophysiology of skin diseases become clearer, treatments have become more focused and effective, but new treatments bring new side-effect profiles and further considerations for the prescribing physician. The diagnostics of skin disease have also progressed and the role of automated systems in the recognition of skin lesions is being explored. Integration of new knowledge and old is a challenge to the modern physician treating patients with dermatological disease.

Published online ***September 2009***

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DECLARATION OF INTERESTS No conflict of interests declared.

SESSION 1 WHAT IS DIFFERENT IN 2009 FROM 1999?
SESSION 2 COMPLEX? NO, MENDEL IS JUST RATHER SUBTLE…

Professor Colin Munro (Honorary Professor of Dermatology, University of Glasgow, and Consultant Dermatologist, Southern General Hospital, Glasgow) opened the symposium with the provocative question: 'We've found the gene! So what?' There are a number of single-gene dermatological disorders which demonstrate that an understanding of the genetic basis of a disease does not automatically translate into an understanding of how the phenotype is produced; nor does it necessarily lead to the development of successful treatment for that disease.[1] Gene therapy in dermatology is in its infancy, and requires imaginative approaches to drug delivery.

Hailey-Hailey disease (benign familial pemphigus) is an inherited blistering disease of flexural sites linked to mutations in a calcium-dependent pump in the membrane of the endoplasmic reticulum. Approximately 20% of sufferers have a base substitution mutation that causes a premature stop condon. A stop condon is analogous to a bent tooth on a zip, which prevents the mRNA being translated into its protein product. Recent studies have found that aminoglycosides have the innate potential to 'fix' such disruptions in translation. Kellermayer et al. investigated the therapeutic potential of the topical aminoglycoside antibiotic gentamicin applied to affected skin in Hailey-Hailey disease, and found a gratifyingly beneficial effect,[2] illustrating a simple form of gene therapy. The state of gene therapy in dermatological disease is perhaps best summarised by a quote from Sir Mark Walport, Chief Executive of the Wellcome Trust: 'Not much just yet – give us another 10 years.'

Professor Chris Griffith (Professor of Dermatology, University of Manchester) discussed how the advent of biological therapies has marked one of the biggest changes in dermatology since 1999. Since Robert Willan's first accurate description of psoriasis in 1808, the concept of psoriasis as a disease affecting only the skin has progressed to the present-day understanding of psoriasis as a chronic systemic inflammatory disease.[3]

Following the initial excitement of, in some cases miraculous, therapeutic success, the reality of progressive treatment failures on biological agents has become apparent. 'Rotational therapy' (in which different agents are prescribed sequentially) as a means of limiting side effects and prolonging disease remission has become popular. The recent withdrawal from the market of efalizumab, a recombinant humanised monoclonal antibody that binds to the CD11a subunit, followed reports of the development of progressive multifocal leukoencephalopathy (PML) in a small number of patients taking this drug[5] and demonstrates that careful monitoring of patients on novel treatment is required. A national registry of patients on biological agents for dermatological conditions has been established and will hopefully aid in the early detection of side effects. Participation in the registry should form an essential part of clinical governance of any specialist clinic managing patients on biological therapies.[6]

Professor Eugene Healy (Professor of Dermatology, University of Southampton) addressed the issue of topical drug delivery. The '500 dalton hypothesis' governing the accepted maximum size of molecule able to enter the skin via the epidermis depends on the 'intactness' of the stratum corneum. Novel drug delivery patches incorporating spicules that act as microcatheters allowing drugs to pass more readily into the skin, have

not been successful. Another method of improving drug delivery has focused on the development of cell-penetrable peptides to deliver compounds into the skin.[7,8] These can be designed to carry a variety of cargo molecules such as proteins, short interrupted ribonucleic acid (RNA) molecules and, of therapeutic importance, drugs. In a series of experiments involving the conjugation of a prototype carrier peptide, polypseudolysine, to melanocyte-stimulating hormone (MSH), Professor Healy's group has demonstrated enhanced delivery of the cargo to the target cell, in this case the keratinocyte, without increased cytotoxicity. Targeted drug delivery will allow us to achieve effective treatment with fewer side effects on 'bystander' organs.

