Chapter 29

MECHANISMS INVOLVED IN IMMUNOMODULATORY TREATMENT OF RHEUMATOID ARTHRITIS

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1. INTRODUCTION

Many inflammatory rheumatic diseases, including rheumatoid arthritis, appear to depend on a dysregulation of the immune system, that is, interference with pathogenetically important immune reactions can be expected to have beneficial or even direct curative effects on the respective diseases. Ideally, an adequate therapy would thus require knowledge of which immune reactions are critical for disease development and access to means whereby these but no other reactions could be down-regulated. Even if we are far from this situation both as to pathogenetic knowledge and access of practically working specific immunomodulatory treatment, our emerging knowledge on the immunopathogenesis of rheumatic joint diseases may be used both to reconsider the mode of action of currently used drugs and to critically approach some of the more experimental treatments that have recently been introduced.

This chapter will thus first touch briefly on some critical aspects of the immunopathogenesis of inflammatory joint disease, particularly rheumatoid arthritis (RA); second, deal with existing therapies with an emphasis on their effects on immunoregulation; and third, describe some results from the application of drugs primarily developed to interfere with immune activation.

2. ASPECTS ON THE IMMUNOPATHOGENESIS OF INFLAMMATORY JOINT DISEASE, PARTICULARLY RA

The immunopathogenesis in RA is characterized both by a T-cell activation, primarily within synovial tissue and synovial fluid of affected joints (Klareskog et al., 1981, Burmester

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et al., 1982), and by immune complex (IC) formation and rheumatoid factor (RF) production, also predominantly seen within the joints (Carson et al., 1987). Cytokines from the activated T cells and effects of the immune complexes may subsequently cause the pronounced activation of macrophages and polymorphonuclear cells that, by their production of proteolytic enzymes (Krane et al., 1982) and a variety of inflammatory mediators such as prostanoids (Klareskog et al., 1985), are responsible for the actual tissue damage. All these processes, including RF and IC formation, are most probably dependent on initial major histocompatibility complex (MHC) class II-dependent T-cell activation, that is, a contact between an antigen-presenting cell (APC), often a macrophage, and a T cell. This process involves processing and binding of one (or several) as yet unknown antigens to the class II antigens of the APC, and a corecognition of the MHC class II antigen complex by the variable T-cell receptor. Additional molecular contacts between the T cell and the APC involving the so-called CD4 molecule also are necessary for T-cell activation, as well as production of cytokines such as interleukin-1 (IL-1) from the APC that can bind to appropriate receptor on juxtaposed T cells (for a review, see Klareskog and Wigzell, 1988). This scenario is rather well characterized concerning the local inflammation in the joints in RA. Less is so far known about the immunopathology of systemic inflammatory lesions; the subcutaneous nodules certainly contain both activated T cells and activated macrophages in their palisading layers (Ziff, 1990), and both skin and heart lesions contain many infiltrating inflammatory cells. Still, the sequence of events is less characterized than in the joints, and we do not know to which extent circulating immune complexes—as sometimes proposed—may play a relatively more important role for systemic lesions such as vasculitis, pleuritis, pericarditis, and so on compared to the situation in the joints.

Of interest in this context is that many of the extra-articular symptoms in RA, such as anemia, fatigue, muscle wasting, and metabolic changes, may be causatively related to the release of defined cytokines resulting from the immune activation described above. In many cases, these symptoms may not go parallel to joint destruction. As will be discussed in other sections of this book, many of the so-called remission-inducing drugs appear to interfere with early events in immune activation, thereby affecting not only local symptoms in joints but also a number of the generalized and often diffuse symptoms. Such considerations may be used as a further argument for early institution of remission-inducing drugs independent of whether signs of joint destruction have occurred or not.

3. POSSIBLE IMMUNOMODULATORY EFFECTS OF CURRENTLY ROUTINELY USED DRUGS IN RA

Although introduced very empirically, and without any primary objective to affect immune functions, there is evidence that most of our current slow-acting antirheumatic drugs (SAARD) may affect such immunologic events that from the description given above are essential for RA development. With the obvious precaution that the actual drugs may have multiple actions, and given the difficulties in extrapolating in vitro data to the in vivo situation, I will briefly summarize some possible immunological effects of SAARDS.

3.1. Antimalarials

These agents are in vitro among the most efficient and commonly used inhibitors of the intracellular processing of protein antigens, that is, in most cases needed before a peptide of this antigen can be appropriately presented to the T cell (Lee et al., 1982; Nowell and