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Review

Immune response and histology of humoral rejection in kidney transplantation

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ABSTRACT

The adaptive immune response forms the basis of allograft rejection. Its weapons are direct cellular cytotoxicity, identified from the beginning of organ transplantation, and/or antibodies, limited to hyperacute rejection by preformed antibodies and not as an allogenic response. This resulted in allogenic response being thought for decades to have just a cellular origin. But the experimental studies by Gorer demonstrating tissue damage in allografts due to antibodies secreted by B lymphocytes activated against polymorphic molecules were disregarded.

The special coexistence of binding and unbinding between antibodies and antigens of the endothelial cell membranes has been the cause of the delay in demonstrating the humoral allogenic response. The endothelium, the target tissue of antibodies, has a high turnover, and antigen–antibody binding is non-covalent. If endothelial cells are attacked by the humoral response, immunoglobulins are rapidly removed from their surface by shedding and/or internalization, as well as degrading the components of the complement system by the action of MCP, DAF and CD59. Thus, the presence of complement proteins in the membrane of endothelial cells is transient. In fact, the acute form of antibody-mediated rejection was not demonstrated until C4d complement fragment deposition was identified, which is the only component that binds covalently to endothelial cells.

This review examines the relationship between humoral immune response and the types of acute and chronic histological lesion shown on biopsy of the transplanted organ.

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Respuesta inmune e histología de rechazo humoral en el trasplante renal

Palabras clave:
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RESUMEN

La respuesta inmune adaptativa constituye la base del rechazo del aloinjerto. Sus armas lesivas son la citotoxicidad celular directa o los anticuerpos. La primera, identificada desde los inicios del trasplante de órganos y la segunda, limitada al rechazo hiperagudo por anticuerpos preformados y no como respuesta alogénica. Ello permitió mantener durante décadas que la respuesta alogénica tenía solo un origen celular. Pero se ignoraron los trabajos experimentales de Gorer que demostraban daño tisular en aloinjertos por anticuerpos secretados por linfocitos B activados frente a moléculas polimórficas.

La especial convivencia de unión y desunión entre anticuerpos y antígenos de membrana de células endoteliales ha sido la causa que retrasó la demostración de la respuesta alogénica humoral. El endotelio, que es el tejido diana de los anticuerpos, tiene un *turnover* alto y la unión antígeno-anticuerpo no es covalente. Si las células endoteliales sufren el ataque de la respuesta humoral, eliminan rápidamente de su superficie las inmunoglobulinas mediante *shedding* o internalización y, a la vez, degradan los componentes del complemento por la acción de MCP, DAF y CD59. Así, la presencia de las proteínas del complemento en la membrana de las células endoteliales es pasajera. De hecho, la forma aguda de rechazo por anticuerpos no se demostró hasta identificar el depósito del fragmento C4d del complemento, que es el único de unión covalente a las células endoteliales.

Esta revisión analiza la relación entre la respuesta inmune humoral y los tipos de lesión histológica aguda y crónica de la biopsia del órgano trasplantado.

Introduction

Renal biopsy is the gold standard diagnostic test for acute rejection (AR) after renal transplantation (RT). Distinctively, it shows an infiltration of mononuclear cells (T lymphocytes), considered specific by the Banff classification when it affects the tubules (tubulitis) and/or the endothelium (endothelitis).[1,2] Based on this, during the first four decades of RT, the cell theory remained the sole theory for AR, and humoral response was limited to hyperacute rejection, caused by preformed antibodies against HLA class I antigens and not secondary to the response of the recipient.[3,4]

However, during this long time the experimental work of Gorer was unknown. His studies demonstrated the formation of antibodies against H-2 histocompatibility antigens in 21 of 22 mice, after implantation of allogeneic sarcoma cells and in skin allografts, in response to antigen stimulation.[5–7] Additionally, Morris showed the presence of cytotoxic antibodies following RT in man.[8]

Not until the early 1990s did Feucht show the presence of C4d deposits in peritubular capillaries as a mark of complement system activation by the action of anti-HLA antibodies.[9,10] Subsequently, the work of Terasaki[11,12] and the successive contributions of the Banff classification[13,14] cleared the way for the diagnosis of humoral AR. Although doubts remain about the cell and molecular pathways regulating antibody-mediated rejection, current understanding of their immunobiology shows that activation of B lymphocytes induced by polymorphic molecules (HLA or non-HLA) results in the formation and secretion of donor-specific antibodies (DSA) that damage the allograft.[15,16] This review examines the relationship between the immune response and the histology of humoral rejection in RT.

Immune system

The foundations of what is now known as the humoral immune response were established millions of years ago when the first living beings shared their habitat with pathogens that posed a threat to their survival. This evolutionary challenge led to the creation of a defense infrastructure known as the immune system (IS).[17]

The most elementary invertebrates developed an IS similar to phagocytosis and the more complex invertebrates developed an IS composed of molecules (cytokines, complement system and acute phase proteins) and eminently phagocytic cells (neutrophils, monocytes, macrophages, eosinophils, basophils, mast cells, natural killer [NK] and dendritic cells). These lacked immunological memory, had limited progeny, a relatively long life and high efficiency receptors encoded in the germline, which only recognized microorganism structures called "**pathogen-associated molecular patterns**"; they were therefore unable to recognize other molecular differences. This response is known as **innate immunity**.[18]

Evolutionary pressure, in a continuous process of "**adapt or die**", allowed vertebrates to complete their IS, adding a new identification and defense infrastructure known as **adaptive or acquired** immune response,[18,19] consisting of T and B lymphocytes. The distinctive element of this system is its ability to generate membrane receptors by random gene rearrangements; representing a high capacity to form very