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Review

Immune checkpoint molecules in solid organ transplantation: A promising way to prevent rejection

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ABSTRACT

Immune checkpoint (IC) molecules modulate immune responses upon antigen presentation; the interaction between different IC molecules will result in the stimulation or, rather, the thwarting of such responses. Tumor cells express increased amounts of inhibitory IC molecules in an attempt to evade immune responses; therapeutic agents have been developed that bind inhibitory IC molecules, restoring tumor-directed immune responses and changing the prognosis of a number of cancers. Stimulation of inhibitory IC molecules could be beneficial in preventing rejection in the setting of solid organ transplantation (SOT), and *in vivo* as well as *in vivo* results obtained in animal models show this to indeed to be the case. With the exception of belatacept, a monoclonal antibody (mAb) in which an IgG Fc fragment is linked to the extracellular domain of CTLA-4, this has not yet translated into the generation of novel therapeutic approaches to prevent SOT rejection. We provide a review of state-of-the art knowledge on the role played by IC molecules in transplantation, confident that innovative research will lead to new avenues to manage rejection in solid organ transplant.

1. Introduction

Antigenic peptides presented in the cleft of a major histocompatibility complex (MHC) molecule initiate antigen-specific immune responses [1–3]. Whether such immune response will result in the activation of antigen-specific clones and their proliferation and differentiation into effector cells, or rather if the signal will be a tolerogenic one depends on the interaction between a number of costimulatory molecules that are present on the surface of T lymphocytes and antigen presenting cells (APC). Thus, if the presentation of the antigenic peptide-MHC molecule binary complex to the T cell receptor (TcR) is within a molecular milieu in which co stimulatory proteins including CD40 and CD80/CD86 interact with CD40L and CD28, respectively, an activatory immune response will ensue [4]. If, instead, antigen presentation will be accompanied by the interaction of inhibitory molecules such as programmed death 1 (PD-1) or galectin-9 (gal-9) with their respective ligands PD-L1 and Tim-3 and/or CEACAM-1, the resulting immune response will be hampered and antigen-specific tolerance will be favored [4].

The relative imbalance between inhibitory and activatory molecules, thus, will determine the quality of an immune response, as these molecules act as immune checkpoint (IC) modulating the nature of immune responses in physiologic and pathologic conditions. Hence, the presence of inhibitory IC molecules is fundamental in immune homeostasis, as these molecules, together with T regulatory cells, play a pivotal role in terminating immune responses and in the phenomenon of tolerance against self-antigens [5,6]. Inhibitory IC are also involved in the extremely complex scenario of fetal tolerance, as successful pregnancy is possible if fetal recognition by the maternal immune system is impeded [7,8].

Tumor cells have been shown to overexpress IC molecules, hampering the generation of protective anti-tumor immune responses by T lymphocytes [5]. Monoclonal antibodies that target inhibitory IC molecules, thus allowing the generation of efficient tumor-specific cell-mediated immune responses, have been developed and have been shown to be extremely efficient in drastically improving the prognosis

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and survival of oncologic patients. The possible role of IC antibodies that stimulate inhibitory IC molecules in determining tolerance lymphocytes [9–11] or, on the other hand, impeding the initiation of graft rejection in solid organ transplantation recipients has been only marginally examined. In this mini-review we will briefly present literature data on the expression and function of the best characterized IC molecules in the setting of solid organ transplantation in animal models and in humans, in the attempt to summarize state-of-the-art knowledge on this topic.

2. Main immune checkpoint pathways

Co-stimulation driven by the ligation of different IC molecules on the surface of immune cells plays a pivotal role in determining T lymphocytes activation or anergy after antigen presentation. Initial analyses identified CD28 as a fundamental activatory molecule upon binding to CD80 or CD86. Interestingly, CD80/CD86 can also bind CTLA-4 and in this case the interaction results in the delivery of a potent inhibitory signal, as indicated by the observation that CTLA-4-deficient mice show a lethal phenotype characterized by a strong pro-inflammatory profile [12–14].

