THE Fc-RECEPTOR FUNCTION OF HUMAN MONONUCLEAR PHAGOCYTE SYSTEM : PHYSIOLOGICAL ROLE, ALTERATION IN IMMUNE DISEASES AND MODULATION.

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SUMMARY

Circulating immune complexes (CIC) are detectable in high titer in patients with various immune diseases and the deposition of these complexes is believed to be important in the pathogenesis of these disorders. The reticuloendothelial system (RES), which includes the Kupffer cells of the liver and the splenic macrophages, is involved in the removal of CIC from the vascular system. A defect in CIC clearance may enhance their tissue deposition. Accordingly, during the past few years, increased interest has been devoted to the measurement of immune clearance mediated by receptors for Fc. IgG-coated autologous red blood cells (IgG-RBC) labelled with ^{51}Cr have been used as immune tracer particles to follow the Fc-receptor function of whole RES in normal and pathological conditions. Prolonged clearance times of IgG-RBC are generally found in most immune complex-mediated diseases. Using IgG-RBC labelled with ^{99m} Tc, it has been thereafter possible to determine not only the clearance half-time of the tracer, but also separated spleen and liver Fc-receptor binding capacities. It has been clearly demonstrated that the spleen to liver ratios per surface area (S/L_s) are deeply pathological in immune disorders, even when clearance half-times (T 1/2) remain within the normal range. Abnormal ratios result from both a decreased splenic uptake and an increased liver uptake of IgG-RBC, this « hepatic compensation » preventing the T 1/2 to be out of the normal values. Abnormal T 1/2 are therefore observed only when the spleen and liver phagocytic capacities are saturated.

The splenic Fc-receptor blockade is generally correlated with the disease activity and, less frequently, with the immune complex plasma levels. Serial measurements of S/L_s may be therefore of clinical interest by delineating those patients in whom the evolutivity of the disease is potentially high. Finally, serial S/L_s measurements have allowed the in vivo study of the modulation of the macrophagic Fc-receptor function by plasma exchange, corticosteroid administration and high-dose gammaglobulin infusion.

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Non usual abbreviations :

RES : reticuloendothelial system
MP : mononuclear phagocytes
MPS : mononuclear phagocyte system
RBC : red blood cell
IgG-RBC : immunoglobulin G-coated red blood cell
HD-RBC : heat-damaged red blood cell
S/L_s : spleen to liver ratio per surface area
T 1/2 : clearance half-time
CIC : circulating immune complexes

The macrophage was first described by Metchnikoff in 1893 who established the phagocytic capacities of the cell (1).

Further studies by Aschoff in 1924 defined the reticuloendothelial system (RES) which included cells other than macrophages, such as lymphatic and sinosoidal lining cells, fibrocytes and endothelial cells (2). From the past 20 years, studies of the morphology, cytochemistry, surface membrane markers and cell properties led to the onset of a new concept : the mononuclear phagocyte system (MPS) whose cells were all bone marrow-derived (3).

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The criteria used for the identification of cells as mononuclear phagocytes (MP) include morphological characteristics by photonic and electron microscopy, the positivity for non-specific esterases, the presence of peroxydase-positive or -negative granules, and that of membrane receptors specific for C3b and the Fc component of Igl and Ig3. Furthermore, these cells share some functional properties such as the phagocytosis of opsonized bacteria, of IgG-coated red cells or of latex beads (4). Defined by the above-mentioned criteria, the MPS includes the histiocytes of the connective tissue, the Kupffer cells of the liver, the alveolar macrophages of the lung, free and fixed macrophages of lymph nodes and spleen, pleural and peritoneal macrophages (serous cavities), osteoclasts of the bone, microglia cells of the nervous tissue, the histiocytes of the skin and circulating monocytes. Some cells among which the Langerhans cells, the interdigitating cells, the synovial type A cells and the mesangial cells from the renal glomerulus are thought to belong to the MPS, but conclusive proofs have not yet been raised. Although unified under the MPS concept, base line characteristics of these cells remain their heterogeneity with respect to their expression of surface membrane markers, their level of phagocytic capacities, their histochemical properties, their response to various stimuli, which prevents extrapolations from one member of the family to another (4-6).

