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Innate immune receptors in solid organ transplantation

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ABSTRACT

The discovery of Pattern Recognition Receptors (PRRs) followed by that of their role in the early detection of pathogens and the ignition of the innate immune response has been a formidable progress for immunological research in the past 15 years. This has massively fueled investigations aiming at developing better strategies to fight off infectious diseases and/or to prevent their occurrence. However, infected individuals are for most part outliers in a given population and therefore, the primary function of these receptors should be considered in pathogen-free conditions. Our current understanding indicates that an important physiological function of PRRs resides in their capacity to maintain epithelial homeostasis in response to colonizing commensals. In addition, endogenous host-derived ligands, expressed under stressed, albeit sterile, conditions (called DAMPs for Danger-Associated Molecular Patterns) are also able to trigger PRR signaling. Solid organ transplantation represents a unique situation where both contributions of PRRs signaling can be studied. Indeed, dysbiosis (either caused by antibiotherapy preceding organ transplantation or simply due to the microbiota differences between the transplanted organ and the recipient host) is a characteristic feature of this situation, which is also marked by a massive synthesis and liberation of DAMPs as a result of hypoxia/reperfusion injury. Therefore, in the transplanted organ, at least two compartments (epithelial and that composed of immune cells) participate in graft rejection/acceptance depending on the activation status of expressed PRRs.

1. Introduction

The identification of Toll-like Receptors (TLRs) as innate immune sensors [1,2] (see [3–5] for reviews), capable of detecting invading pathogens is, no doubt, a major achievement [6]. It enabled a considerable "rejuvenation" of the field of immunology by building a functional continuum between innate and adaptive immunity, in which dendritic cells [7] or other innate immune cells [8] play a prominent role. The description of a catalog of the different TLRs, expressed either at the plasma membrane or on the surface of endosomal compartments, and their respective ligands (or PAMPs for Pathogens-Associated Molecular Patterns) was soon followed by reports revealing that, in addition to the 10 human (12 murine) TLRs (see [9] for a recent review), a constellation of cytosolic sensors which are mostly devoted to the detection of foreign nucleic acids (viral DNA or RNA) are required to enable an efficient anti-microbial (essentially against viruses) defense [10–12]. This improved understanding of pathogen detection by innate immune receptors and their downstream signaling pathways has translated into novel therapies aiming at a better control of bacterial/viral infections as well as autoimmune/autoinflammatory diseases [13].

This success story is mostly the reflection of how Science usually proceeds: by identifying and analyzing variants or outliers – which in Medicine correspond to patients – Science hopes to provide a general lesson. However, one must consider that healthy people – which represent the vast majority of human beings – do not exhibit immune-related disease and simply deal with their commensals. Consequently, the function of innate immune receptors further expanded so that they became, in parallel with the products of the MHC genes, major players in the fundamental process devoted to the mammalian immune system, the self/non-self

Abbreviations: AIM2, absent in melanoma 2; BKV, BK virus; DAMP, damage- (or danger-) associated molecular pattern; GvHD, graft-versus-host disease; HCMV, human cytomegalovirus; HSCT, hematopoietic stem cell transplantation; LPS, lipopolysaccharide; MHC, major histocompatibility complex; MyD88, Myeloid differentiation primary response gene 88; NALP3, NLR family, pyrin domain containing 3; NLR, nucleotide-binding oligomerization domain (NOD) – like receptor; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor; RAGE, Receptor for Advanced Glycation End products; RLR, RIG-I-like receptor; TLR, Toll-like receptor; Trif, TIR-domain-containing adapter-inducing interferon-β.

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discrimination, whatever the nature – microbial or not – of the non-self. This has been illustrated in the context of organ transplantation. In this setting, a model has been extensively developed, in which innate receptors respond to "danger" signals [14–16] which, in the supposedly absence of microbial-derived signals, are able to trigger an inflammatory response with potentially harmful consequences, such as graft rejection. While several experimental evidences concur with the validity of the "danger theory", a recent report indicates that monocytes are able to distinguish allogeneic from syngeneic transplanted murine cells, independently of classical sensors of danger signals (i.e. those which are MyD88 – or NALP3 – dependent), thereby offering novel, potentially drugable pathways and targets contributing to innate allorecognition [17].

In addition, the physiological role of PRRs in a healthy situation has been reexamined in light of the major roles exerted by the microbial communities (described as the microbiota) present on epithelial surfaces in multiple pathophysiological settings [18]. Indeed, epithelial cells, such as the intestinal ones, also express a vast panel of innate receptors, which participate in tissue homeostasis and survey the quality of the intestinal microbial flora [19]. These PRR proprieties, along with the dysbiosis which can occur in the transplanted organ upon antibiotherapy as well as in the donor under immunosuppressive drugs, are presently under active investigations.

In this review, the contribution of innate receptors, both as danger signals sensors and as surveyors of an equilibrated, physiological microbiota will be examined in the context of solid organ transplantation.

