Lessons from transmissible cancers for immunotherapy and transplant

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1. Introduction

Tumor transplantation studies paved the way for an increased understanding of major histocompatibility complex (MHC) biology [1]. At that time, the mechanisms that governed tissue rejection (and, in this case, cancer rejection as well) were not established. Currently, many advances have allowed us to better comprehend these mechanisms, many of which are also significant barriers to a possible cancer transmission through allogeneic responses. The immune response against foreign cells that express different MHCs repertoires (allorecognition) is the main driver of tissue rejection [2]. The MHC codes for critical polygenic and polymorphic molecules (evaluated before transplant donor selection) involved with antigen presentation to T cells. MHC type I molecules (MHC-I), usually expressed by all nucleated cells within vertebrates, interact with T cell receptors (TCRs) from CD8⁺ T cells, mainly responsible for cytotoxic adaptive immune responses. MHC type II (MHC-II), expressed mainly by professional antigen presenting cells, such as dendritic cells (DCs) and activated macrophages, interact with TCRs from CD4⁺ T cells that are responsible for ‘helper’ adaptive immune responses, ‘orchestrating’ different aspects of cellular and humoral immunity. Foreign MHCs are very important to tissue rejection and, as discussed in this review, transmissible cancer immune response.

Transplant rejection is mediated mostly by the adaptive immune system [3]. There are three main mechanisms by which adaptive immunity is triggered to mediate allogeneic tissue rejection: direct, indirect, and semi-direct [4]. The direct pathway is based on the ability of dendritic cells (DCs) from the donor tissue (or transmissible cancer) to present allopeptides and activate host T cells through a non-self MHC. Around 1–10% of T cells can recognize the complex non-self MHC-peptide and mount a specific immune response [5]. The direct pathway is believed to be the dominant immune response during acute rejection. The ability of non-self MHC to present more than one allopeptide, referred as the multiple binary complex model, seems to contribute to the amplification of immune responses and graft rejection [6,7]. The indirect pathway is related to the presentation, by host DCs, of peptides from polymorphic antigens (or neoantigens, in the case of tumors) of the donor [2]. This pathway is associated with late chronic rejection of the transplanted tissues, and it is believed that the T cells clones reactive to this polymorphic alloantigens are distinct from those activated by the direct pathway [2]. The semi-direct pathway is related to the shedding by exosomes, from donor cells, of peptide-loaded MHC into the membrane of recipient DCs, which will present donor MHC-allopeptides to T cells. Several murine studies demonstrated the acquisition of intact alloantigens to recipient DCs after
vascularized allograft challenge [8–10]. The semi-direct and direct pathway would lead to activation of the same T cell clones [2].

Once activated, T cells will induce tissue rejection through multiple mechanisms, like tumor necrosis factor (TNF), granzyme and perforin mediated cell death and liberation of cytokines crucial to innate immune cells activation, like interferon γ (IFNγ) [11–13]. IFNγ increases the expression of MHC-I by nucleated cells, and MHC-II by professional antigen presenting cells (APCs), which improves the ability of T cells to recognize and be activated by polymorphic MHC-peptides. Besides that, IFNγ can significantly impact on the functions of both adaptive and innate immune cells, for example, increasing the ability of monocytes and macrophages to produce nitrogen and oxygen reactive species and perform phagocytosis. IFNγ also sensitizes natural killer cells (NK cells) to induce target cell death.

This complex immune network is present in the case of cancer transmission, a phenom that occurs naturally in two mammalian species and, under specific settings, between humans and, experimentally, in mice. Nonetheless, the immune response contributes to cancer elimination in immunocompetent individuals, especially in the context of allogeneic differences between the tumor and the host. The first part of this review focuses on the naturally occurring transmissible cancer mechanisms to avoid immune response. In the second part, we discuss possible targets for cancer immunotherapy and anti-rejection therapies, based on the interplay between anti-tumor and allograft immune responses.

2. How different immune cells participate in allogeneic and anti-tumor immune responses

For a cell, tissue or organ to establish itself in a new organism, it must be nourished by the circulatory system’s nutrients. This implies that the cells should possess the ability to adhere in an appropriate site for their metabolic needs or induce angiogenesis so that nutrients can diffuse and reach the ‘implanted’ cells. Similarly, cancer metastasis can only occur in appropriate sites, where the tumor cells can proliferate. Metastasis is also influenced by chemokines and chemoreceptors that direct cancerous cells to specific tissues [14]. After colonization, cells must avoid the immune response that will mediate the foreign tissue damage and rejection. Immune-privileged sites or a tolerogenic microenvironment (usually observed around cancers) facilitate cell implantation and proliferation through anti-inflammatory cytokines, like transforming growth factor β (TGF-β) and interleukin 10 (IL-10), that will ease immune responses [15,16]. Moreover, ligands that induce apoptosis, such as Fas ligand, contribute to this tolerogenic environment by inducing cell death of infiltrated immune cells. Apoptotic cells will further control inflammation after being recognized by scavenger receptors, leading to anti-inflammatory cytokines secretion. Nonetheless, the majority of transplants and cancers will occur in sites where there is no immune privilege.