Considerable interest has been devoted to the MPS by the fact that the macrophages play a major role in the immune system. Besides their phagocytic, bactericidal or tumoricidal properties, the monocytes/macrophages are involved in the initiation of the immune response (antigen presentation, interleukin 1 production and release), as well as in its regulation (alloantigen recognition, release of immunoregulatory molecules with stimulatory or suppressive activities such as interferon and prostaglandins) (5-7). Furthermore, macrophages play a crucial role as effectors of inflammatory reactions. They are able to secrete a wide range of pro-inflammatory agents including acid hydrolases, neutral proteinases (collagenase, elastase, plasminogen activator), complement components, prostaglandins (5), and they produce soluble factors i.e. mononuclear cell factor (8), synovial factor (9), catabolin (10), interleukin 1 (5-7), that stimulate the production of neutral proteinases by cells located at the site of tissue injury.

Different receptors localized into the cellular membrane of MP are involved in the control of their metabolic properties (Fc-receptors, C3b-receptors, « lectin-like » receptors) (3-5). Among these receptors, the Fc-receptor focused particular interest. Originally described in 1967 (11), it specifically binds a decapeptide of the CH3 domain of IgG1 and IgG3 (12). Recent studies support the hypothesis that human peripheral blood monocytes possess two types of Fc-receptors, one of high affinity binding monomers and complexes, and one of low affinity which predominantly binds complexes (13, 14). The Fc-receptors of the RES play a major role in the clearance and phagocytosis of immune complexes. In animal models, preformed immune complexes, particularly those of large lattice sizes, injected into the circulation are removed rapidly by cells of the RES. Efficient clearance of these preformed complexes by MP precludes their deposition in other tissue sites such as the kidney (15, 16). It has been shown in vitro that the Fc-receptors mediate different events upon interactions with IgG or immune complexes : the release of prostaglandins (17), the increase of cyclic-AMP levels (18), the secretion of acid and neutral proteinases (19), the generation of superoxide anions and other oxygen products (20), the release of mononuclear cell factor (21) and the antibody dependent cellular cytotoxicity (22).

These examples emphasize the key role of the Fc-receptors of MPS in the regulation of the immune response (23) and therefore explain the potential clinical interest of measuring their functional capacities in normal and

pathological conditions. In this review, we will successively report and discuss :

1. the methods recently set up to measure the Fc-receptor function of circulating monocytes and splenic macrophages in normal subjects;
2. the studies on the Fc-receptor function in patients presenting with various immune diseases;
3. the prognostic significance of a long lasting Fc-receptor blockade of MPS;
4. the modulation of the Fc-receptor function and the most likely causes of its impairment.

Assessment of the Fc-receptor function of MP in vivo.

Over the past 20 years, a number of techniques have been described to follow the MP function in man. These techniques used non-immunological or immunological probes. The formers studied either bloodstream clearance kinetics of inert colloidal suspensions of various labelled particles (carbon, gold, ...) (24) or the phagocytosis of carbon particles using the skin window method (25). The latter measured the clearance kinetics of heat-damaged red blood cells (HD-RBC) or of IgG-coated red blood cells. These techniques suffer from several limitations. The colloidal particles are cleared from the bloodstream by receptors other than Fc-receptors. The clearance of HD-RBC is not mediated by Fc-receptors only (26). Clearance half-times of IgG-coated red blood cells explore a whole MPS function i.e. they do not allow measurements of separated spleen and liver Fc-receptor binding capacities.

Recently, we have described (27-30) a method for the study of the Fc-receptor function of splenic and liver macrophages using autologous, Rhesus-positive, red blood cells labelled with ^{99m}Tc and coated with about 2,000 IgG anti-D antibody molecules (IgG-RBC). It has been shown that the cell membrane of IgG-RBC after labelling with ^{99m}Tc appears unaltered by scanning electron microscopy, that the ^{99m}Tc and IgG binding to erythrocytes remains stable in vivo and in vitro for up to 2 hrs, and that IgG-RBC mainly accumulate into the spleen (27-30). Subsequently, the specificity of the method has been established by following with a gamma camera the splenic and hepatic accumulation curves either of ^{99m}Tc-labelled erythrocytes coated with F $(ab')_2$ fragments of IgG anti-D antibodies or or of ^{99m}Tc-labelled erythrocytes coated with IgG anti-D antibodies and then injected into 6 patients whose spleen has been removed after trauma. It has been found that the clearance of IgG-RBC is mainly mediated by the Fc-receptors of splenic mononuclear phagocytes. This assertion is further supported by the fact that the number of IgG molecules bound per RBC ranges from 1,000 to 3,000, which is insufficient to activate the complement cascade in vivo or in vitro (31). Finally, iterative tests performed in normal volunteers have allowed the determination of the normal values and the reproducibility of the technique. We have shown (27-30) that the clearance half-time of IgG-RBC is 25.4 $\pm$ 8.2 min, (mean value $\pm$ SD), that the spleen to liver uptake ratio per surface area (S/L_s) is 31.97 $\pm$ 3.83 (mean value $\pm$ SD), and that the total spleen uptake of the injected dose is always higher than 30 % whereas the total liver uptake is lower than 3 %. One of the major advantages of our method over the previously described techniques therefore resides in the possibility of measuring not only the whole clearance half-time of the tracer but also its uptake by the spleen or the liver.