Other members of the B7 family molecules were subsequently identified, PD-L1 and its ligand PD-1, which are type I membrane proteins that contain immunoglobulin (Ig) domains and are therefore classified as members of the Ig superfamily, were shown to play a major role in the induction of tolerance [15,16]. PD-1 is expressed as a monomer on activated T and B lymphocytes, thymocytes, and NK cells. Besides its fundamental role in shaping T cell repertoire in the thymus, PD-1 upon binding PD-L1 inhibits cell proliferation, reduces the production of pro-inflammatory cytokines, and blocks cell cycle progression [16,17]. Furthermore, together with CTLA-4 and other, less well characterized IC molecules, PD-1 regulates peripheral tolerance. PD-1 binds PD-L1 and PD-L2 in different tissues, with high levels of expression in placenta, low expression levels characterizing spleen, lymph nodes, and thymus, and a lack expression seen in the central nervous system. PD-L1, in particular, was shown to be constitutively expressed on APCs, and plays an active role in the induction and maintenance of T-cell anergy, down-regulating the effector phase of the cellular immune response.

Since the PD1≈PD-L1 engagement can negatively regulate autoreactive T- and B-cells and plays a pivotal role in the maintenance of tolerance, it is not surprising that an imbalance between positive and negative signals was shown to contribute to the onset of a variety of autoimmune and hypersensitivity diseases [18–20]. Situations characterized by impaired immune responses, on the other hand, take advantage of the PD-1/PD-L1 pathway-mediated suppression of immune activation regulation in a detrimental way. Thus, tumor cells upregulate PD-L1 to evade T-cell recognition, and PD-L1 was observed to be highly expressed by many human carcinomas, including those of the breast, cervix, lung, ovary and colon, promoting tumor growth and apoptosis of tumor-reactive T-cells [21,22]. As indicated above, though, PD1≈PD-L1-mediated dampening of immune responses is also involved in the extremely complex and only partially clarified phenomenon of feto-maternal tolerance to paternally inherited alloantigens during gestation. Thus, PD-L1 is abundantly expressed by villous syncytiotrophoblasts and cytotrophoblasts during the second trimester of normal pregnancy, when chorionic villi come in direct contact with maternal blood, indicating a role for these IC molecules in the immunological protection of the fetus from maternal immune system [7,23].

T-cell immunoglobulin domain and mucin domain-3 (TIM-3), also known as HAVCR2, is another immune checkpoint molecule with a fundamental role in physiological and pathological conditions in humans. TIM-3 is an activation-induced inhibitory molecule playing a fundamental role in tolerance and is a negative regulator of immune responses upon binding its ligand, Galectin-9 (Gal-9). TIM-3/Gal-9 interaction results in the dampening of T cells responses and induces the apoptosis of T lymphocytes and their phagocytosis by monocytes and macrophages [24,25]. The TIM-3/Gal-9 pathway thus, is considered to be a pure immune system inhibitor: it promotes differentiation of regulatory T cells (Tregs), reduces T-helper 17 (Th17) and Th1 cells activation, and induces CD8+ *T* cell apoptosis, resulting in suppression of excessive immunity and inflammation. The Tim-3/Gal-9 pathway is endowed with physiological functions as well, including cell growth, differentiation, adhesion and communication [6,26]. Analogously to what is seen in the PD-1/PD-L1 pathway, the immunosuppressive features of these IC molecules can by high jacked in pathological situations. Thus, Gal-9 increased expression can be seen in tumors, is associated with the tumor occurrence or metastasis, and was shown to promote the colony formation of melanoma cells [27–29]. Notably, another ligand for TIM-3 has been identified: carcinoembryonic antigen cell adhesion molecule 1 (CEACAM-1). Similar to what is seen with Gal-9, TIM-3 ligation of CEACAM promotes TIM-3-mediated inhibition and apoptosis of antigenic-specific T lymphocytes. The reciprocal interactions between TIM-3 and CEACAM-1 are complex as CEACAM-1 enhances the surface expression of TIM-3. Thus, CD4+ *T* lymphocytes from transgenic mice that lack CEACAM-1 (*Tim3Tg CEACAM-1-/-*) exhibit low cell surface expression of TIM-3.