Cellular-mediated immune responses are the main mechanism associated with both allograft rejection and tumor elimination. Humoral immunity can contribute along with the cellular arm of immunity, by antibody and complement-mediated opsonization, formation of membrane attack complex by complement proteins and promotion of antibody-dependent cellular cytotoxicity (ADCC).

Recent studies were crucial to clarify the direct participation of innate immune cells and their components, such as the complement [17,18], in both transplant rejection and anti-tumor immunity. APCs drive T cells activation and many other innate immune cells also participate in allograft rejection or anti-tumor immunity. Innate lymphoid cells [19,20], γδ-lymphocytes [21], myeloid-derived suppressor cells (MDSCs) [22], neutrophils [23], NK cells [24] and monocytes [25,26] are important for both tissue rejection or tolerance, depending on the context, and anti-tumor immunity in multiple ways. Here we will mainly discuss the role of NK cells, monocytes, neutrophils, DCs and MDSCs.

Neutrophils and myeloid-derived suppressor cells, in general, play an opposing role in allogeneic and anti-tumor immune responses. Neutrophils contribute to transplant acute and chronic rejection through secretion of pro-inflammatory cytokines and toxic mediators (proteolytic enzymes and oxygen and nitrogen reactive species) [23]. In addition, neutrophils can directly perform tumor cell phagocytosis or induce trogoptosis, eliminating tumor cells [27,28]. In contrast, myeloid-derived suppressor cells are associated with transplant survival and tumor progression through anti-inflammatory cytokines secretion, counteracting, and silencing pro-rejection/anti-tumor immune responses [22].

NK cells, which are considered a cytotoxic subtype of ILC1s, and monocytes are particularly important, in the case of allograft immune responses, because of their ability to discriminate between self and non-self (or altered self, in the case of tumors). NK cells recognize the expression pattern of specific surface molecules (ligands of NK cell receptors), from which they were ‘educated’ (licensed) to recognize and act, ignoring or killing the target cells [29]. Monocytes can recognize foreign MHC-I through paired immunoglobulin like receptor A (PIR-A), one of the types of typical receptor pair of the immunoglobulin-like family of...
receptors that are expressed on a wide range of immune cells, like macrophages, B cells and DCs [30]. Thus, both NK cells and monocytes can be essential initiators of immune responses. One of the NK cell ligands is the MHC-Is, which will provide a negative signaling pathway, restraining NK cells’ ability to induce target cell death [31,32]. The balance between the surface molecules associated with activation or inhibitory pathways will determine the fate of NK cell-mediated target cell death and is also influenced by the presence of inflammation [33]. Thus, the disbalance or absence of MHCs in foreign tissues, and in some cancerous cells, will favor the activation of NK cells and subsequent target cell death and pro-inflammatory cytokines release, such as IL-6, TNFα, and IFNγ [34]. TNFα can, in large concentrations, induce cell death [35]. Besides that, TNFα increase vascular permeability and chemotactically monocytes and neutrophils contributing to tissue (or cancer) cell damage [36,37]. As already cited, monocytes can recognize non-self-MHC, differentiate into macroDCs, present antigens to lymphocytes, liberate toxic mediators and perform direct cell phagocytosis contributing to non-self-tissue damage [25,38]. IFN-γ can directly, as a third signal for CD4+ T cell polarization into Th1 [39], affect adaptive immune responses as well, governing antibody class switch by B cells [40]. The role of NK cells in transplant rejection is controversial [41], and although it is not completely necessary [42], it supports the early anti-graft immune response [43] and certainly is a barrier that should be surpassed by anti-rejection therapies.

Another important player as the initial activator of the immune response against transplants and tumors is danger-associated molecular patterns (DAMPs), originated in lesions (mechanical and from ischemia/reperfusion) necessary for the transplant or during cancer development and metastasis [44]. DAMPs will activate pattern recognition receptors (such as Toll-like receptors) expressed on tissue macrophages, leading to chemokines and cytokines secretion and subsequent transmigration of neutrophils, monocytes, activation of DCs and T cell presentation.

All these mechanisms of immune activation by foreign tissues can be overcome in at least two known transmissible cancers diseases in vertebrates [45,46]; studies showing allogeneic tumor models in mice, such as B16 melanoma [47,48]; and two case reports of cancer transmission between humans [49,50].

