Meeting News

Dermatological Research 2005: Impressions from the 66th Annual Meeting of the Society for Investigative Dermatology

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This year, the annual Society for Investigative Dermatology (SID) meeting took place in St. Louis (Missouri, USA). In a 4-day scientific marathon nearly 1000 posters were presented and major advances discussed in 12 plenary lectures. Although I do not have the precise statistics, the majority of contributions were clearly from the USA, followed by Germany, Austria, Switzerland, South Korea and Japan. Sadly, only very few abstracts (I counted 6 in total) were from the dermatological departments in the Nordic countries.

Each SID meeting, this one included, has a characteristic profile reflecting current trends and fashions in dermatological research. For example, the 2003 meeting was dominated by the emerging biological therapies for psoriasis and malignant diseases. This year, when the leading research centres have assimilated the biological drugs as a part of the standard therapeutic armamentarium, the focus has shifted again; this time to the hard core of cutaneous research: the cellular and molecular biology of the skin. There was a particular emphasis on the understanding of the cellular pathology of skin diseases and search for novel therapeutic targets.

Search for the "master cytokines" in skin diseases

The enormous search speed allowed by the modern genomic and proteomic approach led to the discovery of multiple cytokines and lymphokines involved in the pathogenesis of skin diseases. With the current technology of gene arrays, one is able to simultaneously screen for the activity of over 12,000 genes in the diseased tissue. Taking psoriasis as an example, over 20 different soluble mediators have been implicated in its pathogenesis. *Jaques Banchereau* from Baylor Institute for Immunology (Dallas, TX) identified expression profile of 370 genes highly characteristic for SLE. The natural question is which of these should be approached as potential therapeutic targets? Fortunately, although many players are involved, only a few cytokines are in control of the whole pathogenic cascade. One that we already know about is TNFα. Anti-TNFα treatments have a tremendous effect in psoriasis and psoriasis arthritis. *Bharat Aggarwal*, the world leading TNF scientist (and the person who originally cloned TNFα) predicted the discovery of small molecules able to block TNFα function. He showed his data where screening of several hundred natural products yielded 3–4 interesting candidates. Another approach in TNF pharmacology is manipulation with the so-called ADAM proteases. These enzymes are important for cleavage of TNFα chains off the membrane and releasing the cytokine to the circulation. ADAM blockade may be a useful anti-TNFα strategy.

New exciting targets are emerging. Probably the most interesting development is blockade of the p40 protein that is a building block for IL-12 and IL-23. A single injection of the anti-IL12p40 antibody has produced very long remissions in patients with psoriasis. IL-12/IL-23 is involved in psoriasis at a very early step; it allows dendritic cells to stimulate the development and proliferation of Th1 cells. Interestingly, the dendritic cells themselves are activated by IFNγ that may provide another interesting target in psoriasis. We know from many oncological studies that treatment with IFNα worsens psoriasis and can even trigger psoriasis in susceptible individuals. Moreover, IFNγ is one of the four central cytokines controlling the immune response, the other being IFNα, TNFα and IL-4. In an elegant model of the "immunological rose of winds" Banchereau proposed that imbalance between these crucial cytokines explains all major classes of autoimmune reaction: lupus (excess IFNγ), inflammation (excess IFNα), arthritis/psoriasis (excess TNFα) and allergy (excess IL-4). If true, this model would in future allow for pharmacological correction of the disturbed immune system simply by stimulating or blocking the relevant cytokines.

The renaissance of dendritic cells

There is again a tremendous interest in the function of dendritic cells, partially precipitated baay the fact that the main function of many master cytokines is to regulate dendritic cell function (true for IFNγ, TNFα, IL-12/IL-23). There are at least three classes of dendritic cells in the skin: Langerhans' cells in the epidermis, dermal dendritic cells and the plasmacytoid dendritic cells. In contrast to what has been previously assumed, in many situations the dendritic cells do not activate T cells, but rather cause a tolerance to allergens/autoantigens. They can also produce master cytokines, for example plasmacytoid dendritic cells are the most important source of interferons in the skin in psoriasis and lupus erythematosus. Subsets of dendritic cells may not only initiate the immune response, but also licence the effector cells to drive chronic cutaneous inflammation. *Brian Nickoloff* (Loyola University of Chicago Medical Center, IL) did not hesitate to announce a paradigm shift – transition from polarizing T-cell responses to polarizing or inactivating dendritic cell subsets.

