Studies on cell-mediated immunity in the rat
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1976

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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This thesis deals with some aspects of cell mediated immunity (CMI) in the rat. In chapter I a short introduction to the manifestations of CMI in vivo and in vitro is outlined. The "classical" delayed type hypersensitivity reaction (DTH or type IV skin reaction) is discussed, as well as the histological changes occurring in draining lymph nodes associated with a state of CMI. Furthermore some major aspects of CMI in vitro are considered. The objectives of the experimental studies presented in this thesis are formulated as three major issues evolved from previous studies, dealing with experimental glomerulonephritis in the rat: 1) the development of a simple reproducible in vivo and in vitro assay for CMI using soluble test antigens in the rat. 2) in preparation for the studies of the effect of drugs in experimental glomerulonephritis, the influence of drugs on the CMI state in rats, was first evaluated. 3) after these studies were completed, the CMI was estimated in drug treated and untreated glomerulonephritic rats.

In chapter II the results of an in vitro and in vivo CMI investigation in CFA sensitized and non sensitized (IFA) rats are described. Thymic cells, spleen cells, peritoneal exudate cells (PEC), and peripheral blood lymphocytes were tested for their ability to produce MIF in vitro after specific stimulation, whereas DTH reactions were studied in sensitized animals using the same soluble test antigens. It was shown, using different MIF assays, that MIF production in vitro could be detected in thymic, spleen and PEC, but not in peripheral blood lymphocytes. A correlation was observed between positive skin tests and MIF production in the sensitized groups of animals. The main finding, demonstration of a "thymus MIF", suggested that lymphoid cells must be present in the thymus of sensitized rats, which are
capable of generating lymphokines after specific stimulation in vitro. It was shown by gel filtration methods, that the molecular weight of this lymphokine ranged between 20,000 and 70,000 daltons.

In chapter III the in vivo character of this thymus MIF was investigated with emphasis on the two activities well described in the literature: "Skin reactive activity" (Bloom, 1971) and "lymphnode activating activity" (Kelly et al., 1972). It was shown that after intradermal injection only the MIF containing solutions caused inflammatory skin responses in contrast to control supernatants. Similarly characteristic changes in draining lymphnodes were observed only after subcutaneous injection of MIF containing supernatants. These typical histological changes resembled those seen in regional lymphnodes in rats sensitized with CFA. These observations supported and extended our previous suggestion of the presence of "educated" cells in the thymus which were capable of producing substances with the properties of lymphokines in vitro and in vivo.

In chapter IV the influence of corticosteroid (C.S.) treatment on CMI in the rat was studied. Therefore CFA sensitized and non sensitized (IFA) rats were treated with prednisolone or with other drugs, believed to suppress CMI, including anti lymphocyte serum (ALS), and oxisuran (2-[(methylsulfinyl)acetyl]pyridine. Data were obtained by MIF studies, DTH skin reactions, regional lymphnode and spleen histology, and leukocyte counts, as well as T-cell estimations in the bone marrow of C.S. treated rats. It was concluded that prolonged C.S. administration in this "C.S. sensitive" species, did not suppress T-effector cells but rather modified the homing properties of lymphoid cells and macrophages including "educated" T-cells present in the thymic cortex.

Chapter V evaluated the question of whether CMI is present against in vitro prepared soluble immune complexes in an experimental immune complex glomerulonephritis in the rat, and whether CMI might play a role in causing glomerular damage in this experimental model and type IV skin test antigens. Further, suppressed MIF responses be demonstrated, phase. Furthermore, drug treatment could be suppressed simultaneously with the suppression of protein excretion. We concluded that CMI not play a significant role in glomerulonephritis, at damage.

In chapter VI were reviewed in detail as formulated in 1972. The principal over of the relevant c...
The mitogen stimulation in the molecular weight range of 30,000 and 70,000 of the thymus MIF was well described (M. et al., 1972). The MIF concentrations in contrast to changes in cutaneous injections induced histological lesions in rats and extended "activated" cells in an advanced state with the (C.S.) treatment of sensitized and non-sensitized rats with anti lymphocyte methylpyridine. Sections, regional counts, as well as urinary protein excretion in this "C.S. treated rats. CMI responses as well as DTH against the antigens used could be demonstrated, in an advanced state of the disease (autologous phase). Furthermore it appeared that with prolonged immunosuppressive drug treatment, beginning early in the autologous phase, CMI could be suppressed without detectable influence on urinary protein excretion. However prolonged drug treatment which began simultaneously with the onset of the disease caused: CMI suppression, suppression of rat IgG deposition in the immune complexes in the glomeruli, as well as suppression of the proteinuria. It was concluded that CMI, as evaluated by the methods used, probably did not play a significant role in this experimental complex glomerulonephritis, at least with respect to the degree of glomerular damage.

In chapter VI the major points from the preceding chapters were reviewed in relation to the starting point of this study as formulated in chapter I.

The principal overall conclusions were discussed in the context of the relevant data reported in the literature.