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SKIN DEEP: REPORT FROM THE ANNUAL MEETING OF THE BRITISH SOCIETY FOR INVESTIGATIVE DERMATOLOGY

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Skin cancer is arguably the most common form of cancer worldwide encompassing an enormous range of morbidity and mortality. Yet due to its unique anatomical position it offers an exceptional opportunity for early diagnosis, treatment, follow up and scientific exploration. Lessons learnt from these easily discovered and accessible neoplasms help to illuminate further research and facilitate shortcuts in the comprehension of carcinogenesis, treatment and prevention of other types of malignancies.

The latest ideas on the skin cancer front were presented at The British Society for Investigative Dermatology annual meeting, which took place in the University of Nottingham on 16–18th April of 2007. It brought together clinicians and academic research staff from the United Kingdom, Europe and the North America. Energetic discussions took place; fundamental research was symbiotically complemented by its translational aspects. One fifth of presentations were dedicated to carcinogenesis, tumour surveillance, cancer diagnosis and treatment; here we will reflect on some of these.

In his lecture *Professor S.E. Ullrich* outlined current understanding of the mechanisms of systemic immunosuppression caused by sunlight. In addition to its direct carcinogenic effects, sunlight also exerts systemic immunosuppressive effect, which can be demonstrated by suppression of the delayed type of hypersensitivity elicited on the non-irradiated side of the body. Suggested mediators of such immunosuppression include interleukin 4, interleukin 10, platelet activating factor and *cis*-urocanic acid [1]. Following ultraviolet irradiation, trans-urocanic acid, present in skin, acts as photoreceptor and isomerizes into the *cis* isomer, probably representing the very first steps in the chain of immunosuppression. More recently it has been shown that *cis*-urocanic acid exerts its immunosuppressive effect via the serotonin receptor [2]. Platelet activating factor is also induced upon ultraviolet irradiation and may cause potent immunosuppression [3]. Professor S.E. Ullrich presented exciting data on synergistic effects of *cis*-urocanic acid and platelet activating factor in the induction of immunosuppression and squamous cell-like carcinomas in mice, following ultraviolet irradiation. Mast cells might to be intimately involved in these complex interactions. Intriguingly, the treatment with *cis*-urocanic acid and platelet activating factor antagonists, initiated after irradiation, appears to reduce number of subsequently developing tumors, suggesting a therapeutic approach.

Cutaneous squamous cell carcinomas (SCCs) are the second most commonly diagnosed cancers in white-skinned populations. *Dr K. Purdie* analysed human primary and metastatic SCCs with the aid of single nucleotide polymorphisms microarray analysis. According to the presented data the protein tyrosine phosphatase receptor type D was identified as a novel candidate tumour suppressor gene for cutaneous SCCs, possibly associated with metastasis. Recessive dystrophic epidermolysis bullosa (RDEB) is characterised by a mutation in the gene of type VII collagen and a frequent development of metastatic SCCs. Half of the patients with this genodermatosis die from metastatic SCCs by their forties. *Dr X. Mao*, using integrated genomic and transcriptomic studies, was able to identify distinct molecular signatures of SCCs derived from patients with RDEB and non epidermolysis bullosa patients. Furthermore, *Dr V.L. Martins* used an elegant organotypic culture model and COL7A1-transduced SCC cell lines, established from RDEB patients, to investigate whether type VII collagen levels might affect cancer cell migration and invasion. RNA interference blocked type VII collagen protein production and was associated with an increased cell motility and abnormal differentiation, as well as augmented metalloproteinase-2 expression.

Skin cancers and especially SCCs are a significant therapeutic challenge for patients with organ transplantation. In a prospective study *Dr A. Lally* examined 308 patients with renal transplant and found that patients with seborrheic warts but not other benign cutaneous changes were more likely to develop SCCs (adjusted for confounding factors odd ratio 3.67, $p = 0.001$). It has been therefore suggested that seborrheic warts and SCCs may share a common, for instance, viral aetiology. *Dr R.F.L. O'Shaughnessy* showed that the early genes of high-risk human papilloma virus 8, unexpectedly, downregulated serine phosporylated Akt1 expression but upregulated Akt2 expression; the latter correlated with the severity of cutaneous neoplasms. A Cochrane systematic review showed that acitretin and retinol but not isotretinoin or selenium can be used to reduce risk of the deve-

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Abbreviations used: RDEB – recessive dystrophic epidermolysis bullosa; SCCs – cutaneous squamous cell carcinoma.

lopment of non melanoma skin cancers in high risk patients (*Dr F. Bath-Hextall*).

Keratinocytes can process and present endogenous and exogenous antigens to CD4 and CD8 T cells (*Dr A.P. Black*). This is in line with the generic ability of epithelial cells to interact with and present antigens to T lymphocytes [4]. RANK molecule and its ligand, members of the tumours necrosis factor superfamily signalling pathway, play an important role in the crosstalk of antigen presenting and T cells [5]. *Dr J-B.O. Barbaroux* demonstrated that these molecules were expressed by keratinocytes and could protect them from apoptosis. Furthermore, actinic keratosis and basal cell carcinomas showed an increased and dysregulated expression of RANK and its ligand. It remains to be seen whether RANK pathway is involved into SCC pathogenesis as well as interaction between tumour and immunocompetent cells following stimulation with such immune modulators as imiquimod.

Malignant melanomas are responsible for annual death till of 2000 in the UK alone, with over 8000 new cases diagnosed each year in the UK [6]. Although these neoplasms are often curable, if detected early, they are extremely hard to treat, once metastasised [7]. This is thought to be related, at least in part, to the resistance of melanomas to apoptosis. There is, therefore, a significant interest in inducing apoptosis in melanoma cells by targeting endoplasmic reticulum stress. Therapeutic agents, targeting endoplasmic reticulum stress, can induce apoptosis of the malignant cells while not affecting normal melanocytes (*Dr P. Lovat*). However, melanoma cells can use protein disulphide isomerase family mediated mechanisms to clear unfolded proteins and protect themselves against endoplasmic reticulum stress. In a novel approach, *Dr P. Lovat* demonstrated that combination of endoplasmic reticulum stress inducing agents, such as fenretinide or velcade, with protein disulphide isomerase inhibitor bacitracin, exerted a synergistic effect on the induction of apoptosis in melanoma cells, without causing an increased toxicity on normal melanocytes.

Seventy percent of melanomas demonstrate mutated B-RAF kinase. Such mutation may activate extracellular signal-regulated kinase and increase tumour survival [7]. Using RNA interference-mediated knockdown of B-RAF^{v600E} in B-RAF-mutated melanoma cells, *Dr D.S. Hill* tested the hypothesis whether mutation of B-RAF protected melanoma cells from apoptosis by means of the activation of inhibitor of apoptosis proteins. His group was able to show that knockdown of B-RAF^{v600E} downregulated inhibitor of apoptosis proteins and increased susceptibility of the melanoma cells to induction of apoptosis by agents inducing endoplasmic reticulum stress (fenretinide or velcade). It would be tantalising to see whether the combination of these two approaches would lead to a long-awaiting breakthrough in the treatment of metastatic malignant melanomas.

In conclusion, this well organized meeting summarized the progress, achieved in carcinogenesis, treatment and prevention of cutaneous cancers to date, and outlined goals for future developments in this important area. We shall await the next annual meeting with impatient anticipation.

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