2.1. Transmissible cancers in Tasmanian devils: lessons from the devil facial tumor diseases (DFTDs)

The most aggressive and newly emerged of the naturally occurring transmissible cancers are the DFTDs, which has been threatening the Tasmanian devil (Sarcophilus harrisii) with extinction. These two diseases (DFTD1 and 2) are clonally transmitted cancers, as proven by genetic analysis [45,51]. The two tumors possess the same cellular background, Schwann cells [52], but originated from different individuals, as concluded after karyotypic analysis, which demonstrated several differences between each other, including sexual chromosomes [53,54]. These cells also differ between themselves by MHC-I expression, as DFTD1 express very low or none of this important molecule [55,56]. The cancer cells are transmitted between animals through face biting during mating interactions. When a healthy devil bites a devil with DFTD, its mouth may receive some tumor cells. These malignant cells can implant themselves in wounds, at the oral cavity, caused by the scavenging behavior of the healthy individual. Also, when a devil with DFTD bites a healthy one, some tumor cells may be inoculated in the recipient, providing an opportunity for implantation. These tumors progress rapidly and can metastasize, with high death rates occurring between 6 and 12 months after lesions appear [57,58]. The deaths are generally associated with starvation due to severe lesions in the mouth and nose or organ failure after metastasis [54].

Several studies indicate different reasons that can combine to explain the inefficiency of Tasmanian devils to mount an effective immune response against DFTDs. Low expression of MHCs in the tumors, associated with limited polymorphic MHCs and T cell repertoire from the host species, the Tasmanian devils, contributes to a reduced allorecognition of implanted tumor cells and ineffective activation of adaptive immunity [56,59,60]. CD8+ T cells depend on antigen presentation by APCs to promote tissue rejection and will mediate cell death in MHC-I expressing DFTDs [61]. For this reason, the low expression of MHC-I by DFTDs is an important escape mechanism. This low expression of MHCs by the tumor cells can be mediated by heterozygous mutations and epigenetic changes. The epigenetic changes can occur on DNA promoters of different proteins involved in antigen presentation, like transporter for antigen presentation 1 (TAP1), TAP2, β2-microglobulin and MHCs (I and II), contributing to the low antigencity of DFTDs. Although the genetic diversity of Tasmanian devils is low, Kreiss et al. [62] reported that they can reject skin grafts from other individuals, suggesting that the immune system should be able to respond against cancerous cells from other individuals too. As such, recent manuscripts [63–65] provide interesting insights about the mechanisms that govern DFTD immune escape, and offer valuable targets to
immunotherapy. These studies demonstrate that ERBB3 overexpression in DFTD1 activates the signaling protein and transcription factor STAT3, while inhibiting STAT1 activity, blocking the transcription of β2-microglobulin (B2M), an essential component of MHC class I, leading to immune evasion. STAT3 also induces the expression of MMP2, which remodels the extracellular matrix promoting cell migration and metastasis. Poly(ADP-ribose) polymerase (PARP) also plays a critical role in DNA damage control in cancer cells. Blocking ERBB-STAT3 axis with Afatinib or Sapatinib was demonstrated to inhibit cancer progression and increase tumor surveillance by re-activating STAT1 and inducing MHC-I expression. Blocking ERBB-STAT3 axis with Afatinib or Sapatinib was demonstrated to inhibit cancer progression and increase tumor surveillance by re-activating STAT1 and inducing MHC-I expression. This activation results in the release of Granzyme B and Perforin, followed by the expression/secretion of Fas ligand (FasL), interferon γ (IFN-γ), and tumor necrosis factor α (TNF-α), which together induce apoptosis in cancer cells. The anti-tumor response of cytotoxic T cells is amplified by cytokines IL-2, IFN-γ, and TNF-α, which can attract other effector cells into tumor milieu. In addition, DFTD was demonstrated to be sensitive to the PARP inhibitors Olaparib and Talazoparib. Created with BioRender.com. DFTD: devil facial tumor disease; STAT: signal transducer and activator of transcription; ERBB: receptor tyrosine–protein kinase erbB-2 precursor; MHC: major histocompatibility complex; IL-2: interleukin-2.
kinase [68]. This study suggests that the ERBB3-STAT3 axis might lead to chemotherapy resistance in human cancers, but the role of ERBB3 for immune escape, recapitulating the findings in DFTD1, still needs to be evaluated in human cancers.

PD-L1 is expressed by a range of innate immune cells, like monocytes and neutrophils, endothelial cells [69], and some cancerous cells [70]. PD-L1 is an important negative regulator of T cell-mediated immune response [70] and binds to the inhibitory PD-1 receptor expressed by T cells. Upon binding, PD-L1 promotes inhibitory signaling pathways from the PD-1 ITIM motif (immunoreceptor tyrosine-based inhibitory motif). Thus, cancer immunotherapies based on anti-PD-1 are currently being used in different human clinical trials [71]. Anti-PD1 therapy contributes to tolerance break against tumor antigens, enabling T cell activation. In this sense, PD-L1 expression by DFTDs can be an essential mechanism to circumvent IFN-γ induced MHC-I expression, as both are induced by this cytokine and may explain the ability of DFTDs to keep immune response silenced in some animals, even in the presence of IFN-γ [72].

