Preface by David Wallach

The Biennial International TNF Conferences and Their Proceedings

This volume presents a collection of essays by the speakers at the 12th Biennial International TNF conference, which took place at San Lorenzo del Escorial, Spain, in April 2009.

The TNF conferences have seen an immense advance in our knowledge of the TNF family. At the time of the first meeting (at Heidelberg, Germany, in September 1987), the only known ligands of the TNF family were tumor necrosis factor itself (TNF) and lymphotoxin (LT). There was as yet no indication that there were any other related ligands, and certainly no hint of the existence of a family of receptors to which these ligands bind. In fact, scientists were still arguing over the question of whether TNF was a cytokine, i.e., a cellular regulator that acts by triggering a specific cell-surface receptor; indeed, practically nothing was known of the mechanisms by which TNF acts. Moreover, most of the numerous activities of TNF (and of the other members of the TNF family) were not yet known. TNF and LT were still mainly perceived as agents destined to combat tumors, either by killing their cells or by initiating their hemorrhagic necrosis.¹ This primordial state of knowledge was

¹In that connection I wish to pay tribute to the late George Gifford, a wonderful person who, together with Holger Kirchner, raised the idea of holding conferences on TNF and was largely instrumental in organizing the first conference. The scientific organizing committee for that meeting comprised scientists who had begun to study TNF at a time that we subsequently liked to refer to as ‘B.C.’ (before cloning of TNF and LT). At the time of the conference all of them were still studying either the anti-tumor function or the cytotoxic activity of TNF (or in my case, the ability of TNF to induce resistance to its cytotoxic effect, a function that we now mainly ascribe to its activation of NF-κB). A few years before that first conference, George had written a comprehensive review of the state of knowledge of TNF at that time. Two hypotheses from that review illustrate the conceptual gap between the ‘B.C.’ and ‘A.C.’ periods: “...Could the protein component of TNF serve as a specific carrier for phospholipid toxin...alternatively, could TNF exist as a zymogen in the more traditional sense...perhaps proenzyme?” (1). (Also mentioned in his review was the possibility that TNF is a cytokine that acts by binding to specific receptors.) And yet, although he was probably the oldest of the conference organizers and had thus had the longest acquaintance with such ‘B.C concepts,’ George was the one most alert to the new advances. I recall him saying,
reflected in the title of that meeting, ‘Conference on TNF and Related Cytotoxins’ [1], which differed from that of all subsequent meetings in the series. Since then, studies by the numerous groups who were increasingly attracted to the TNF research field have gradually revealed the existence of many TNF-related ligands and as many interrelated receptors through which the ligands induce their effects. It was further disclosed that triggering of these receptors leads to a plethora of functional consequences affecting virtually every cell in the body and practically all known immune functions as well as multiple embryonic developmental and homeostatic processes. Vast knowledge has also been acquired of the molecular mechanisms by which these effects are induced and of their potential relevance for disease and therapy.

The scientific community studying the functions of the TNF family has grown immensely and the research subjects upon which these functions have a bearing are remarkably heterogeneous. Nevertheless, there is still much of common interest that induces these scientists to meet with their peers. Such meetings enable them to share information and ideas on common proximal signaling molecules activated by different ligands and receptors of these families, mechanisms by which these molecules act, modes of regulation of receptor and ligand activities, cooperation among the various molecules, techniques for therapeutic modulation of ligand functions, and many other common pursuits. Despite the fact that these scientists possess neither an official organization nor funds to support their cooperation, they have continued to convene approximately every second year, each time in a different part of the world. For close to a quarter of a century these international conferences on TNF have successfully taken place, thanks to untiring efforts on the part of ad hoc chosen chairpersons and organizing committees.

Inevitably, the scientific progress made over this period required some changes in organization of the meetings. In particular, to accommodate the vast expansion of knowledge about the TNF family within acceptable time limits it became necessary to prune discussions of subjects that were related only tangentially to the central issues. At the initial meetings the sessions had encompassed the relationship of TNF functions to those of bacterial endotoxin and other pathogen-associated molecules and insults, the functions of other inflammatory cytokines such as IL1 and IL6, as well as infectious diseases, tumor immunology, and many other subjects. Discussions of these fringe issues and their implications for the field of TNF research had promoted a more profound understanding of TNF function. At the more recent meetings, however, their inclusion was a luxury that the organizers could not afford. Stringent restrictions were now placed also on presentations of progress in the TNF field itself. Most chairpersons chose to do this by focusing on those research aspects showing the most dramatic advances while devoting very

“There is a guy called Tony Cerami who, together with his PhD student Bruce Beutler, reached findings that provide a new point of view of the function of TNF. They actually call it ‘cachectin’. We must also discuss the potential pathogenic role of TNF in our conference. Why don’t we invite Tony to join us in organizing this meeting?” (which we did).
little time to the numerous other aspects in which progress has been more difficult to achieve and might therefore appear less impressive.