A scientific story that captured the headlines in recent years was the discovery of 'the gene for eczema',[9] an oversimplification of the discovery of filaggrin, a filament aggregating protein essential for maintaining the barrier function of the skin. This research was headed by Professor Irvine McLean, of the Division of Molecular Medicine, University of Dundee, who addressed the symposium. Mutations in the filaggrin gene predispose the individual to dry, flaky skin, and to the development of atopic disease, chiefly atopic dermatitis (AD).[10] According to one study, one in 90 British Caucasians is homozygous for filaggrin mutations and therefore make no filaggrin. Such individuals have severe ichthyosis vulgaris and have a very high risk of developing AD. As AD is a polygenic trait, it is possible to suffer from AD without having any filaggrin mutations; however, filaggrin-associated AD tends to be earlier in onset, is more likely to be associated with other atopic disease such as asthma and is more resistant to treatment.[11] The therapeutic potential of topical aminoglycosides in 'rescuing' nonsense mutations in the filaggrin gene is showing promise in experimental settings.

THE STANLEY DAVIDSON LECTURE

Drawing on a distinguished career in research and clinical work in the field of bullous disorders, Professor Leena Bruckner-Tuderman, Professor of Dermatology and Venereology at the University of Freiburg, reported many interesting observations on inherited blistering diseases. The dermoepidermal junction (DEJ) is a complex structure well characterised at a molecular level, but few therapeutic measures have yet been designed to take advantage of this ultrastructural knowledge, and considerable genotype-phenotype discrepancy has yet to be explained.

Professor Bruckner-Tuderman illustrated this genotype-phenotype discrepancy of blistering disease with reference to two specific diseases, dystrophic epidermolysis bullosa (EB), in which the individual has a mutation in the Col7A1 gene coding for production of collagen VII, and Kindler syndrome, in which a mutation in the KIND1 gene leads to absence of Kindlin 1, a component of the upper part of the DEJ complex.[13] Although these two proteins have different locations in the DEJ, collagen VII being infra-basal, and Kindlin 1 being supra-basal, their clinical manifestations are very similar, characterised by epidermal atrophy and dermal fibrosis. Both conditions predispose the individual to the development of squamous cell carcinoma in the scarred tissue.

The malignant potential of these diseases has focused attention on the possibility of gene therapy as a means of treating patients, who at present rely on careful monitoring as the only means of invasive skin cancer prevention.[14] Professor Bruckner-Tuderman's group demonstrated that murine fibroblasts (which produce collagen VII) could increase the levels of this protein in the skin by 10–40% when injected subcutaneously. Improved skin stability was detected clinically for three to four months, after which time levels of collagen VII fell to pre-treatment levels, and severe skin fragility again became evident clinically. This experiment showed the potential of in vivo cell transfer to alter the management of and quality of life for these patients by a huge order of magnitude.

SESSION 3 MORE THAN SKIN DEEP: LOOKING AT THE WHOLE PATIENT

The afternoon session opened with a broad review of the management of AD by Professor Nick Reynolds (Professor of Dermatology, University of Newcastle upon Tyne), commencing with a discussion of the importance of holistic care of patients suffering from the most severe forms of AD, with an emphasis on recognising the aspects of management that depart from the skin and the prescription pad. He cited two memorable examples – firstly, the neurocognitive impairment suffered by children who have sleep continuously disturbed by itch[15] and, secondly, the question of compliance with topical treatment, estimated to be only in the region of 40%.[16] The detection of these issues is integral to the management of the AD patient, with specialist nurses playing an important role.