The TIM-3-Gal-9/CEACAM pathway has been associated with susceptibility to the development and the severity of multiple autoimmune diseases, including autoimmune colitis and experimental autoimmune encephalitis (EAE), in murine models [30–32]. Notably, the use of a CEACAM-1-Fc fusion protein in the same models resulted in the attenuation of disease activity, further reinforcing the idea that this pathway plays a fundamental role in regulating immune responses.

3. Immune checkpoint molecules in solid organ transplantation: animal models

The beneficial effect of molecules that block immune checkpoint (IC) molecules interaction in improving the efficacy of tumor-directed immune responses in oncology has been established by a remarkably robust body of work cells [5,11,33,34]. The possibility of intervening in the opposite way, i.e. stimulating IC interaction to down-regulate immune responses directed toward the MHC antigens expressed on the surface of the transplanted organ to favor induction of tolerance has been much less explored. Indeed, whereas a number of IC-blocking monoclonal antibodies (mAbs) has been developed and are clinically available; many fewer IC-stimulating mAbs are at hand. The success of IC blockade in cancer patients has nevertheless stimulated research and industrial development to envision novel therapeutic pathways based on IC manipulation.

An initial question in developing IC-stimulation based approaches to tolerance induction is whether it could be sufficient to directly stimulate ICs or if it would be necessary to combine IC stimulation with inhibition of CD4 T lymphocyte-mediated help. At least from a theoretical point of view, the combination of IC stimulation (e.g. PD1≈PD-L1) and the simultaneous inhibition of immune costimulatory pathways (e.g. CD80≈CD28) would result in an optimal tolerance-inducing synergistic effect. [35,36] Notably, blocking of costimulatory pathways, leading to reduced CD4+*T* helper help, is one of the conditions inducing T lymphocyte exhaustion of CD8+ *T* lymphocytes; this would surely contribute to the induction of immune tolerance [37]. The possibility to reduce or prevent rejection of solid organ transplantation has been analyzed in mice, rats and non-human primates (NHP) models using a cadre of different IC-stimulating molecules.

The best characterized IC pathway is the one involving CD80/86 and CD28/CTLA4; it is thus somehow logical that amongst the first Abs produced with potential use in the clinical world were Abs with an agonist or an antagonist effect on this pathway. Initial results in animal models showed that the use of CTLA4 Ig was associated with long-term xeno and allograft survival in murine models [38]. Subsequent results with an improved molecule with higher molecular affinity (belatacept) resulted in significantly prolonged allograft survival in kidney transplant models in NHPs [39,40]. The interaction between CD80/CD86 and

CTLA4 results in the inhibition of immune responses, the one between CD80/CD86 and CD28 instead triggers T cells activation; thus at least in theory the same effect: inhibition of an immune response, can be reached by stimulating CTLA4 or by blocking CD28. The idea of intervening on CD28 rather than on CTLA4 is more recent and has led to some promising results. Thus, the use of an anti-CD28 mAb was shown to results in prolonged allograft survival and inhibition of donor-specific antibodies in a model of NHP kidney allotransplantation [35,36,41].

Early results showed that manipulation of another important IC pathway, CD40≈CD40L could prolong cardiac allograft survival in both naive and sensitized mice [42,43]. Additional data confirmed that the use of an anti-CD40L molecule significantly prolonged kidney, skin, and heart allograft survival in NHPs [34]. The observation that anti-CD40L monoclonal antibodies: 1) can activate platelets directly, as these blood elements express CD40L on their surface [44], and 2) can form immune complexes with soluble CD40L, that can indirectly activate platelets through the Fc-γ receptor IIA (FCGR2A) [45], justified the observation that thromboembolic complications could be observed upon the use of these antibodies. This led to the development of engineered IgG1 that are devoid of Fc-binding and complement-fixing effector functions; this new molecule was shown to prolong kidney allograft survival in NHPs in the absence of thromboembolic complications [46].