NK cells activity in DFTDs is observed mainly in the presence of DFTDs specific antibodies [73], suggesting dependency on the adaptive immune response. The reason why this happens can be diverse. First, an intrinsic feature of Tasmanian devils NK cells may contribute to its limited ability to recognize DFTDs: reduced variability of NK cells’ receptors compared to other mammals, like mice, dogs, and humans [74]. Second, NK cells’ ability to govern an immune response against allogeneic cells is limited, without antibody-dependent cellular cytotoxicity (ADCC), and can even, under some circumstances, contribute to tolerance of the ‘transplants’ [41].

Another possibility is that monocyes from Tasmanian devils may not respond as effectively as other mammals’ monocyes, a feature that has not been explored in the devils’ biology. As an example, some marsupial-derived monocyes had limited ability to control mycobacterial infections [75]. Thus, investigation of Tasmanian devils’ monocyes’ ability to recognize self and non-self-tissues and respond to IFN-γ, could provide interesting insights to explain these animals’ inability to initiate an anti-allogeneic (in this case, tumoral) adaptive immune response. Nevertheless, is important to point out that other marsupials, aside from Tasmanian devils, were never identified with transmissible tumors. This suggests that the lower ability of a marsupial’s immune system to respond to some infections and antigenic challenges [76,77] are not the sole key factor to drive DFTDs transmissibility. Similarly, it is important to note that no immune function inability could be observed in Tasmanian devils [78–80], at least, in the circumstances evaluated.

DFTDs tumors also induce an anti-inflammatory microenvironment with cytokines like IL-10 and TGF-β [75,81,82], in the majority of the histological specimens. These cytokines are known to restrict antigen presentation and anti-tumoral adaptive immune responses [83]. In conclusion, DFTDs are unique in their ability to prevent immune activation from the host, but immunotherapy is still a worthy methodology to pursue, especially because DFTDs showed resistance to chemotherapy [84].

2.2. Canine transmissible venereal tumors (CTVT)

The other naturally transmissible tumor known in mammals is the canine venereal tumor in dogs. CTVT is less aggressive to the host, compared to DFTDs, and usually will not lead to high death rates and metastasis [85]. Present among dogs, CTVT can also infect other canines (like foxes and coyotes). It progresses in three phases after transmission: the growth, the stationary, and the regressive phases [86,87]. The growth phase is associated with low MHC expression and high TGF-β secretion, contributing to a tolerogenic and permissive microenvironment with cancer cell proliferation and little or no anti-tumor immune response [88,89]. However, after a rapid progression, the tumor stops growing and starts to regress. In these stationary and regression phases, the immune system can mount an anti-tumor immune response. The antitumoral response is based on the presence of antibodies, cytokines and chemokines. The antibodies are important for ADCC mediated by monocyes, neutrophils and NK cells. Cytokines and chemokines, like IFNγ, IL-6, RANTES and CCL28, lead to MHC-I expression (contrasting with the anti-inflammatory TGF-β [90]) by the tumor cells and activation of both innate and adaptive immune cells, generating increased release of antimicrobial and cytotoxic products, and infiltration of T cells [89,91].

Recently, Baez-Ortega et al. [92] reported the origin of the CTVT through DNA exome sequencing of 546 samples, showing that it has been transmitted between dogs for 6000 years. CTVT evolved to evade the host immune system, but the long-term presence of CTVT in dogs suggests a coevolution between host and tumor, resulting in a transmissible non-lethal disease. Two main concepts are reinforced by these recent reports: (i) the longer the period between cancer establishment and death lasts, the possibility of transmission is increased; and (ii) the findings showing that CTVT has been transmitted
between dogs for thousands of years demonstrated that there is no limit to cancer cell divisions.

When comparing DFTDs and CTVT, several differences appear. For instance, CTVT is sensitive to radio and chemotherapy, while DFTDs are not [93–95]. This difference can be attributed both to intrinsic differences in the cancerous cells (originated from Schwann cells for DFTDs [53] and from histiocytes for CTVT [96]) and to the immune response of the hosts since radiotherapy success can be potentiated by a secondary anti-tumor immune response [97]. Besides that, CTVT metastasis is less common than DFTDs. This feature can be associated with differences in chemokine receptors expression and cancerous cells’ phenotypes between these two tumors, or the host’ NK cells intrinsic ability to control metastasis, since NK cells are important players of tumor dissemination impairment [98]. We highlight that CTVT is a milder disease than DFTDs, co-evolving with its host for a much longer time, spreading among different individuals without killing the majority of them, causing significant morbidity and high transmission rates.