Assessment of the Fc-receptor function of MP in vitro.

Most of the cellular events mediated by Fc-receptors after interactions with IgG or immune complexes have been studied in vitro on circulating monocytes. Phagocytosis, one of the most spectacular aspect of these events, has been studied with non-immunological or immunological probes. The formers used carbon particles, latex beads or bacteria (32, 33), whereas the latter, more specific, are based on the binding and endocytosis of opsonized

yeasts (34) or of labelled monomeric and aggregated IgG (35). We have examined the status of the Fc-receptor function of circulating monocytes in vitro by a rosette assay using either sheep red blood cells coated with rabbit IgG anti-sheep antibodies or O, Rhesus-positive, red blood cells coated with human IgG anti-D antibodies (28, 30). When freshly prepared normal monocytes are allowed to adhere onto microtiter wells, most (60 to 90 %; mean value $\pm$ SEM : 77 $\pm$ 9 %, n = 32) cells exhibit a demonstrable Fc-receptor function, as evidenced by the binding or ingestion of IgG-coated erythrocytes. The specificity of the test is ascertained by the inhibition of rosette formation when normal monocytes are permitted to adhere onto wells coated with monomeric IgG and by the lack of inhibition in wells coated with their F $(ab')_2$ fragments (28-30).

Fc-receptor activity of RES in patients with immune diseases.

— *Transversal studies*

In patients presenting with a rheumatoid arthritis, we have observed that the Fc-receptor function of splenic macrophages is altered in most cases (80 %), albeit the clearance half-times generally remain within the normal range (29). Our results therefore confirm those obtained by other workers (36, 37) in terms of normality or subnormality of clearance half-times of HD-RBC. The reasons why clearance half-times remain normal despite the fact that a defective splenic Fc-receptor function is noted remain poorly understood, but the following hypothesis may be held. Firstly, at the spleen level, the relationship between saturated phagocytosis and delayed clearance half-times (T 1/2) might not be linear and therefore scanning analysis is able to detect « minimal » defects. Secondly, the S/L_s can be altered by a decreased splenic uptake, an increased hepatic uptake, or both. Our data (29) plead for this latter hypothesis. Indeed, we have observed that for a similar radioactivity level into the spleen, a greater liver uptake is noted in patients with rheumatoid arthritis, as compared to control subjects. An impaired spleen to liver balance therefore occurs in this disease. An absolute or relative decrease in the spleen phagocytic capacity might theoretically induce a prolonged T 1/2 of IgG-RBC. However, in the majority of cases, some hepatic compensation appears, preventing the T 1/2 to be out of the normal range. In 12 out of 42 patients only, we have observed abnormal T 1/2, suggesting an overflow of the spleen and the liver phagocytic capacities. The mechanisms involved in the « liver compensation » remain unknown.

The impaired Fc-receptor function is not specific of rheumatoid arthritis, since it has been observed in other so-called immune complex-mediated diseases, i.e. in systemic lupus erythematosus (38), in glomerulonephritis (26, 39), in vasculitis (26, 39), in Sjögren's syndrome (40) and in mixed cryoglobulinemia (41).

