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Editorial:

APOPTOTIC BODIES AND GLOMERULONEPHRITIS

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Version en español

Inspite of many glomerular damage patterns are associated with other diseases such as cancer, lupus, eclampsia, antiphospholipid syndrome and different autoimmune diseases, the pathophysiological origin of glomerulonephritis (the etiology of these associations) is still unknown. Currently the immunosuppressive treatment in the glomerulonephritis is defined according to the histopathological pattern of the renal biopsy.

The process of apoptosis is part of normal cellular homeostasis of the organism. The cell that undergoes apoptosis suffers important changes until its fragmentation in vesicles or apoptotic bodies, which are structures surrounded by a modified plasma membrane and with intracellular residues in its interior. The apoptotic bodies are rapidly destroy by macrophages thus avoiding their permanence and the generation of an autoimmune response to damaged internal antigens or internal antigens externalized in the modified lipid membrane, being therefore apoptosis a mechanism that tends to avoid inflammation. But this rapid mechanism of phagocytosis can be altered, for example by having excess apoptotic bodies by increased generation in patients with cancer, altered phagocytosis, etc., generating the permanence of cellular debris leading to the development of an inflammatory activity (secondary necrosis) and autoimmunity production[1].

Usually the phospholipids of the cellular lipid membrane are in an asymmetric state, so that phosphatidylserine and sphingomyelin are found in the inner side, looking inward while the phosphatidylcholine is on the outer side of the membrane. In the process of apoptosis and formation of apoptotic bodies the exteriorization of internal phospholipids to the outer layer of the lipid membrane occurs and the phosphatidylserine is exposed, so the normal asymmetry of the lipid membrane is lost[2].

Apoptotic bodies are apoptotic cell fractions wrapped in a lipid membrane which have

externalized phosphatidylserine. The externalized phosphatidylserine acts as the main signal for the apoptotic body to be recognized and destroyed rapidly by phagocytes such as macrophages and dendritic cells, but if this removal mechanism fails, it may act to promote platelet activation or stimulate the formation of antiphospholipid antibodies [1,3].

The formation of apoptotic bodies (vesicles) facilitates the remodeling of cellular debris generated by apoptosis and prevents the development of inflammatory and autoimmune events[3].

The annexin V is a calcium binding protein distributed in various tissues of the body, and specifically is found at the kidney in the glomerulus and in the distal tubule. It is an early marker of apoptosis that is used as a method of detecting apoptosis experimentally. Its function is linked to apoptosis since it binds to phosphatidylserine, phospholipid that is externalized in the cell membrane during apoptosis[4].

A hypothesis about the origin of systemic lupus erythematosus (SLE) refers to a defect in the elimination of apoptotic cells associated with an increase of circulating apoptotic bodies (by default in the clearance of apoptotic bodies), where these could act as autoantigens generating the creation of antiphospholipid antibodies, antibody antigen reaction and inflammatory reaction[3].

C1q is one of the early factors of the complement that participates in the clearance of apoptotic bodies and it was demonstrated that mice with C1q (mutated) deficits generate lupus nephritis. This was called the paradox of lupus because in the inflammatory environment of SLE there are complement consumption. In mice deficient in C1q, there is also an increase in apoptotic cells in the glomerulus (suggesting apoptotic cells in the periphery), which may be a direct result of the failure to remove apoptotic bodies in vivo[5].

In addition, it has been documented that in SLE there is an increase in circulating apoptotic bodies and an increase in apoptotic cells in the germinal centers of the lymph nodes[6-7].

It has recently been found that failure in the degradation of chromatin contained in apoptotic bodies or the inappropriate removal of apoptotic cells contributes to the development of autoimmunity. It has also been found that this latter situation leads to an autoimmune phenotype development in murine models, since these cells, when not ingested, evolve towards secondary necrosis, generating danger signals, and becoming available for ingestion by dendritic cells and macrophages but under an inflammatory environment[1].

On the other hand, in idiopathic membranous nephropathy a target against which antibodies are formed, called the target "phospholipase A2 receptor" (PLA2-R), a transmembrane receptor expressed in glomerular podocytes and autoantibodies directed against this receptor[8-9]. These receptors are increased in the kidneys of patients with biopsy compatible with membranous nephropathy[9], with phospholipase A2 being responsible for cleaving the externalized internal phospholipids (phosphatidylserine) of the apoptotic bodies. Phospholipase A2 also has as its main function to act on internal phospholipids of the lipid membrane, or on these internal

phospholipids externalized by processes of apoptosis[10].

In women with eclampsia, loss of recurrent pregnancies and / or antiphospholipid syndrome, a mutation in the annexin V gene was demonstrated with lower levels of circulating annexin V. Additionally, to a lesser amount of annexin V in the placenta of women with eclampsia and loss of recurrent pregnancies, it is considered annexin V as a protective molecule because it is immunomodulatory and thromboprotective[11-12].

Annexin V is a molecule that has the ability to bind to the externalized phosphatidylserine of the apoptotic bodies, avoiding that this externalized internal phospholipid acts as an autoantigen and triggers the formation of antiphospholipid antibodies, so it is seen as a protective shield of the formation of autoantibodies in antiphospholipid syndrome.

In addition, phosphatidylserine, when externalized, also acts as a procoagulant factor triggering platelet activation, with annexin V being a protective factor against thrombosis by hiding externalized phosphatidylserine[13].

Given the uncertain origin of many glomerulopathies, the overlapping and difficult classification of them, we could ask: are different glomerulopathies mediated by similar pathophysiological mechanisms? Could glomerular damage be associated with an inflammatory reaction generated by the deposition of circulating apoptotic bodies at the glomerular level? The excess of circulating apoptotic bodies (generated by defects in their clearance in SLE or by excess production of them in patients with tumors or chronic inflammatory processes) would be deposited in the glomerular barrier generating inflammation and renal damage? These are the questions that currently guide the research in glomerulonephritis, looking for an answer.

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