### 2.3. Mice models of transmissible cancers

Tumor models can also be replicated in mice, including allogeneic ones. The B16 melanoma cell line was originated from C57Bl 6 mice strain (MHC-I = H2Kb) and is widely used as a tumor model after syngeneic transfer (between MHC compatible individuals). Surprisingly, some studies described the ability of B16 cells to grow in Balb-c mice (MHC- H2Kb), but not in B10.D2 mice (also H2Kb) [47,48]. The exact mechanism that governed the ability of B16 cells to establish and grow in Balb-c, but not in B10.D2, is not entirely understood, although differences in the immune response between these two strains may explain it, at least in part. It is known that Balb-c mice are prone to develop a Th2 immune response after some infections, while B10.D2 mice develop Th1 [99]. Generally, it is accepted that Th1 responses are associated with tumor regression, while Th2, to tumor progression [100–102]. Also, PD-1/PD-L1 axis in B16 models is an essential target for immunotherapy [103] and would be compelling to evaluate potential differences between PD-1 expression among T cells from these two strains of mice.

As observed in naturally occurring transmission, B16 cells express low MHC-I levels and will possess an anti-inflammatory microenvironment (with the presence of host Treg cells and anti-inflammatory cytokines), restricting immune response [104,105]. Treg cells are a sub-type of CD4+ T cells that will mediate immune silencing through multiple mechanisms, including anti-inflammatory cytokines secretion (IL-10, TGF-β, IL-35, among others); decreasing IL-2 levels through competition (an important stimulatory cytokine for activated T cells); inducing T effector cell death; enzymatic conversion of ATP into the regulatory molecule adenosine; and generation of immunoregulatory DCs [106–108].

In the context of low MHC-I expression, full activation of NK cells should occur. NK cells from mice have a much more diverse repertoire of receptors compared to NK cells from Tasmanian devils. These receptors would be able to recognize the pattern of surface molecules in non-self-cells, not being restricted to ADCC by NK cells. The evaluation of monocytes, macrophages, and monoDCs in their ability to recognize B16 melanomas as non-self-cells, with IL-12 secretion, from Balb-c and B10.D2 mice, may point out important differences between these two strains’ innate immunity as well. Finally, it would be important to evaluate other mechanisms, such as the ability of B16 cells to be implanted, and induce angiogenesis, between these two strains, as they are also crucial for tumor establishment.

### 2.4. Reports of cancer transmission between humans

Transmission of cancer is extremely rare in humans, and the described cases occurred after transplantation, maternal to fetal or infant transmission, or after accidental lesions [109–113]. In the case of cancer transmission after transplantation, the mechanisms that would prevent tissue rejection ended up allowing donor cancer establishment. Similarly, cancer transmission between mother and fetus has also been described [112]. Once more, the tolerance against fetus antigens and the undeveloped fetus’ immune system contribute to cancer transfer and establishment in both individuals. In this case, maternal tolerance is directed by innate and adaptive mechanisms. Placenta trophoblasts express low MHC-I levels and secrete neurokinin B that will restrain immune activation [114]. Yet, fetus antigens can still be recognized, and regulatory T cells are crucial to the tolerance and, probably, contribute to cancer transmission and progression [115,116]. Recently, the vaginal transmission of uterine cervical tumors from non-related mothers to 2 non-related infants (23 months and 6 years old boys) was described and confirmed by next-generation sequencing tests [115]. Interestingly, in the infants, the tumors developed into lung cancers, probably due to accidental aspiration/infiltration of tumor cells during childbirth. The tumors presented a slow growth rate in the eldest child, and spontaneous regression of some lesions occurred in the youngest.
These findings suggest the presence of alloimmune responses [113], despite the fact that the transmission much likely occurred during birth, when the infant immune system is known to be immature. The tumor in the youngest infant was chemotherapy-resistant and immune checkpoint inhibitor (anti-PD1) therapy, led to a strong regression. Surprisingly, the tumors in both mother and infant did not express PD-1 or PD-L1 [113]. The oldest infant received chemotherapy and had to underwent a total left pneumonectomy. Both infants were disease-free at the time of the case report publication, but their mothers died of the disease [113].

In addition to these specific cases, in which cancer transmission occurs under immune suppression or in infants with an immature immune system, there were two case reports among fully immunocompetent individuals. Both cases occurred due to accidents. The first one was a laboratory accident, after a researcher punctured himself with a syringe containing colonic adenocarcinoma cells [49]. HLA typing demonstrated irreconcilable differences between the tumor and host cells [49]. The other one occurred during a sarcoma surgery, after the surgeon cut himself with a contaminated scalpel [50]. Analysis of polymorphic short tandem-repeat sequences and HLA typing demonstrated a mixed phenotype with both features of the surgeon and patient histologic and immunologic findings. This is probably due to the analysis encompassed both tumor (derived from the patient) and infiltrated host cells (from the surgeon). The mechanisms governing this transmissibility are probably shared by the already known, naturally occurring transmissible cancers such as low expression of MHCs by the tumor cells, expression of anti-inflammatory cytokines associated with a tolerogenic microenvironment and low ability of tumor infiltrated DCs to present antigens.