Our results in rheumatoid arthritis (29) show a relation between the S/L_s and the Steinbrocker functional class, the disease duration and the total immunoglobulin plasma levels. Evidences for a relation between immune complex-plasma levels, extra articular manifestations and overall disease activity have been previously published (42). A negative linear correlation exists between circulating immune complex-levels and the splenic uptake, which further pleads for a relation between the alteration of the Fc-receptor function and the severity of active disease. As others (43), we have observed no relation between the T 1/2 and the disease activity. This strongly suggests that the measurement of T 1/2 is far less useful than that of S/L_s to follow patients with rheumatoid arthritis. In systemic lupus erythematosus, it is generally admitted (44, 45) that the Fc-receptor functional activity is decreased, and that the magnitude of the defect is correlated with the disease activity (and particularly with « active » lupus nephritis) and the immune complex-plasma levels.

Taken together, these in vivo studies on the Fc-receptor functional activity of RES in immune complex-mediated diseases reveal a pro-

found splenic defect, frequently compensated by the liver, and related to the disease activity. This RES dysfunction may play an important role in the pathogenesis of these diseases. For example, it may be that decreased removal of soluble immune complexes from the bloodstream by the MPS may lead to enhanced tissue deposition and thefore tissue damage. The measurement of the splenic RES macrophage function may be therefore a complementary tool to evaluate the potential evolutivity of immune disorders (see longitudinal studies).

We have used a « rosette technique » to measure in vitro the Fc-receptor function of human monocytes in rheumatoid arthritis (46) and in Henoch-Schönlein disease of childhood (47). In both groups of patients, we have observed a decreased Fc-receptor function of circulating monocytes. The Fc-receptor blockade is at least the consequence of an occupancy of receptor sites by some proteic material, since the Fc-receptor function of monocytes is improved after their trypsin treatment (performed under conditions avoiding any degradation of the Fc-receptors) (48). The inverse relationship between the percentage of recovery and the basal status of Fc-receptor binding activity also support a receptor occupancy. We were unable to find any correlation between the Fc-receptor function of circulating monocytes and the immune complex-plasma levels (and the disease activity). Such an absence of relationship has been evoked by others in rheumatoid arthritis (49) and very recently a similar conclusion arises from studies in SLE patients (50). Several reasons may be raised. Firstly, the methods used for the detection of circulating immune complexes have their own limitations (51). Secondly, more and more evidences arise that blood monocytes possess two types of Fc-receptors, one of high affinity and binding IgG monomers, and the other of low affinity which predominantly binds complexes (13). Our experimental conditions (monomeric IgG-coated red blood cells) mainly explore the former binding sites. We have found an inverse relation between the percentage of recovery of Fc-receptor binding activity after trypsin treatment and the total immunoglobulin and IgG plasma levels (46). Furthermore, a more effective inhibition of the Fc-receptor function of normal monocytes is obtained when plates are coated with monomeric IgG purified from patients with rheumatoid arthritis than when plates are coated with normal monomeric IgG. IgG from patients with rheumatoid arthritis exhibit abnormalities in their sialic acid content (52) and in their circular dichroism (53). It seems therefore reasonable to suggest that in this disease, some Fc-receptors are blocked by « altered » immunoglobulin G.

Despite the fact that the Fc-receptor function of splenic macrophages and of circulating monocytes has been measured in the same patients and at the same time (46, 47), no correlations exist between the in vivo and in vitro parameters. Indeed, some patients presenting with the lowest spleen to liver ratios exhibit a quite subnormal in vitro Fc-receptor function. These results suggest that the abnormalities of Fc-receptors on tissue-bound macrophages are not necessarily reflected on circulating monocytes. They are therefore inconsistent with a genetically determined defect in the high affinity Fc-IgG receptor elaboration by those cells (see below).

— *Longitudinal studies*

Sequential measurements of the splenic RES Fc-receptor functional activity have been performed in children presenting with a Henoch-Schönlein purpura (47). During the acute phases of the disease (i.e. purpura), most children exhibit an impaired S/L_s ratio, mainly related to an alteration of the splenic Fc-receptor binding capacity. After the acute phases, the S/L_s normalizes in recovering patients. On the contrary, all patients with persistent urinary findings (microscopic hematuria or/and proteinuria) or relapsing purpura continue to present impaired RES function, increased IgA plasma levels and circulating immune complexes. A statistically significant inverse linear correlation has been observed between the splenic macrophage function and the IgA plasma levels

(47). Comparable results have been recently obtained in patients with systemic lupus erythematosus (44), in which clinical course and changes in receptor functional activity over time have been found to be significantly correlated. On the contrary, T 1/2 of IgG-RBC tends to return to normal in all patients who clinically improve (44). These two examples illustrate the clinical interest of the sequential measurements of the Fc-receptor function of splenic macrophages during the course of some immune disorders. Indeed, the persistence of an Fc-receptor blockade might be useful for predicting potential relapsers.

