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### **P.29 Human C3a induces synthesis and secretion of interleukin 1 by human monocytes**

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The ability of the complement components, primarily C3, to regulate the immune system has been the recent focus of numerous investigations. Immune modulation by C3 cleavage products results from their interactions with complement receptors present on monocytes/macrophages, B lymphocytes and some T cells. Human monocytes possess surface receptors for the C3 fragments, C3b and C3bi as well as for C3a. No functional consequence of C3a to activate human monocytes by measuring the synthesis and release of interleukin-1 (IL 1). The presence of synthesized IL 1 in the cytoplasm or released IL 1 in the culture medium was assessed using the mouse thymocyte proliferation assay in the presence of suboptimal doses of Concanavalin A. The C3a fragment, purified from zymosan-treated plasma in the absence of carboxypeptidase inhibitor, was quantified using the radioimmunoassay (RIA) developed by Upjohn Cie, and migrated as a single band upon SDS-PAGE analysis. The content in LPS of the C3a/C3a desArg preparation was 0.010 % as assessed by the colorimetric limulus assay and the content in C5a desArg antigen was below 0.005 % as measured by the Upjohn's RIA. A concentration of the C3a/C3a desArg preparation of 1.1  $\mu$ M induced 14 % histamine release from leucocytes of normal donors. Human C3a/C3a desArg induced in a dose-dependent fashion the synthesis and the release of IL 1 by human monocytes. The capacity of 0.1–0.2  $\mu$ M of C3a/C3a desArg to induce IL 1 by human monocytes was dependent upon the donors, but higher concentrations (2.2  $\mu$ M) induced the release of IL 1 by monocytes from all tested donors (20 exp.). A culture of human monocytes in the presence of C3a/C3a desArg (1.1  $\mu$ M) during 6 h was sufficient to induce synthesis of IL 1 (assessed by IL 1 activity found in cell lysates) whereas 24 h were required to detect IL 1 release. Induction of IL 1 release is markedly enhanced when cultures were performed in the presence of indomethacin. Neither gangliosides, nor polymyxin B, inhibitors of LPS-induced IL 1 secretion, inhibited IL 1 release from monocytes stimulated by C3a/C3a desArg (2.2  $\mu$ M). Our results demonstrated that the C3a fragment which is generated during infection can modulate the inflammatory processes and the immune response via the release of IL 1. Moreover it can be suggested that the release of IL 1 induced by C3a may be one of the underlying pathophysiologic events occurring during hemodialysis or cardiopulmonary bypass.

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### **P.30 Molecular specificity of human heterophile antibodies (HHA) in normal human serum (NHS) reacting with xenogeneic cells**

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HHA that are present in NHS play an important role in hyperacute xenograft rejection. The aim of this study was to analyze the occurrence, mode of action and molecular specificity of

HHA directed against xenogeneic lymphocytes (isolated from mouse, rat, guinea pig, rabbit, cattle and pig) and isolated rat pancreatic islets. All sera ( $n = 30$ ) contained variable amounts of HHA that killed the target cells via the classical complement pathway. The cytotoxic activity of these HHA was specifically inhibited by some carbohydrates ( $\alpha$ -D-melibiose,  $\beta$ -lactose,  $\beta$ -Gentiobiose,  $\beta$ -cellobiose, D-mannose, N-Acetyl- $\beta$ -D-mannosamin and  $\alpha$ -D-rhamnose) and by rat IgM. By means of affinity chromatography with immobilized inhibitors we obtained an antibody preparation of mainly IgG type from NHS (up to 3.5 mg/10 ml serum) that reacted strongly with rat lymphocytes and isolated rat pancreatic islets. Though thus far there was residual xenospecific antibody activity in the sera even after multiple immunoadsorptions, these data suggest that specific elimination of HHA is feasible and thus it may be possible to overcome a major obstacle to xenotransplantation.

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### **P.31 Restriction fragment length polymorphisms of the human C3 complement gene**

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A cloned gene-specific probe for human complement C3 was hybridized to DNA samples digested with various endonucleases. The C3 probe detects one restriction fragment length polymorphism (RFLP) that occurs frequently in the French population when DNAs are digested with *Sac* I; three patterns are visible: a single 12 kb fragment, two fragments of 9 + 9 kb, or all three fragments 12, 9 and 3 kb. These patterns are interpreted to be the result of the products of two alleles, the frequency of the rarer one in our population being  $f = 0.28$ . These alleles can be readily used in linkage analysis of loci on chromosome 19, and such a polymorphism can be followed through myotonic dystrophy families.

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### **P.32 Distortion of the maternal segregation of the silent alleles of the 4th complement factor in normal and type I diabetic families**

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Fifty four normal Caucasian families and 169 families in whom at least one child had type I diabetes (IDDM) were genotyped for HLA-A,B,C,DR and for the complement factors Bf and C4. The paternal and maternal transmission of the different alleles and of haplotypes and complotypes on linkage disequilibrium have been analysed.

No distortion of the paternal transmission has been observed on the offspring of the two series of families. On the contrary, a distortion of the maternal segregation of the silent alleles at the complement factor C4A and B locus was found: mothers transmitted C4AQO more often than expected to their male offspring ( $p < 0.04$  in normal families,  $p < 0.001$  in IDDM families) while they transmitted C4BQO in excess to their female offspring ( $p < 0.01$  and  $p < 0.03$  in normal and IDDM families, respectively).