3. Current therapies for organ transplants

We will focus on two mechanisms that allow transplant survival, despite alloimmune responses: (i) avoidance of immune system recognition; (ii) regulation of cytokines and other effectors and players of the host cytotoxic immune responses. Thus, immunosuppressors aim to: regulate and restrain lymphocytes proliferation (such as cyclophosphamide and mitoxantrone); restrain immune receptors activation (intravenous immunoglobulins); modulate cytokine secretion and immune cells activity (glucocorticoids); depletes different lymphocytes (cladribine, rituximab, alemtuzumab); and inhibits intracellular activation pathways (cyclosporine A and tacrolimus) [117].

As already mentioned, the direct pathway of the acute immune response to transplants is triggered by DCs and macrophages of the donor tissue that can activate specific T cells from the recipient (host). In this sense, transmissible cancers may possess an advantage, compared to tissue transplants, since many of the tumors infiltrated DCs and macrophages possess limited ability to present antigens and activate T cells [118].

4. Therapeutic opportunities based on crossed mechanisms between allogeneic and anti-tumor immune responses

The possibility of cancer transmission between humans is frightening, but lessons can be learned from the success of naturally occurring transmissible tumors to improve transplant survival. The treatment of transplanted tissues with anti-inflammatory cytokines or targeting donor DCs and macrophages to reduce their ability to present antigens are fascinating opportunities. This approach was already used in animal models in which donor dendritic cells’ ability to present antigens was abrogated by ultraviolet treatment leading to increased pancreatic island xenograft survival [119]. Different pharmacological approaches can be used to inhibit MHC-I and MHC-II presentation by dendritic cells [120,121], and are compelling targets for improved xenograft survival. A regime of anti-inflammatory treatments of donor tissues applied in the donor subject before transplantation (in the case of programmed living donor transplantation) could be a stimulating possibility for reducing the transplant rejection, but this would not be possible in post mortem transplantations. Increasing tissue survival after its excision from the donor would allow ex vivo anti-inflammatory treatment, possibly leading to increased xenograft survival, and it is, by itself, a crucial aspect to tissue transplantation. Furthermore, new strategies to improve anti-tumor immunity, like the use of biomaterial-based scaffold for continuous delivery and site-specific chemio and immunotherapy [122] could also be applied in the site of transplantation, with the use of anti-inflammatory mediators and pharmacological agents that restrain immune cells activation and functionality, such as immunosuppressors.

Another interesting possibility is adoptive cell transfer to the transplant recipient. Once more, immune cells involved in silencing anti-tumor immunity would be promising targets for suppressing anti-graft immune response. Recently, elegant results have been published with adoptive transfer of cells from adaptive immunity, regulatory T (Treg) cells, and innate immunity, myeloid-derived
suppressor cells (MDSC) and tolerogenic DCs, all of them involved in tolerance induction [115,123–126]. Myeloid-derived suppressor cells secrete anti-inflammatory cytokines, like IL-10 that restrain MHC expression and antigen presentation, and induce Treg activation, supporting the tolerogenic environment [125]. Induction of tolerogenic DCs ex-vivo, followed by transfer in vivo, is another promising therapy, already applied for other inflammatory disorders, like Chronic’s disease and rheumatoid arthritis [127,128]. Tolerogenic DCs can be induced by different anti-inflammatory cytokines, such as TGF-β and IL-10, and immunosuppressants, like rapamycin and dexamethasone [126,129]. Vitamin D3 can also induce tolerogenic DCs associated with CD4+ T reg s polarization [130]. One of the T reg s’ main receptors is cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which is involved on induction of immunoregulatory DCs [131]. Besides that, CTLA-4 competes with CD28 for binding into co-stimulatory molecules from DCs, providing negative signaling for effector T cell activation. Thus, activation of CTLA-4 receptors in effector T cells is also an intriguing strategy that can be used to promote transplant tolerance [132,133]. Metabolic changes support the tolerogenic potential of both MDSCs and Tregs and can be explored to modulate immunity in favor of antitumor immunity [134–136] or transplant tolerance. Finally, other molecular targets known to reduce anti-tumor immune response, like p38 mitogen-activated protein kinase (MAPKs), can also be exploited in order to improve xenograft survival [137].

