The involvement of various liver cell types in the clearance of immune complexes.
Laan-Klamer, Susanne Marina van der

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1986

Citation for published version (APA):

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SUMMARY

When foreign antigens are introduced into the body an immunological reaction occurs. Antibodies are synthesized and released into the blood and other body fluids. When antigens and their specific antibodies combine, immune complexes are the result. The ratio between antigen and antibody in the immune complexes and therefore the size of the complexes can vary enormously. The composition of the complexes depends on the concentration of both components and the affinity and class of the antibody. Because immune complexes in principle possess phlogistic characteristics because of their capacity to activate the complement system they have to be cleared from the circulation efficiently. Until recently, Kupffer cells, the macrophages of the liver were predominantly thought to be responsible for this clearance. Kupffer cells contain Fc receptors on their surface that recognize the Fc part of the antibody molecule. Both the multivalency and the conformational change of Fc parts in immune complexes may contribute to a stronger binding of these complexes to Fc receptors than is encountered in single antibody molecules. Kupffer cells also contain complement receptors on their surface that recognize complement component C3b. Complement components are integrated into immune complexes during their formation. This incorporation prevents precipitation of ICs in tissues and also plays a role in the degradation process of immune complexes.

In this thesis we have investigated whether liver cells other than Kupffer cells are also involved in immune complex clearance and if the composition of the immune complexes (soluble and insoluble as well as heterologous and autologous immune complexes) influences the localization or disappearance. We also investigated which receptors play a role in this clearance.

Chapter I, the general introduction describes some general features about liver anatomy and cellular composition. The origin and formation of immune complexes as well as the influence of their size and composition upon their clearance rate is discussed. Moreover this chapter deals with Fc receptors, their occurrence, specificities and function.

Chapter II describes the localization in the liver of heterologous soluble (small) and insoluble (large, particulate) immune complexes made from bovine serum albumine and rabbit antibodies against it following administration to normal rats. The localization after various time intervals was studied. The localization was demonstrated using the immunoperoxidase method on the light and electron microscopic level. Insoluble immune complexes localize within 5 minutes only along the plasma membrane of the Kupffer cells and in the Kupffer cells. This localization pattern does not change from 5 to 120 minutes. Soluble immune complexes bind to endothelial- and Kupffer cells and to the microvilli of the hepatocytes within 5 minutes. At 30 and 120 minutes immune complexes appeared to be endocytosed by endothelial and Kupffer cells but not by hepatocytes. The main conclusion is that besides Kupffer cells also endothelial cells are involved in immune complex clearance from the circulation.
Chapter III describes the mechanism by which binding of immune complexes occurs. The possible role of the asialoglycoprotein receptor, the complement receptor and the Fc receptor was studied. Inhibition of immune complex binding by preinjection of an asialoglycoprotein could not be established eliminating the role of the asialoglycoprotein receptor. Administration of immune complexes to the perfusion medium (not containing serum complement components) of an isolated perfused liver demonstrated the same binding pattern as is observed in vivo excluding the influence of complement receptors. Inhibition of immune complex binding could only be achieved by preinjection of aggregated swine antibodies in vivo. Therefore, we concluded that Fc receptors are involved in immune complex binding to liver endothelial cells, Kupffer cells and hepatocytes.

In order to investigate the possible influence of the heterologous nature and the in vitro formation of the RABSA/BSA complexes upon their liver localization, in Chapter IV results are described upon the localization of autologous immune complexes which occurred following antigen administration to immunized rats. In addition, the disappearance rate was investigated of labeled antigen injected into rats with high respectively low antibody levels. Autologous immune complexes localize in and along endothelial and Kupffer cells. In contrast to heterologous immune complexes they were also taken up by hepatocytes and can be localized in very large vacuoles especially in those rats having high antibody titers. The plasma disappearance curves show an increased disappearance of antigen in rats having high antibody titers. It is concluded that the level and the affinity of the antibodies influence the disappearance rate and localization of the antigen.

Chapter V describes the binding of soluble and insoluble heterologous immune complexes to isolated cultured liver endothelial cells. It appeared that endothelial cells bind both soluble and insoluble ICx and that this binding was mediated by Fc receptors. Binding of insoluble ICx did not occur in vivo and is possibly caused by the absence in vitro of the phagocytosing Kupffer cells which in vivo will rapidly phagocytose the insoluble immune complexes before the endothelial cells are able to bind and internalize these immune complexes.

In Chapter VI binding experiments are described with isolated cultured hepatocytes using homologous (rat anti BSA/BSA) and heterologous immune complexes. It appeared that isolated cultured hepatocytes contain endogenous immunoglobulins on their surface but that they did not bind immune complexes.

In Chapter VII the disappearance rate of various immune complexes are described. Heterologous, homologous and autologous immune complexes are labeled with a fluorochrome and administered to normal rats. It turned out to be that the more self the antibody was the more efficient it was cleared from the circulation. Autologous ICx were cleared more efficient than heterologous ICx and homologous ICx were cleared in between.

To investigate whether binding of ICx to liver endothelial cells could be used as a functional test for these cells and if so whether this test could be used to
investigate heterogeneity of binding between antibodies from various origin we used a model in which liver cryostat sections were incubated with heterologous and homologous immune complexes, antibody aggregates and monomeric antibodies. The results are described in Chapter VIII. No binding was demonstrated upon binding of monomeric antibodies, rabbit and swine antibody aggregates. Binding was demonstrated upon incubation with aggregates of human and rat antibodies and upon incubation of rat and rabbit immune complexes. These findings emphasize the influence of the origin of the antibodies upon results from investigations with immune complexes.

In Chapter IX the discrepancies are discussed found between the in vivo and in vitro binding specificities of the endothelial Fc receptor as well as the possible involvement of coated pits and coated vesicles in ICx uptake by liver endothelial cells. This chapter also discusses the possible re-utilization of the IgG molecule present in the ICx after internalization into the cell.