Modulation of the Fc-receptor function of RES

Before describing a few examples of modulation of the Fc-receptor macrophage function, it is necessary to discuss the two major hypotheses advanced to explain the occurrence of an Fc-receptor blockade, i.e. an occupancy of the receptors or an inherited defect (or both). Saturation of Fc-receptors by immunoglobulin G (monomeric or involved in immune complexes) leads to a competitive inhibition between these Fc fragments and those of IgG coating the erythrocytes. The Fc-receptor of monomeric IgG is resistant to trypsin treatment in man (48). We have observed that the Fc-receptor function of monocytes from patients with rheumatoid arthritis is improved after trypsin treatment, which suggests a receptor occupancy by some proteic material (46). What is the nature of the molecules occupying the Fc-receptor sites ? Our data in rheumatoid arthritis suggest a role for immune complexes in the Fc-receptor blockade. Indeed, we have observed a negative linear correlation between the immune complex-plasma levels measured by the Clq binding assay and the splenic uptakes in the « Clq-positive » patients (29). Furthermore, it has been shown recently (54) that the Fc-receptor function is depressed after immune complex-like material injection in patients suffering from hemophilia. However, the immune complexes are probably not the sole accountable agent responsible for the altered Fc-receptor function in rheumatoid arthritis since « Clq-negative » patients also exhibit pathological S/L_s ratios. We have noted a negative linear correlation between the S/L_s and the total immunoglobulin concentrations (29). IgG from patients with rheumatoid arthritis are able to block the splenic function of rats to the same degree as normal human aggregated IgG taken as a model of immune complexes (unpublished observations). Furthermore, a more effective inhibition of the Fc-receptor function of normal monocytes is obtained in vitro when plates are coated with monomeric IgG purified from patients with rheumatoid arthritis instead of normal monomeric IgG (46).

Taken together, these data support the hypothesis that in rheumatoid arthritis the Fc-receptors are saturated by the Fc domain of some « abnormal » IgG. It must be recalled that IgG purified from patients with this disease exhibit both biochemical (52) and structural (53) abnormalities.

Another hypothesis is a genetic defect. It has been shown indeed (55) that the relatives from patients with dermatitis herpetiformis and presenting the HLA-B8/DRw3 haplotype have a decreased Fc-receptor function of their splenic mononuclear phagocytes. Furthermore, normal young adults with a DR2 and MT1 haplotype also present a defect of their Fc-receptor RES function (56). These results suggesting that the basal in vivo MPS clearance is immunogenetically determined are however in contradiction with the following observations. Firstly, in systemic lupus erythematosus, the number of Fc-receptors of circulating monocytes is normal or increased, despite the fact that the Fc-receptor function of splenic macrophages is defective (50, 57). These data are inconsistent with a genetically determined defect in Fc-receptor elaboration by MPS. Secondly, in macrophages derived from C3H/HeJ mice, - a strain genetically « hyporesponsive » to endotoxin, a potent macrophage differentiating agent-, an alteration in the Fc-receptor function exists, which induces a decreased capacity of these cells to phagocytose via Fc-receptor-dependent mechanisms (58). After incubation

with lymphokine-rich spleen cell culture supernatants from endotoxine-sensitive mice (C3H-/HeN), the C3H/HeJ macrophages exhibit an almost complete correction of their Fc-receptor expression and, simultaneously, of their Fc-receptor-mediated phagocytic defect (58). These experiments clearly show that, in this model, an abnormal phenotypic expression of Fc-receptors rather than a primary genetic abnormality in their elaboration is responsible for the decreased phagocytic activity of mononuclear phagocytes. Furthermore, they demonstrate that the Fc-receptor defect is corrigible and that the phenotypic expression op Fc-receptors may be under control of a lymphokine-affecting monocyte function.