Despite the continuing proliferation of laboratories devoted to studying the functions of the TNF family, the numbers of conference participants have remained constant for several years, and in recent times have even decreased. In the course of publicizing the current international conference and while searching the Internet for laboratories supported by the National Institutes of Health or the European Union for research on ligands of the TNF family, we were astonished not only to see how numerous these laboratories have become but also to discover how many of them have never been represented at a TNF conference. In pondering this paradox we concluded that planners of these meetings, by opting to focus on the more spectacular advances in the field, have inadvertently restricted the circle of scientists who attend the meetings.

Therefore, in order to reach out to the many research laboratories which, despite their intimate involvement in subjects central to the TNF field, do not participate in these meetings, we decided that at the 12th TNF conference we would not restrict the scope of subjects, but would instead strictly limit the presentation length. To compensate for this restriction it was decided that each session would be followed by a round-table discussion in which the principal open questions pertaining to that session would be thoroughly discussed. To our satisfaction, this approach substantially boosted participation in the meeting and greatly extended the scope of the subjects discussed. A short review of these subjects is presented in [2].

Each of the first four TNF conferences (held between 1987 and 1992) was followed by the publication of Proceedings in which talks from all of the sessions were summarized [3–6]. This practice was then discontinued, perhaps because as time went on the focus of the conferences became more restricted, as explained above. Since the range of subjects addressed at the 12th conference represented a wide overview of the current state of TNF research, and because a compendium of articles in this field had not been published for quite some time, we opted to publish the Proceedings of this meeting. In addition to the articles written by the speakers, this volume contains some short overviews contributed by the scientists who chaired the discussions held after each session.

Although almost two decades have passed since the first four conferences were held, their Proceedings are still of interest, both as source of reference for data or hypotheses and as snapshots of the state of knowledge at the time of their publication. We hope that the Proceedings of this most recent meeting will be at least as valuable, and that it will serve as an effective complement to the conference itself in facilitating interactions among the numerous scientists who contribute to the different facets of research on the TNF family.

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References

Preface by Marc Feldmann

Introduction

The TNF/TNF-R Family: A Gold Mine for Clinical Therapeutic Targets?

The potential importance of TNF in therapy was first described in animal models of sepsis [1] and the attempts to replicate it in humans started the evaluation of the clinical relevance of TNF in disease. The first success was with anti-TNF antibody in rheumatoid arthritis, soon followed by anti-TNF antibody in Crohn’s disease, and this documented the importance of the TNF family in major diseases.

From that time, therapeutic and clinical studies have grown and TNF blockade, by either monoclonal antibodies or TNF receptor fusion proteins, has become a huge therapeutic market, about 2 million treated patients and drug sales of $17 billion in 2008 [2].

But TNF is not the only therapeutic target in the TNF/TNF-R family. The monoclonal antibody to RANK ligand is very effective in many clinical trials at preventing bone loss for osteoporosis or bone cancer and is likely to be another ‘blockbuster.’ There are other promising leads, but some do not progress. Thus anti-LTβ was not successful in arthritis, but has a potential against cancer.

The ligands also are potential therapeutics. TNFα was not useful systemical for cancer due to life-threatening effects, but local infusion has been successful in limbs, provided sensitizing IFNγ pre-treatment is administered and TNF is not allowed to disseminate systemically. TRAIL, inducing apoptosis in cancer cells, may be more useful, and preliminary studies were encouraging.

But what is the future for the TNF/TNF-R in the therapeutic domain? It looks bright. Inhibition of TNF-R may be a better alternative to TNF blockade, as a number of mouse knockout experiments suggest that, but proof with selective inhibitors is lacking. Inhibiting other TNF-R family members for a variety of diseases is being explored. As the TNF family receptors are susceptible to activation on being cross-linked, monomeric blockers are essential, but the reciprocal opens up
another opportunity, of activation by cross-linking receptors, for inducing apoptosis in cancer cells, for example.

Thus there will be interesting reports in the future in the field of therapy for the TNF and TNF receptor family.

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Reference


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