



B-Cell Targets to Treat Antibody-Mediated Rejection in Transplantation

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Antibody-mediated rejection (AMR) in allograft transplantation can be defined with a rapid increase in the levels of specific serological parameters after organ transplantation, presence of donor specific antibodies (DSAs) against human leukocyte antigen (HLA) molecules, blood group (ABO) antigens and/or endothelial cell antigens (e.g. MICA, ECA, Vimentin, or ETAR) and also particular histological parameters [1,2]. If the AMR persists or progresses, the treatment to eliminate the humoral component of acute rejection include three sequential steps: (a) steroid pulses, antibody removal (plasma exchange or immuno-adsorption) and high doses of intravenous immunoglobulin-IVIG, (b) Rituximab (anti-CD20) or Bortezomib (anti-proteasome), and finally (c) Eculizumab (anti-C5) and rescue splenectomy.

The true role of DSA response to solid allograft and the role of the ontogeny of B cells are not fully understood in all types of transplant, especially in liver transplantation [3-5] but it is known the eventual potential of B cell managing to prevent and treat an antibody mediated rejection.

In this sense, B-cell precursors, immature B cells, transitional B cells, activated B cells, memory B cells, plasmablast and plasma cells are all the possible cellular targets that block alloantibody production. However, we have to take into account a potential risk of targeting B cells, particularly in regard of the infectious risk.

Firstly, cellular markers of B cells are being studied to modify antibody-mediated response. In this group we have molecules as important co-receptors of BCR (B cell receptor). CD19, CD79, CD21 or CD81 molecules are examples of target molecules. Other important activating receptors in B cells are CD40, CD80, CD86, CD27, CD70 and CD30. Important used agents commercially available against particular molecules are Rituximab, ⁹⁰Y-Ibritumomab Tiuxetan, ¹³¹I-Tositumomab, Ofatumumab (CD20), Blinatumomab (CD19), Abatacept (anti-CD80) and Brentuximab vedotin (CD30). New agents in study are Polatuzumab-vedotin (CD79b), Dacetuzumab and Lucatumumab (CD40), Vorsetuzumab mafodotin (CD70) and Galiximab (CD80).

Second, B-cells also receive co-activation and survival signals via cytokines as IL-6, IL-7, IL-21, BAFF (B-cell activating factor) and

APRIL (a proliferation-inducing ligand). These co-activation signals are required for B-cell differentiation into plasma cell and enhancing their posterior survival and are a key determinant of whether developing B-cells will survive or die during the establishment of immuno-tolerance [5,6]. Important used agents commercially available are Tocilizumab (anti-IL6R) and Belimumab (BAFF).

The receptors of BAFF and APRIL could also be important as eventual targets, for example BAFF-R, TACI (transmembrane activator and calcium modulator and cyclophillin ligand interactor) and BCMA (B-cell maturation antigen). These receptors are important in B cell maturation and in antibody production. New agents in study are Atacicept (TACI) or GSK2857916 (BCMA).

Third, co-receptors that down-modulate the B cell receptor (BCR) signal may act as double agents, since they could act as a marker to kill B cells or suppress B cell activation via agonist agents, between these, CD22, CD72 and the low-affinity receptor for Ig-G (FcγRIIB) could also be important targets [7]. In this sense, CD22 functions as a negative regulator of B cell signals transduction and seems to be a promising target. Important agents are Epratuzumab or Inotuzumab-ozogamicin (CD22).

Finally, other molecules that appear in B cell ontogeny may be of interest although they are less specific. In this group, we can find molecules as CD10, CD23, CD24, CD25, CD38, CD52 or CD138. Important used agents commercially available are Daclizumab (CD25) and Alemtuzumab (CD52). New agents in study are Lumiliximab (CD23) and Daratumumab (CD38).

However, one of principal problem to find a definitive target is that the majority of molecules described above are shared by other cells of the immune system or by different tissues carrying out important functions.

On the other hand, before considering the best targets for preventing antibody production, we must take into account that B-cells not only participate in antibody production but also play an important role as antigen presenting cell (APC) to activate CD4 lymphocytes. Moreover, a specific subpopulation of B cells has also been identified as regulatory B-cell (Bregs) with capacity to release immunomodulatory cytokines (i.e. TGF-β, IL-10 and IL-35) [5]. Therefore, there is growing evidence that

B-cells are essential contributors to transplant tolerance, so it would be interesting to design strategies to minimize the damage of immunoregulatory B-cells. The eventual interaction and the balance between Tregs and Bregs is matter of controversial, needing more future research studies [8,9]. However, the majority of agents that target against many of the B-cell molecules are used to treat B-cell malignancies or some autoimmune conditions such as lymphomas, leukemia, multiple myeloma, lupus, rheumatoid arthritis or multiple sclerosis. Therefore, the design of the better targets on B-cells should consider that the proposed targets should be as B-cell restricted as possible, that they should be present on all antibody producing B-cell stages, and that they should protect the regulatory B-cell profiles.

In conclusion, B-cell targets to prevention and treatment of antibody-mediated rejection will be a key point in a better graft survival outcome and define a therapeutic arsenal to avoid graft failure. However, further efforts by researchers and clinicians are needed to translate research into clinical practice. Indeed, more and, retrospective and prospective data are also needed with well-discussed and well-designed studies to define whether these targets would be useful in accurate prediction of organ function outcome after transplantation.

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References

1. Muro M, Llorente S, Marín L, Moya-Quiles MR, Gonzalez-Soriano MJ, et al. (2005) Acute vascular rejection mediated by HLA antibodies in a cadaveric kidney recipient: discrepancies between FlowPRA™, ELISA and CDC vs luminex screening. *Nephrol Dial Transplant* 20: 223-226.
2. Muro M, González MJ, Salgado G, López R, Boix F, et al. (2010) Specific "intra-allele" (IA) and "intra-broad antigen" (IBA) HLA alloantibodies in kidney graft transplantation. *Hum Immunol* 71: 857-860.
3. Archdeacon P, Chan M, Neuland C, Velideodeoglu E, Meyer J, et al. (2011) Summary of FDA antibody-mediated rejection workshop. *Am J Transplant* 11: 896-906.
4. Tait BD, Susal C, Gebel HM, Nickerson PW, Zachary AA, et al. (2013) Consensus Guidelines on the Testing and Clinical Management Issues Associated With HLA and Non-HLA Antibodies in Transplantation. *Transplantation* 95: 19-47.
5. Galian JA, Mrowiec A, Muro M (2016) Molecular targets on B-cells to prevent and treat antibody-mediated rejection in organ transplantation. Present and Future. *Expert Opin Ther Targets* 20: 859-867.
6. Muro M, Moya-Quiles MR, Mrowiec A (2016) Humoral response in liver allograft transplantation: a review of the role of anti-human leukocyte antigen (HLA) antibodies. *Curr Protein Pept Sci*.
7. Smith KGC, Clatworthy MR (2010) FcγRIIB in autoimmunity and infection: evolutionary and therapeutic implications. *Nature Rev Immunol* 10: 328-343.
8. Boix-Giner F, Millán O, San Segundo D, Muñoz-Cacho P, Mancebo E, et al. (2016) High frequency of central memory regulatory T cells allows detection of liver recipients at risk of early acute rejection within the first month after transplantation. *Int Immunol* 28: 55-64.
9. San Segundo D, Millán O, Muñoz-Cacho P, Boix F, Paz-Artal E, et al. (2014) High proportion of pre-transplantation activated regulatory T cells (CD4+CD25highCD62L+CD45RO+) predicts acute rejection in kidney transplantation: results of a multicenter study. *Transplantation* 98: 1213-1218.