Another IC pathway that is potentially interesting from a therapeutic point of view is the ICOS≈ICOSL pathway. The observation that ICOS is expressed upon T lymphocyte activation but is not present of naïve T cells raised the hypothesis that the effect of its modulation could synergize with that of molecules that are instead constitutionally expressed on immune cells (e.g.CD80/86) [47]. Results, though, were disappointing as ICOS≈ICOSL blockade using a novel ICOSIg did not increase kidney allograft survival in NHP models, either when used alone or when combined with belatacept [48]. A similar rationale is at the basis of the idea of modulating the OX40≈OX40L pathway: also in this case, these molecules are expressed on activated but not on naïve T lymphocytes. Recent results showed that the use of anti-OX40L in combination with belatacept resulted in a significantly prolonged survival of kidney allograft in NHPs [49].

PD-1, PD-L1, and PD-L2 were described to be upregulated in murine models of allogenic cardiac transplantation during rejection [50]; interestingly, the use of PD-L1 Abs resulted in increased tolerance with an improved transplant acceptance and, in some cases, permanent engraftment [50]. In murine models of kidney graft, rejection was shown to be modulated by the PD1≈PD-L1 pathway. Thus, the majority of CD4+ and CD8+*T* lymphocytes were observed to express PD1 during the initial phase of immune responses directed toward the transplanted organ [51]. In animal models, the use of PD-L1-blocking Ab caused acute rejection whereas the employment of a PD-L1 molecule anchored onto the surface of rat glomerular endothelial cells [52] reduced T cell graft infiltration and increased the infiltration of Treg cells upon binding PD-1, with a beneficial effect on organ survival. In the setting of lung transplantation, seminal observations showed that CD8+ *T* lymphocytes expressing PD1 are pivotal in mediating tolerance. Thus: 1) co-stimulation blockade-mediated tolerance after lung transplantation was observed to be dependent on PD-1 expression on CD8+ *T* cells, and 2) if PD-1 expression is deficient, the differentiation of CD8 T lymphocytes was detected to be skewed towards an effector memory phenotype, resulting in acute lung rejection [53]. Very recently, the administration of PD-L1-recombinant proteins was demonstrated to decrease inflammatory cytokine production and down-regulate CD4+ *T*-cell proliferation, significantly reducing allograft airway fibrosis and inhibiting rejection in a heterotopic tracheal allograft model of lung transplantation [54].

An exciting biotechnological advance was recently developed that combines IC modulation with the use of "classical" immunosuppressive drugs. Thus, cell membrane-derived PD-L1 nanovesicles were engineered to carry low doses of rapamycin. Results showed that such nanovesicles inhibited T-cell activation and proliferation by enhancing the PD-1≈PD-L1 immune co-inhibitory signaling, down-regulated activation of the mTOR pathway, and favored the induction of splenic Treg cells; this resulted in allograft tolerance in a mouse skin transplantation mode [55,56]. Finally, porcine neonatal islets overexpressing PD-L1 were shown to be characterized by better engraftment and reduced rejection in a humanized mouse model, suggesting that the IC-modulating approach could also be useful in the scenario of xenotranplantation. [57,58]

Another possibility which has been explored in several animal models is to modulate SOT rejection by interfering with the CD40≈CD40L pathway. The most consistent and promising results stem from studies performed in NHP undergoing kidney transplantations [59]. Both CD40– and CD40L (CD154)-specific mAbs could reduce the severity of acute and long-term graft rejection, with a more potent effect observed in animals receiving CD154-specific mAbs. Unpredicted target toxicity due to Fc effector function binding to platelets [60,61]temporarily stopped clinical development of this approach.

Data on other IC molecules are scarcer. To summarize results obtained in a series of experiments performed in murine models focusing on the Tim-3≈Gal-9 IC pathway : (1) blocking Tim-3 accelerates acute rejection whereas Tim-3 overexpression delays the onset of liver rejection; and (2) upregulation of Gal-9 prolongs survival of islet transplantation [62], as well as that of liver [63], skin [64], and cardiac allografts [65], indicating the likelihood that this IC pathway could be a used in developing novel therapeutic approaches in transplantation.