The Fc-receptor function can be modulated in vivo by plasma exchanges (26, 38, 59), by corticosteroid administration (28) and by high-dose intravenous gamma globulin (60, 61). Plasma exchanges represent, as far as we are aware, the first well-documented example of modulation of the splenic Fc-receptor function in human diseases. It has been found (26) that, in 9 out of 10 patients presenting with nephritis or vasculitis, plasma exchanges induced a reversal of splenic Fc-receptor blockade. In most patients, a clinical improvement occurred and circulating immune complexes were no longer detectable when splenic function had improved. The mechanisms involved remain poorly understood. It seems reasonable to suggest that the reversibility of the Fc-receptor blockade is related to the ex vivo removal of large amounts of circulating immune complexes or immunoglobulins, leading to a displacement of the equilibrium rate between macrophage-bound and free IgG or immune complexes. Since reversible hyposplenism can also be found in patients without detectable circulating immune complexes (26, 59), it is conceivable that other mechanisms may also operate. Whatever mechanisms involved, the finding of splenic Fc-receptor blockade may serve to identify those patients in whom plasma exchange is a useful component of therapy.

We have shown (28) that after one single ingestion of 32 mg of methylprednisolone, the Fc-receptor function of splenic macrophages is impaired in five out of ten volunteers. Our results in human are therefore in complete agreement with those obtained by Atkinson and Franck in guinea pig., using a quite different methodology, i.e. the measurement of the whole clearance of IgG-coated erythrocytes (62). We have further demonstrated that in human the functional defect is located not only on splenic macrophages, but also on circulating monocytes. In our experimental conditions, the Fc-receptor function of the spleen remains unchanged in five subjects after corticosteroid was given (« non-responders »). Since the clearance rate of IgG-coated erythrocytes varies according to the amount of antibody bound, we have measured the anti-D IgG binding capacity of erythrocytes from « responders » and « non-responders ». We have shown (28) that the « non-responders » are not different from the « responders » with respect to the degree of red cell sensitization. Solubilized hydrocortisone inhibits the mononuclear Fc-receptor function in a dose-response fashion in vitro (63). The relatively low dose of methylprednisolone given might therefore explain that some subjects did not respond to corticosteroid by a defect in their Fc-receptor function. However, precise correlations between plasma methylprednisolone concentrations and S/L_s must be established before assuming that such a dose-response relationship might also operate in vivo. Our studies clearly show an impairement of the Fc-receptor function of MPS in some subjects receiving a rather low dose of methylprednisolone. This Fc-receptor blockade may contribute to the infectious complications occurring in some patients receiving comparable doses of corticosteroids. Conversely, the absence of Fc-receptor blockade in other subjects might be of practical interest during corticosteroid therapy by delineating the patients in whom infectious complications might be conceptually less probable.

Treatment of patients with idiopathic thrombocytopenic purpura by high-dose intravenous

gamma globulin usually leads to a prompt increase in the circulating platelet count (64, 65). This increase is associated with a parallel prolongation of both hepatic and splenic Fc-receptor-mediated MPS clearance of IgG-RBC (60, 64). Because monomeric IgG can inhibit Fc-receptor ligand interactions (48), the rapid increase in monomeric IgG serum concentration which occurs during gammaglobulin therapy (64) might enhance the competition of monomeric IgG with IgG-coated platelets in vivo and therefore delay their clearance by splenic macrophage Fc-receptors. Alternatively, because gammaglobulin does contain some small IgG aggregates, it might induce an Fc-receptor blockade as observed in patients with hemophilia receiving factor VIII infusion (54). In vitro assessment of blood monocyte Fc-R function shows a strong decrease in the affinity of Fc-receptor-specific IgG oligomer binding,- but not in the maximum number of binding sites-, after gammaglobulin therapy, which supports the second explanation i.e. a possible role for small IgG aggregates in the modulation of the affinity properties of some Fc-receptors (61).