New insights into carcinogenesis and cancer treatment

Skin cancer remains in the centre of scientific interest and several exciting developments were reported at the meeting. We are now very close to a definite proof that keratinocyte stem cells are the target for carcinogens and UV and they are responsible for tumour formation. Stem cells are located in the bulge region of the hair follicles and in the tips of dermal papillae in the basal epidermal cell layer. They can survive for decades (in principle for an entire life) and proliferate at a very low rate. Using an extremely clever genetic technique allowing for permanent labelling of the stem cell and their progeny, it was reported that virtually all squamous cell carcinomas in mice originate from stem cells in the follicles. This hypothesis makes perfect sense and is probably also true for human skin. It is now readily understandable why human carcinomas occur with a 10–15 year delay after carcinogen exposure and why epidermal ablation (e.g. by laser) does not reduce the incidence of cancer.

Barbara Gilchrest (Boston, MA) presented several posters with a new approach to cancer treatment: anti-telomeric oligonucleotides. Very short oligos, e.g. TTAGGG or GTTAGGGTTAG bind to telomeric loops and cause senescence and apoptosis of cancer cells. Normal cells are not affected since only cancer cells are dependent on the activity of telomerase and constant telomere renewal. Gilchrest et al. showed in vitro and in animal models of carcinomas and melanoma that oligonucleotide injection causes tumour regression, even in chemotherapy-resistant neoplasms. This is a very exciting and innovative approach, especially in relation to the alleged activity in melanoma.

Pemphigus: pathogenesis still controversial

The history of pemphigus research is probably the most amazing among all dermatological diseases. Despite the fact that it is one of the most thoroughly studied diseases, its pathogenesis evokes fierce discussions among different group of researchers. The dominant view represented by the labs of *John Stanley* (University of Pennsylvania School of Medicine, Phladelphia) and *Masayuki Amagai* (Keio University School of Medicine, Tokyo, Japan) envisage pemphigus vulgaris as an autoimmune disease caused by the autoreactive antibodies against the desmosomal protein desmoglein 3 (dsg3). These researchers did a tremendous job, first showing the activity of pemphigus sera against dsg3, subsequently purifying the anti-dsg3 antibody and reproducing blisters in neonatal mice. The puzzle of pemphigus seemed to be solved, but not for long. Several years ago *Sergei Grando* (originally from Kiev, Ukraine, now at University of California, Davis, CA) showed that the method for anti-dsg3 antibody purification used by Stanley et al. is probably flawed. Using Stanley's dsg3 affinity columns he found that not one, but several different antibody species can be eluted, among them antibodies against acetylocholine receptor. These antibodies are also able to produce acantholysis in vitro, so the question which antibodies are really pathogenic remains open. At this meeting the group of Amagai and Stanley produced seemingly unshakeable evidence favour-

ing their theory: they produced monoclonal anti-dsg3 antibodies from B cells of patients with pemphigus and showed their activity in producing blistering in neonatal mice. Grando's supporters (being in a minority) rebutted however, that the concentrations of this antibody necessary to block cell cohesion are far beyond what is achievable in vivo. Moreover, pemphigus antibodies produce blisters in dsg3 knockout mice, excluding the possibility that dsg3 is a target. After following this discussion, I can better understand what late professor Chorzelski (a co-discoverer of pemphigus autantibodies) meant by saying that the day we solve the pathogenesis of pemphigus we would probably understand the pathogenesis of all other inflammatory skin diseases.

Concluding remarks

SID conventions are probably the best international meetings dealing with cutting edge dermatological research. The meetings bring different types of people together: the "big shots" of skin research, scientific novices, and non-dermatologists such as biochemists and cell biologists working in the field of skin biology. There is a unique opportunity to meet and talk to fellow researchers in a relaxed, informal atmosphere. Many leading scientists can easily be reached at their posters and are available for questions, discussions and advice. I would especially urge young researchers to attend a SID meeting. They will have the possibility to identify important problems in skin research, discuss their thoughts with the leaders in the field, and on the top of that get a 4-day intensive course in the molecular biology of the skin. Highly recommended!