BTLA, a molecule belonging to the CD28 superfamily was also shown to play a role in the acceptance of partially mismatched heart and kidney allografts in mice. [66–68] Finally, TIGIT agonists were observed to protect against rejection and to induce the polarization of APC toward an anti-inflammatory M2 phenotype [69] in a murine model of skin grafting (minor antigenic mismatch). It is important to observe that the beneficial effect of these IC agonists on preventing rejection was often potentiated by the concurrent manipulation of the CD80/86≈CTLA4 interaction, a major co-stimulatory pathway, with belatacept [40], underlining the possible need to interfere with multiple immune pathways to obtain a beneficial synergistic effect.

Finally, despite not being classified as an IC molecule, modulation of CD26 was shown to result in the abrogation of acute rejection and prolongation of allograft survival in a rat cardiac transplantation model. Even more recently, inhibition of CD26 was observed to attenuate rejection by suppressing T-lymphocyte activation in an experimental mouse model of lung transplantation. CD26 is an immune molecule expressed on hematopoetic, epithelial, and endothelial cells whose stimulation results in increased IL-2 production. CD26 inhibition is associated with suppression of T cell proliferation and reduced Ab production, justifying how CD26 antagonist have a beneficial effect on transplantation, at least in the animal model [70].

Taken together these data confirm the pivotal role played by the modulation of immune cells on the outcome of solid organs transplantation, indicating the need to design in-depth analyses to generate results that could lead to the development of novel therapeutic approaches to prevent organ rejection.

4. Immune checkpoint molecules in solid organ transplantation: clinical results

Data stemming from clinical trials aiming at verifying the possibly beneficial effects of IC stimulation-based therapies on preventing solid organ rejection are limited and are mostly based on the use of belatacept. An indirect proof of the importance of IC in inducing tolerance comes from the numerous observations that immune checkpoint inhibitors-based therapies in transplanted patients who developed malignancies favors the development of rejection and graft loss, supporting the idea that the modulation of immune checkpoint molecules modulates allograft tolerance [71].

As briefly indicated above, belatacept is a mAb in which the Fc

fragment of a human IgG1 is linked to the extracellular domain of CTLA-4; this mAb binds CTLA-4 with very high avidity and potently inhibits T-lymphocytes-mediated immune responses *in vitro* and *in vivo* [72].

Results of an initial phase II clinical trial in kidney transplanted patients showed that the efficacy of belatacept-based therapy was similar to that of cyclosporine in preventing rejection and improving allograft function at 1 year [73]. These results were confirmed in a phase III trial, BENEFIT, with a longer follow up (7 years), in which the of belatacept was shown to result in improved renal function, reduction in cardiac and metabolic toxicities, and a survival advantage at compared to cyclosporin [74]. Results of the BENEFIT trial led the FDA to approve belatacept for the prevention of rejection in kidney transplantation and the drug, in combination with corticosteroids and mycophenolic acid (MPA), is currently indicated for the prophylaxis of graft rejection in adults undergoing renal transplantation. These results notwithstanding, it has to be underlined that the use of belatacept is associated with an increased risk of lymphoproliferative disease in Epstein-Barr virus (EBV)-seronegative kidney recipients [21] and with a still unexplained higher rate of early acute cell-mediated rejection [20].

Results obtained in a different clinical setting, lung transplantation, were more controversial. Thus, initial results obtained in 11 lung recipients who failed calcineurin inhibitors-based therapies showed that after belatacept conversion rapid graft decline or loss from acute rejection were not observed and no treatment limiting adverse events occurred [75]. These results, though, were not confirmed by a subsequent study in which 27 lung recipients were randomized to receive either “classical” (tacrolimus, mycophenolate mofetil and prednisone) or belatacept-based immunosuppression (tacrolimus, belatacept, and prednisone). Five patients in the belatacept arm died compared to none in the “classical arm” [76]. Notably, conversion to belatacept was reported to result in severe acute cellular rejection of in fulminant acute respiratory distress syndrome in two other cases in patients who underwent lung transplantation [77,78].