CD8+ T cells exhaustion is associated with transplant success and tumor progression and new studies are showing a positive relation between exhausted CD8+ T cells emergency and graft survival [138]. Two transcription factors, TOX and NRA4, cooperate to CD8+ T cell exhaustion and are interesting molecular targets for T cell adoptive transfer or pharmacological therapies [139–141] in order to improve xenograft survival. Furthermore, NFAT-dependent expression of anergy inducing genes, responsible for T cell silencing, could be a major molecular target for transplant survival, as it is associated with tumor progression [142].

In general, as discussed above, the cells and molecular mechanisms responsible for tumor progression can be exploited to improve xenograft survival (summarized in Table 1).

On the other hand, molecules and cells important to transplant rejection can be crucial for antitumor immunity. MHC-I expression can be enhanced by cytokines, and enzymes modulation within the cells, such as IFN-γ and PCSK9 (Proprotein convertase subtilisin/kexin type 9), offering important targets for cancer immunotherapy [64,149].

CD40 is an important co-stimulatory molecule expressed by many different cell types, like APCs, B, T cells, fibroblasts, stellate cells, epithelial cells, endothelial cells, among others [150]. Distinctly, CD40 ligand (CD40L) is expressed by a limited number of cell types, like activated CD4+ T cells, activated B cells and platelets, although, under inflammatory conditions, it can also be transiently expressed by monocytes, NK cells, basophils and mast cells [151,152]. The interaction of CD40, expressed by B cells, and CD40L, expressed by activated CD4+ T cells, is crucial for antibody class-switch [153]. CD40 (expressed by APCs) is also crucial for CD4+ T cells mediated licensing of APCs antigen presentation for CD8+ T cells [154]. In addition, CD4+ T cells support CD8+ T cells response and memory differentiation through CD40L–CD40 interactions [155]. Interestingly, CD40 can be differentially required for adaptive immune responses against bacterial pathogens or allogeneic tissue, being crucial for CD8+ T cells-mediated allogeneic responses while dispensable for bacterial, at least in the case of Listeria sp. [156,157]. Thus, the significance of CD40 for transplant biology, while its dispensability for at least some pathogens-mediated immune responses, like Listeria sp., makes it, along with its importance for CD8+ T cell memory and exhaustion phenotypes [156,158–161], an interesting target for antitumor immunotherapies.

The importance of innate immune cells in the microenvironment of tumors and transplanted tissues has also been explored by different studies. Trained immunity stands for the innate immune cells’ (like neutrophils, macrophages, monocytes, and NK cells) ability to manifest a differential
immune reaction after a second exposure to inflammatory inducers (in general of microbial origins), a memory-like feature governed by epigenetic changes. The impact of trained immunity as an immunotherapy strategy for cancer was evaluated by several studies [162]. Trained immunity exerts positive effects, eliciting tumor immunity, both combined with checkpoint inhibitors and without other combined therapies [163–166]. Innate immune cells will influence and be influenced by the tumor microenvironment and, as such, combined therapies, targeting both innate and adaptive immunity, can give an important double strike to circumvent the regulatory ambiance of tumors [167,168]. Direct manipulation of innate immune cells can also exert beneficial effects. Chimeric antigen receptors (CARs), a strategy widely implemented for engineered TCR activation [169], can also be used in macrophages or natural killer cells to induce antitumor immunity [170,171], and small molecule inhibitors of TAM (Tyro3, AXL, and MERTK) tyrosine kinase receptors are also interesting targets to overcome regulatory programs of macrophages and improve NK cells mediated cytotoxicity [172]. Furthermore, monoclonal anti-CD24 that blocks interaction of this protein, expressed by tumor cells, with the inhibitory receptor of macrophages, siglec-10, showed promising results on reducing tumor growth by eliciting anti-tumoral immune responses [173]. As such, CD24 and TAM can also be considered fine molecular targets for anti-rejection therapies.

Although trained immunity has been linked to transplant rejection [174], it can also be associated with a regulatory phenotype of macrophages, especially after LPS stimuli, in a process similar to anergy [175]. Thus, trained immunity can regulate opposing immune responses and is a compelling concept to be explored depending on the dose and microbial product used. Altogether, different immune components associated with tissue rejection can be manipulated to drive cancer immunotherapy (as summarized in Table 2).

The exact role of other innate immune cells in antitumor immunity, such as innate lymphoid cells and neutrophils is still under debate. The microenvironment will greatly influence the outcome, in relation to a beneficial or detrimental effect of these cells [182,183]. For instance, infiltrating neutrophils will probably depend on a positive ratio between type I IFNs and TGF-β to exert its antitumor effects [182], and netosis (neutrophil extracellular traps) can contribute to tumor development [184]. In this sense, the tumor microenvironment may act as an important barrier to the immune response, as, in general, it possesses a tolerogenic profile.

