TUMOUR NECROSIS FACTOR AND RELATED CYTOTOXINS
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Tumour necrosis factor and related cytotoxins.

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Contents

Symposium on Tumour Necrosis Factor and Related Cytotoxins, held at
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Editors: Gregory Bock (Organizer) and Joan Marsh

L. J. Old  Introduction  1

G. E. Gifford and D. A. Flick  Natural production and release of tumour
necrosis factor  3
Discussion  14

M. A. Palladino Jr, J. S. Patton, I. S. Figari and M. R. Shalaby  Possible
relationships between in vivo antitumour activity and toxicity of tumour
necrosis factor-α  21
Discussion  30

Human tumour necrosis factors: structure and receptor interactions  39
Discussion  47

C. Baglioni, V. Ruggiero, K. Latham and S. E. Johnson  Cytocidal activity
of tumour necrosis factor: protection by protease inhibitors  52
Discussion  61

N. H. Ruddle, C.-B. Li, W.-L. Tang, P. W. Gray and K. M. McGrath
Lymphotoxin: cloning, regulation and mechanism of killing  64
Discussion  79

General discussion I  The role of phospholipase activation in cell killing  83
Protective and cytolytic effects of tumour necrosis factor  84
K. J. Tracey, S. F. Lowry and A. Cerami  Physiological responses to cachectin  88
Discussion  102

Discussion  120

J. L. Rothstein and H. Schreiber  Relationship of tumour necrosis factor and endotoxin to macrophage cytotoxicity, haemorrhagic necrosis and lethal shock  124
Discussion  135

K. Haranaka, N. Satomi, A. Sakurai and R. Haranaka  Antitumour effects of tumour necrosis factor: cytotoxic or necrotizing activity and its mechanism  140
Discussion  149

F. R. Balkwill, B. G. Ward and W. Fiers  Effects of tumour necrosis factor on human tumour xenografts in nude mice  154
Discussion  164

J. S. Pober  Effects of tumour necrosis factor and related cytokines on vascular endothelial cells  170
Discussion  179

General discussion II  Lymphotoxin and tumour necrosis factor as possible mediators of an inflammatory response  185
Haemorrhagic necrosis and coagulation necrosis  187

J. H. L. Playfair and J. Taverne  Antiparasitic effects of tumour necrosis factor in vivo and in vitro  192
Discussion  198

D. R. Spriggs, M. L. Sherman, E. Frei III and D. W. Kufe  Clinical studies with tumour necrosis factor  206
Discussion  219

L. J. Old  Summary  228

Index of contributors  233

Subject index  235
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Introduction

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With the rapid growth of knowledge about tumour necrosis factor (TNF) and lymphotoxin (LT) over the past two years, this Ciba Foundation Symposium could not have come at a better time. Although there continues to be a preoccupation with the antitumour activities of these molecules, the role of TNF and LT in inflammation and immunity is now a focus of attention. As we view current research on inflammation, immunity and the response to infectious agents in relation to past work, we find ourselves in the middle of a revolution in our knowledge of polypeptide mediators. Whether described as growth factors, differentiation factors, interleukins or cytokines, these mediators have taken centre stage as key molecules in phenomena as diverse as immunity, sleep and neoplasia. It should be remembered that earlier claims for mediators, particularly those, like TNF, thought to be involved in the action of bacterial endotoxins, did not meet with easy acceptance. Because of the ubiquity of endotoxin and the enormous range of reactions that it elicits, the pre-polypeptide era in the study of inflammation was characterized by scepticism and disbelief in such mediators. At that time non-peptide mediators, such as histamine, serotonin and, later, the prostaglandins, leukotrienes and reactive oxygen intermediates, came to be regarded as the central molecules. With the recent recognition and cloning of so many regulatory polypeptides a new synthesis is beginning to emerge that integrates the peptide, polypeptide and non-peptide mediators in the cellular and molecular events of inflammation and immunity.

A number of themes will recur in our discussions of TNF but three deserve special mention. One is the central role of the macrophage in many of the phenomena we shall consider. This remarkable cell, which began its scientific life with the prosaic function of phagocytosis, is now known to be a veritable factory of secretory molecules. The macrophage is returning to the central place that Metchnikoff envisaged for it in the biological hierarchy. Another
theme inseparable from discussions of TNF is endotoxin, or lipopolysaccharide, a component of the outer cell wall of Gram-negative bacteria. Endotoxin is the most potent inducer of TNF yet found, and TNF clearly mediates many of its actions. In retrospect, the multiple actions of TNF should have come as no surprise, considering the extensive list of activities ascribed to endotoxin.

The third theme was quite unexpected. TNF and IL-1, another macrophage product elicited by endotoxin, do many of the same things, despite lack of sequence homology and separate receptors. Redundancy of this sort is known for molecules with limited sequence homology and a common receptor, such as TNF and LT, IFN-α and IFN-β, and IL-1α and IL-1β, but it was surprising in the case of TNF and IL-1.

Studies of TNF, LT, IL-1 and other polypeptide mediators have made it clear that these molecules are part of a complex network of interacting signals, where each mediator has a multiplicity of actions; single biological end-points, such as fever, can be elicited by structurally unrelated molecules; and complex interactions, both synergistic and antagonistic, occur between different mediators. Undoubtedly, the complexity observed with TNF and other mediators is a manifestation of Nature's preoccupation with homeostasis, wherein signal redundancy and convergent pathways from divergent signals are safer and more effective than what appear to be simpler solutions.
Natural production and release of tumour necrosis factor

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Abstract. Tumour necrosis factor (TNF) was first described as an oncolytic factor found in sera of animals injected (primed) with reticuloendothelial stimulators and subsequently (days later) given lipopolysaccharide (LPS). TNF is not found in the serum of 'primed' animals but can be found in animals given LPS alone when sensitive assays are employed. TNF appears almost immediately upon LPS injection, reaches a maximum from about 1.5–2 hours and disappears rapidly thereafter, and is almost undetectable by 4–6 hours. When such mice are injected again with LPS, they are unresponsive (tolerized) and do not produce TNF again, at least for seven days. Other unrelated substances, such as muramyl dipeptide, viruses and mitogens, also induce TNF production. A high percentage of patients with some parasitic infections (but not cancers) demonstrate low levels of TNF in their sera; thus, they do not seem to be tolerized but produce it continuously. TNF can also be produced in macrophage cultures by treatment with LPS, muramyl dipeptide and other substances. Again, it appears almost immediately and synthesis is maintained for about 8–12 hours. Synthesis is dependent upon the continuous presence of LPS. After synthesis stops it cannot be reinitiated by adding more LPS; thus, the macrophages also appear to be tolerized. Macrophage cell lines eventually become sensitive again after cultivation in LPS-free conditions. Synthesis of TNF is inhibited by actinomycin D or cycloheximide, indicating that it is an inducible protein. Its production is also inhibited by glucocorticoids and prostaglandin E₂, indicating that these substances play important roles in the regulation of TNF synthesis.


The tumour necrotic effects of bacterial endotoxins have been known for a long time and are mediated by tumour necrosis factor (TNF) (reviewed by Ruff & Gifford 1981). TNF was discovered, described and defined at the Memorial Sloan-Kettering Cancer Center and published in a classical study by Carswell et al (1975). It was originally described as a soluble factor found in sera from animals that have been sequentially treated with a reticuloen-