2. PRRs respond to danger-associated molecular patterns

DAMPs (e.g. ATP, HMGB1, uric acid, see [20] for a recent review providing a classification of the DAMPs presently identified) are endogenous molecules which were conceptualized following the observation that, in specific occasions (such as pregnancy), self and non-self encounters do not trigger inflammation and the subsequent activation of an immune response; and conversely, that of inflammation can be induced in sterile conditions [16]. Once released in the extracellular milieu, upon pathological cell damage, such as those occurring during necroptosis [21] (and not following normal apoptosis), DAMPs are exposed to innate immune receptors, some of which are identical to those responding to the presence of PAMPs. For instance, TLR4 and TLR2, respectively identified as the LPS and lipoteichoic acid receptors [22], can also interact with HMGB1 [23]. Similarly, the NOD-like Receptor (NLR) family member NLRP3 shares the capacity to induce an inflammatory response upon viral [24] and bacterial [25] infections, as well as in response to classical DAMPs such as uric acid crystals [26]. The Receptor for Advanced Glycation End products (RAGE) is another example of these sensors capable of detecting both pathogen- and host-derived molecules such as LPS or S100A proteins, respectively [27,28]. This interaction of DAMPs with PPRs recognizing microbial ligands has been regularly challenged [29]. However, a recent report showing that synthetic peptides engage the murine TLR4/MD-2 complex helps to establish that PRRs are indeed capable of interacting with structurally dissimilar molecules [30]. On the other hand, some receptors appear to be devoted to either DAMPs or PAMPs detection. For instance, P2X7 recognizes ATP (which is released following cell damage), a ubiquitous and identical molecule produced during both the microbial and eukaryotic metabolism [31]. On the contrary, innate immune receptors playing major roles in antiviral defense, such as RIG-I or AIM2, interact with well-identified microbial products such as viral RNA or DNA [10,32], but their endogenous ligands (which existence is predicted given the involvement of these receptors in autoimmunity [33]) still remain elusive, despite recent reports suggesting the endogenous retroviruses might fit this role [34]. Interestingly, receptors able to recognize DAMPs and PAMPs have been involved in transplantation, with a specific emphasis on TLRs and NLRs. The first evidence reporting the involvement of TLR-dependent signaling in acute allograft rejection came shortly after the discovery of TLRs in antibacterial immunity [35]. In this seminal investigation performed in mice, the authors showed that MyD88 ablation, in both the recipient and the donor, was necessary to promote permanent skin allograft acceptance in a minor histocompatibility mismatch model (male donor and female recipient). However, since MyD88 depletion was not sufficient to promote graft acceptance in a fully allogeneic model, the contribution of the TRIF-dependent pathway was later explored [36]. The prolonged survival of the skin graft harvested from combined MyD88- and TRIF-deficient donor in a wild-type recipient demonstrated the importance of TLR-dependent signals in the strength of the allogeneic immune response. The contribution of individual TLRs to the success or failure of transplantation was extensively analyzed in mice using many experimental graft procedures. Altogether, these studies reported that single or combined deficiency in TLR2 and TLR4 in transplanted organs reduces the inflammatory reaction and improves the chances of graft acceptance, as for instance illustrated in the case of pancreatic islets [37] or renal graft ischemia/reperfusion injury [38]. In humans, the presence of various SNPs was instrumental in analyzing the impact of TLR-dependent signaling in transplantation. In the case of renal transplantation, variants within *Tlr3* and *Tlr9* genes appear linked to episodes of acute rejection or adverse cardiovascular events, but the data are less convincing regarding other *TLR* genes. Furthermore, the authors found no association between any of the polymorphisms and graft survival, graft function or all-cause mortality during the 6-year observational period [39]. Interestingly, SNPs in *Tlr3* have been linked to susceptibility to Hepatitis C virus (HCV) infection, a major cause for liver transplantation, and subsequent allograft failure [40]. A similar analysis of genetic polymorphism this time in allogeneic hematopoietic stem cell transplantation (HSCT) also revealed contrasting results with regards to the role of TLRs in human studies [41]. The implication of NOD-like receptors (NLRs) is also the focus of intense attention. Interestingly, a specific transcriptomic signature, characteristic of IL-1b and NLRP3 pathways, appears during the development of primary graft dysfunction in lung transplant patients [42]. While large-scale genetic studies are still lacking to definitely establish the central role of NLRs and the activation of the inflammasome, several reports describing mouse studies confirmed the involvement of the NLRP3 family member, at least in the initiation of graft-vs-host diseases (GvHD) following allogeneic hematopoietic cell transplantation [43]. These studies, which are illustrative of the discrepancies that are commonly encountered between mouse models and human studies, also reveal that the relative contribution of the microbial-derived signals and the damage-associated molecules produced as a result of various injuries (e.g. ischemia/reperfusion) still requires extensive clarification. Nevertheless, studies performed in mice set the grounds for anti-rejections therapies based on modulation of innate immune receptors such as NLRP3 by using uricase to deplete uric acid, a well-known DAMP responsible for IL-1 secretion [43].

Lastly, the role of P2X7 receptors in kidney allograft rejection is now increasingly studied because of the availability of many chemical inhibitors for clinical use [44]. Of note, the role of RIG-I, AIM2 or cGAS (which recognize well-defined molecular signatures of viral origin) in the self/non-self differentiation in the context of organ transplantation has not been proven yet. However, some of these receptors were discovered only recently [10] for their