5. Promising targets for anti-tumor immunity, described in transplant biology

Among the already discussed targets, two players in transplant biology are highlighted in this section: coronin-1 [185] and paired immunoglobulin-like receptors (PIR receptors) [30]. We highlighted these two players because their importance to allograft rejection has been recently characterized. We believe that many studies focusing in anti-cancer therapies development might explore them as targets as well, leading to an expansion in the literature concerning the anti-tumor effects of both.

Coronin 1 belongs to an evolutionary-conserved family of proteins, involved in cytoskeleton dynamics in yeast [186] and T cell survival and signaling regulation in mammals [187]. Expressed in different leukocytes, coronin 1 has been described as an essential and specific target for transplants, without restraining immune response against infectious agents [185,188]. Coronin 1 deficiency leads to reduced phosphodiesterase 4 (PDE4) activity, resulting in increased cyclic AMP (cAMP) levels in T cells. Higher cAMP levels in T conventional cells renders them ineffective to drive immune response against allogeneic antigens, but not microbial-derived ones. Thus, the axis coronin 1-PDE4-cAMP is an intriguing molecular target to be evaluated as an activator of T cell-mediated anti-tumor immunity. PDE4 activators or protein kinase A inhibitors are already described as pharmacological modulators [185,189] that can be used to decrease cAMP or modulate cAMP downstream signaling, respectively.

**Table 2.** Immune components directed to foreign tissues as targets for cancer immunotherapy.

| Immune responses that mediate transplant rejection | Anti-cancer immunotherapies |
|-----------------------------------------------|-----------------------------|
| NK cell activation by a distinct pattern of surface ligands in the foreign tissue | NK cell activation by cytokines\’ trained immunity [164] |
| DC mediated presentation of polymorphic MHC and/or peptides | Increased DC-mediated T cell activation through immune checkpoint inhibitors [176] |
| PIR-A-mediated monocyte activation | Inhibition of PIR-A negative regulators [177] |
| T cell-mediated immune responses: | - IL-27 and IFN-γ potentiates antitumor immunity [178,179] |
| - IFN-γ secretion | - CD8⁺ T cells mediated antitumor immunity [180] |
| - MHC-I mediated target cell death by TCD8⁺ cells | - Agonistic anti-CD40 therapy to enhance T cell function [181] |
| - CD40 dependent allogeneic immune responses | |

DC: dendritic cells; NK: natural killer cells; MHC: major histocompatibility complex; IL-27: interleukin-27; PIR: paired immunoglobulin-like receptors; IFN-γ: interferon γ; CD40: cluster of differentiation 40.
in T cells and possibly improve adaptive immunity against neoantigens (similar to allogeneic ones).

PIR-A receptors mediate monocyte memory to allograft through allogenic MHC recognition and is an interesting molecular target to improve the rejection of naturally transmissible cancers. Activated PIR-A receptors signals after interaction with the adaptor molecule FcRγ, which possesses a cytoplasmic immunoreceptor tyrosine-based activating motif (ITAM), important for Src and spleen tyrosine (Syk) kinases signaling [190]. In the case of non-transmissible tumors, the human orthologs of PIR-B (the inhibitory counterpart of PIR-A), leukocyte Ig-like receptors B (LLR-B), were the target of antagonist antibodies therapy, with promising results in a lung carcinoma model [177]. PIR-B receptors signal through immunoreceptor tyrosine-based inhibitory motif (ITIM), leading to Src homology region 2 domain-containing phosphatase 1 (Shp-1) activation and tyrosine phosphatase activity, opposing kinases-mediated signaling [191]. Interestingly, mice genetically deficient in PIR-B presented exacerbated graft-versus-host disease [192]. Thus, these studies reinforce the idea of opposite modulation of common molecular targets in order to drive anti-tumor immune response or anti-rejection therapies.

6. Concluding remarks

The occurrence of transmissible cancer in mammals depends on a complex combination of molecular and behavior features. Improved comprehension of transmissible cancers will impact the development of new immunotherapeutic strategies for already known cancers and immune-suppressive targets for transplants. The combination of immunotherapies with different targets of innate and adaptive immune responses is very interesting and is being used with positive outcomes. It is essential to highlight that the majority of these ‘transmissible’ tumors, with DFTD2 as an exception, have in common low or no expression of MHC-I by the cancerous cells, showing the importance of direct and semi-direct presentation of antigens to unleash an immune response against allografts (tumors in this case). Besides this, peptides from cancerous MHCs may be important determinants to unleash the indirect pathways of immune activation (host MHC derived presentation). New strategies aiming to modulate the indirect pathway could be used to improve transplants and anti-tumor immune responses. Finally, we believe that the direct relation between anti-tumor immunity and transplant rejection inspires caution in therapy development and is an important subject to be explored by researchers of both fields, while cooperation between them can generate significant advances as well.

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