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Free immunoglobulin light chains: A role in minimal change disease

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Abstract Immunoglobulins are tetrameric molecules consisting of two heavy and two light chains linked by disulfide bonds. Single light chains are normally secreted in the plasma under soluble form. These immunoglobulin free light chains circulating in the blood may hold unexpected roles in diseases.

Minimal change disease is defined as a renal disease with massive proteinuria and no obvious damage on light microscopy. We hypothesize that minimal change disease is not a primary renal disease but an immune disease due to a defect in B cells mediated by a special immunoglobulin chain. The efficiency of drugs targeting the immune system and the association to Hodgkin disease as well as: (1) the efficiency of B cell depletion to prevent relapse; (2) the association with B leukemia; and (3) the activation of CD23 during relapse point up a primary involvement of B cells. We hypothesize that an immunoglobulin chain with special polymorphism might be the link between the immune system and the dysfunction of the glomerular wall while immunoglobulin depletion leads to a transient remission of proteinuria in graft recurrence of the disease and nephropathy mediated by a monoclonal immunoglobulin chain may feature minimal change disease.

Other diseases where free light chains may be involved include atopy, thromboembolism, glomerular inflammatory diseases and autoimmune diseases. We conclude that free circulating light chains, through infinite possibilities of polymorphisms determined by the variable domain are potential disturbing agents of many biological cascades or structures and could likely play the first role in multiple diseases.

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Introduction

Immunoglobulins are tetrameric molecules consisting of two heavy and two light chains linked by disulfide bonds and assembled in the endoplasmic reticulum of B and plasma cells. Single heavy chains are sequestered in the endoplasmic reticulum through specific binding to the chaperone BIP until they bind a light chain, which leads to the release of the chaperone BIP and the complete immunoglobulin [1]. Therefore, heavy chains are not normally detectable in the blood circulation in physiological conditions. However, pathologic truncated gamma chains that express a reduced number of binding sites to BIP in the CH1 domain are able to circulate in the blood, leading to kidney diseases [2]. Light chains also bind to the chaperone BIP and are retained in the endoplasmic reticulum but, depending on the conformation of the variable domain, some of them are normally secreted in the plasma under soluble form through a peptide signal [3,4]. They have a low molecular weight (25—27 kD), a large range of isoelectric point, are filtrated up to 40% of the creatinine clearance mostly reabsorbed and hydrolyzed in the proximal convoluted tubule [5]. Physiological secretion and urinary output allow a balanced plasma concentration up to 3—25 mg/L of lambda and kappa chains, respectively [6]. Light chains can form dimers with a functional epitope domain able to recognize antigens but are likely to lack the ability to challenge a specific immune response in the absence of Fc domains [7]. Light chains are also members of the immunoglobulin superfamily that are able to interact with other members of the Ig superfamily through their beta sheets sandwich inasmuch they share at least 30% sequence homology or by a series of different adhesion domains like fibronectin, laminin or integrin domain [8]. The physiological role of free light chains is unknown but they may have a significant functional contribution in the immunoglobulin network. We suggest that this function has a pathologic counterpart and that immunoglobulin free light chains circulating in the blood may hold unexpected roles in diseases. In particular, minimal change disease that was the most striking enigma of Pediatric Nephrology for a century might be figured out through the involvement of B cells and immunoglobulin light chains.

Minimal change disease

Minimal change disease is defined as a renal disease associated with massive isolated proteinuria without obvious abnormalities of the glomeruli under light microscopic examination. Only electron microscopy or very close light microscopy are able to show damage limited to the effacement of podocyte foot processes. The name ''minimal change disease'' underlines this paradox between apparent minimal damage of the kidney and a heavy functional consequence. Both changes in the sieving coefficient of proteins by the glomerular wall and in the podocyte morphology are functional alterations completely reversible within a few days under steroid therapy [9]. As a matter of fact, the complete response to steroid therapy is the second paradox in this disease where glomeruli are free from immunoglobulin deposits and inflammatory cells. A biochemical or metabolic defect that leads to episodic and potentially reversible changes in the permeability of the glomerular basement membrane was formerly considered as the basic abnormality of the disease [10]. Further demonstrations of the efficiency of alkylating agents, cyclosporine and mycophenolic acid as well as the recurrence of proteinuria after renal transplantation have pointed out the potential links between a dysfunction of the immune system and the kidney through the mediation of a soluble glomerular permeability factor circulating in the blood during flares of massive proteinuria [11,12]. However, direct evidence of the abnormal subset of immune cells necessarily involved in the disease is always lacking. Moreover, several attempts to identify the glomerular permeability factor, which is responsible for a 1000—10,000-fold increase of albumin clearance, systematically failed (reviewed in ref. [13]). In response to this disappointment, some authors recently suggested that immune mechanisms have been overstated in steroid sensitive minimal change disease, and that podocyte damage may be the direct target of environmental factors [14,15]. They based their prospect on the regulation of the actin cytoskeleton in podocyte by cyclosporine and the direct effect of glucocorticoids on the protection and the recovery of cultured podocytes through the stabilization of actin filaments [16].

B cells, main protagonists in minimal change disease?

Minimal change disease may be considered as a B cell disease, mainly because the remission of proteinuria is closely dependent on agents that are able to disrupt B cell viability and the production of immunoglobulins:

(1) Remission of minimal change disease following measles: measles dose-dependently impairs the proliferation of EBV-transformed B cell lines [17], and binding of the viral glycoprotein N to Fc-gamma-R_2 directly affects the synthesis of immunoglobulins, whether B cells are stimulated by antibody or by CD40L [18].

(2) Rapid remission of proteinuria under prednisone: glucocorticoids have been reported for a long time as potent T cell killers. However, glucocorticoids are also efficient B cell killers. The sensitivity of B cells to dexamethasone-induced apoptosis varies with their differentiation status: pre B cell are resistant to glucocorticoids whereas splenic immunoblasts and mature B cells respond to low concentrations of dexamethasone [19].

(3) Prolonged remission following cyclophosphamide therapy: according to several studies measuring peripheral B cell count in patients, cyclophosphamide is a potent B cell killer [20].

(4) Cyclosporine and tacrolimus are antagonists to calcineurin widely used in minimal change disease to prevent relapses and to avoid steroid intoxication [9]. Calcineurin plays a central role in TCR signaling. In addition, calcineurin regulates cytoskeleton organization in the podocyte and may impact the level of proteinuria in experimental glomerulonephritis [16]. However, calcineurin has also been involved in the regulation of apoptosis and selection of B cells as well as in the process of B cells differentiation