Taken together these results leads to the decision to reconsider the use of belatacept in these patients. Similar discouraging results were obtained in liver-transplanted patients. Thus, results of a clinical trial comparing belatacept- and tacrolimus-based therapies showed that the percentage of patients meeting primary end points (acute rejection, graft loss, death by month 6) was higher in the belatacept group, in whom a higher number of deaths and grafts losses was observed as well [73,79].

Curiously, on the other hand (no pun intended…), results of a case report showed that acute rejection could be resolved upon conversion from a tacrolimus, mycophenolate mofetil and steroids-based to a belatacept and sirolimus-based therapy in a hand transplant recipient [80].

PD-1 and its ligands, PD-L1 and PD-L2, constitute the inhibitory regulatory pathway with the highest potential therapeutic use to prevent rejection of solid organs. A series of results obtained in the clinical setting support this possibility. Thus, PD-L1, PD-L2, and PD-1 expression was shown to be upregulated in biopsies of patients with renal allograft rejection [81]. In samples of human transplanted hearts, acute cellular rejection was demonstrated to be associated with decreased PD-L1 expression [82,83].

We focused our attention on lung transplantation (LTx), analyzing both rejected organs, trans-bronchial biopsies (TBB), and plasma. Results obtained in rejected lungs showed the presence in the organs of increased percentages of PD-1-, PD-L1-, and CTLA4- expressing T lymphocytes; in these same lungs exhausted PD-1-expressing T lymphocytes (PD-1pos/TOXpos) and exhausted Treg (PD-1pos/FOXP3pos) T lymphocytes were significantly reduced [71]. PD-1-expressing T lymphocyte should result in dampening of immune responses, it is thus apparently counterintuitive that the detection of these cells was associated with worst clinical outcomes in LTx. A possible explanation is that the accumulation of PD-1- and PD-L1-expressing cells in organs that are rejected is a late and futile attempt to prevent such process. Of course, in rejected organs we can only analyze the final portion of the cascade of events leading to rejection, studies in animal models designed to perform longitudinal follow-up of immunological responses after SOT would be extremely informative, but are difficult to design. In TBB we observed that the presence of high amounts of PD-1-expressing T cells was associated with a higher likelihood to develop chronic rejection and the presence of a restrictive allograft syndrome (RAS) phenotype [20,71]. Also in this case, consecutive samples from the same patients during post-LTx surveillance will be needed to shed light on the timing of immune checkpoint molecules activation after SOT. Finally, in plasma we observed that soluble Galectin9 (sGAL9) concentration was greatly reduced in patients undergoing acute or chronic rejection [84]. These results are complex and need to be interpreted and understood, they nevertheless unequivocally confirm that IC are involved in solid organ rejection.

To our knowledge, with the exception of the trials using belatacept and of an anti-CD40L study in kidney transplantation that was halted by the FDA because of thromboembolic complications, results of other IC-based clinical trial in the setting of solid organ transplantation are not available.

5. Conclusions

The identification of IC molecules shed light on the intricacies of immune stimulation/tolerance and led to the design of novel, extremely useful molecules currently used in oncology. Results obtained in animal models of solid organ transplantation clearly demonstrate that such IC molecules play a fundamental role in acceptance or lack thereof of solid organs; these results have not yet translated into the clinical scenario. More science, more experiments, more research in ampler cohorts of patients undergoing transplantation and enrolled in longitudinal studies are needed to advance our understanding of how the different IC pathways interact in determining the clinical outcome of transplanted patients. Doubtlessly, though, and accordingly to what has happened in oncology, IC based therapies are the future of therapy in transplantation.

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CRediT authorship contribution statement

Ilaria Righi: Conceptualization. **Daria Trabattoni:** Conceptualization, Writing – review & editing. **Lorenzo Rosso:** Investigation. **Valentina Vaira:** Conceptualization, Data curation. **Mario Clerici:** Conceptualization, Funding acquisition, Writing – original draft.

Declaration of competing interest

The authors have no competing interests to declare.

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