RESUME

Des titres élevés de complexes immuns sont décelés dans la circulation de patients souffrant de maladies immunologiques diverses. Le dépôt tissulaire de ces complexes pourrait jouer un rôle important dans la pathogénie de ces maladies. Le système réticuloendothélial (SRE) comprenant notamment les cellules de Kupffer du foie et les macrophages spléniques, est responsable, du moins en partie, de l'élimination de ces complexes immuns du sang circulant. Un déficit de cette fonction de clairance pourrait donc faciliter le dépôt tissulaire des complexes immuns et le développement de la réaction inflammatoire. C'est pourquoi, durant ces dernières années, un intérêt particulier s'est porté vers l'étude de la fonction Fc-récepteur, qui intervient directement dans l'élimination des complexes immuns. La fonction Fc-récepteur globale du SRE peut être étudiée par l'utilisation d'hématies autologues recouvertes d'IgG et marquées au ^{51}Cr. Dans la plupart des maladies à immun-complexes, une augmentation de la demi-vie du traceur est généralement trouvée. Utilisant comme traceur des hématies autologues recouvertes d'IgG mais marquées au ^{99m}Tc, il a alors été possible de déterminer non seulement la demi-vie plasmatique de ce traceur mais aussi de calculer son accumulation splénique et hépatique dépendant du fonctionnement des récepteurs Fc. C'est ainsi que l'on a pu clairement démontrer que les rapports d'accumulation dans la rate et le foie, calculés par unité de surface, sont profondément pathologiques dans ces maladies immunes, même lorsque la demi-vie plasmatique du traceur restait dans des valeurs normales. Ces rapports pathologiques sont le résultat à la fois d'une diminution de l'accumulation splénique et d'une augmentation de l'hépatique, cette « compensation hépatique » empêchant le T 1/2 de s'écarter des valeurs normales. Une demi-vie pathologique du marqueur ne s'observe donc que lorsque les capacités de phagocytose de la rate et du foie sont dépassées.

Le blocage de la fonction Fc-récepteur de la rate est généralement corrélé avec l'activité de la maladie et moins fréquemment avec le taux plasmatique des complexes immuns. Des mesures séquentielles des rapports rate/foie par unité de surface peuvent ainsi être d'un intérêt pronostique, car elles permettent de définir les patients chez qui l'évolutivité de la maladie est particulièrement élevée. Enfin, la réalisation d'études séquentielles a autorisé l'étude in vivo de la modulation de la fonction Fc-récepteur des macrophages par les plasmaphérèses, l'administration de corticostéroïdes et la perfusion de hautes doses de gammaglobulines.

SAMENVATTING

Circulerende immuuncomplexen kunnen worden teruggevonden bij patiënten met allerlei immuunziekten en men denkt dat het neerslaan van deze complexen belangrijk is bij de pathogenese van deze aandoeningen. Het reticulo-endotheliaal systeem, met inbegrip van de Kupffercellen van de lever en van de makrofagen in de milt, is betrokken bij het verwijderen van deze circulerende immuuncomplexen uit de circulatie. Een defect in de klaring van deze complexen kan leiden tot een verhoogd neerslaan in de weefsels. Vandaar dan ook dat gedurende de laatste jaren er meer en meer interesse is voor het meten van deze immuunklaring gemedieerd door Fc-receptoren. IgG-coated autologe rode bloedcellen (IgG-RBC) gemerkt met ^{51}Cr werden gebruikt als immuun-tracers om de Fc-receptor functie van volledig reticulo-endotheliaal systeem te volgen in normale en pathologische situaties. Vertraagde klaring van IgG wordt over het algemeen gevonden bij de meeste immuuncomplexgemedieerde ziekten. Met IgG-RBC gemerkt met ^{99m}Tc, is het mogelijk niet alleen de halfwaardetijd van klaring van de tracer te kennen maar ook de bindingscapaciteit van Fc-receptoren van lever en milt afzonderlijk te meten. Er kon duidelijk worden aangetoond dat de milt-lever ratio's per oppervlakte (S/L_s) abnormaal zijn bij immuunziekten, ook wan-

neer de halfwaardetijden voor klaring binnen normale grenzen blijven. Deze abnormale ratio's zijn het gevolg zowel van een verminderde miltopname als van een verhoogde leveropname van IgG-RBC; de compensatie door de lever maakt dat de halfwaardetijd binnen normale grenzen blijft. Abnormale halfwaardetijden worden dan ook slechts gezien wanneer de fagocytaire capaciteit van lever en milt verzadigd is. Fc-receptor blokkering in de milt is in het algemeen gecorreleerd met de aktiviteit van het ziekteproces en, in minder mate, met de plasmaconcentraties van immuuncomplexen. Seriële meting van S/L_s kan dan ook in de kliniek interessant zijn om patiënten te definiëren met een hoge kans op sterke evolutie van de aandoening. Ten slotte laten seriële metingen van S/L_s toe in vivo de modulatie van de makrofage Fc-receptorfunctie te volgen die gebeurt bij plasmawisseling, toediening van corticosteroïden en infusie van gammaglobulines in hoge doses.

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