Professor Reynolds commended the use of the Symptom, Area and Severity Score in Atopic Dermatitis (SASSAD) as a means of recording quantitatively a patient's response to treatment.[17] The evidence base for the major treatments for AD has become stronger in recent years.[18,19] While the specialist may often treat with systemic agents, the contribution of the topical calcineurin inhibitors (tacrolimus, pimecrolimus) to the management of AD has been felt more widely, impacting upon community management of the disease as well as that in secondary care. With concerns about the deleterious side effects of prolonged use of topical steroids, a meta-analysis provided reassurance that tacrolimus is equivalent in effect to potent topical steroids, without the side-effect profile of the latter.[20] However, there is a

paucity of data comparing the topical calcinuerin inhibitors to milder topical steroids and, with considerable cost implications of these newer topical agents, their place in the market remains unclear.

Dr Neil Cox (Consultant Dermatologist, Cumberland Infirmary, Carlisle) gave a practical guide to the management of acute skin infections. The 'red leg' is a common presenting complaint to the general physician, and a broader differential diagnosis than infective cellulitis should be considered: venous eczema, contact dermatitis, Lyme borreliosis and, more rarely, eosinophilic cellulitis. Of the risk factors for infective cellulitis, perhaps the one most commonly overlooked by general physicians is the potential for tinea pedis to create portals of entry for infection; fungus in the webspaces should always be sought out.

Drug eruptions are among the most common dermatological presentation found on general medical wards. Maculopapular rashes represent one end of the spectrum of drug eruptions, but more severe drug reactions in the skin which have a high mortality may also occur. These include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug eruption with systemic symptoms (DRESS) and acute generalised exanthemous pustulosis (AGEP). Characterisation of these rare diseases has been difficult, but with the advent of the Register of Severe Cutaneous Adverse Reactions (RegiSCAR), the collation of experience from multiple European centres has become possible. Professor Jean-Claude Roujeau of the University Hospital Henri Mondor, Creteil, Paris, discussed the work of the Register and the information which has been gathered thus far. For example, allopurinol is the most common precipitant of SJS/TEN.[21] Other agents reported commonly on the registry included sulphonamides, carbamazepine and barbiturates as well as newer agents in epilepsy and pain management, such as lamotrigine, and antiretrovirals, such as nevirapine. Non drug-related episodes of SJS/TEN entered in the registry, such as those linked to mycoplasma or klebsiella pneumonia, or acute graft versus host disease account for a much smaller proportion of the overall number of cases, less than 20%.

Under the session banner of 'Some difficult tasks remain', Professor Jonathan Rees (Professor of Dermatology, University of Edinburgh) led the audience back from the realms of treatment to that of diagnostics. Speaking on the topic of automated diagnostic systems for skin disease, Professor Rees described how facial recognition technology has developed in security, military forces and the recreational games industry.[22,23] Meanwhile, efforts in medicine to develop analogous systems to recognise skin cancers have encountered both organisational and economic resistance. The case for developing such technology is underpinned by the reasoning that expertise is expensive and unevenly distributed. Given that the average GP sees about 200,000 benign lesions for every melanoma, it is unsurprising that GPs are not expert melanoma diagnosticians. The role of automated recognition systems for skin lesions has yet to be fully explored; this will require the creation of a large database of images against which algorithms can be tested. This forms part of the work of Professor Rees's group.

The symposium was concluded with an excellent presentation on the topic 'Do we really understand atopic dermatitis?', the answer implicit in the question being 'no'. Despite considerable milestones being reached in the management of atopic disease, such as the advent of the pollen skin test in 1873, the discovery of topical corticosteroids in 1946 and the elucidation of the role of filaggrin in 2007, we know little about the interplay between atopy, allergy and infection, although it is known that AD sufferers have staphylococcal carriage rates more than twice that of non-atopic individuals (79% vs 30%). Antibiotics can have a beneficial effect in acute disease flares independent of topical steroid and emollient use. Staphylococcal protein enhances keratinocyte presentation of allergen to T cells;[24] this observation lends some justification to the current practice of attempting to eradicate staphylococcal carriage in atopic patients. The possible role for vaccination against *Staphylococcus aureus* is one of the therapeutic implications for the future.

CONCLUSION

There is little doubt that much progress has been made in the understanding of dermatological disease in the past decade. However, translating this into meaningful improvements in treatment has proved more challenging, and the task for present-day and future researchers will be to bring bench discovery to the bedside.

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