REVIEW

Risk stratification and immunogenetic risk for infections following stem cell transplantation

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ABSTRACT

Patients undergoing haematopoietic stem cell transplantation (HSCT) are highly exposed to infectious agents. However, it is not known why certain HSCT recipients rapidly develop severe infections while other, despite similar immunosuppressive conditions, do not. Increasing evidence suggests that such differences may be due, in part, to polymorphisms in immune genes. Thus, the identification of genetic factors influencing susceptibility to infections in HSCT recipients may lead to the development of individualized management strategies. However, studies are challenged by several issues, including the relative small size of existing cohorts, the frequent use of prophylactic or preemptive antimicrobial agents, and the fact that genes responsible for immune functions can be inherited either from the donor or the host. Consequently, the major challenge for today’s researchers is to overcome these limitations and find associations that are robust enough to be translated into reliable risk stratification strategies for infectious diseases.

Infectious complications and risk assessment of HSCT recipients

Opportunistic infections caused by bacteria, fungi and viruses represent a major challenge in patients undergoing haematopoietic stem cell transplantation (HSCT). HSCT is characterized by different phases, each associated with a different pattern of immunosuppression. The risk of infection is particularly important for allogeneic HSCT recipients, in which 3 distinct periods are typically described (Table 1).1,2 The pre-engraftment period starts with the beginning of the conditioning regimen and extends up to 1 month after transplantation. This phase is characterized by profound neutropenia, which together with the alteration of natural host defense barriers (chemotherapy-induced mucositis, presence of venous catheters) make patients at risk to develop severe bacterial infections (i.e., bacteremia due to Enterobacteria, viridans Streptococci, Enterococci or coagulase-negative Staphylococci). The same factors combined with the extensive use of antibacterial agents subsequently expose patients to the risk of developing invasive fungal infections, in particular candidemia, hepatosplenic candidiasis and early onset invasive aspergillosis (IA).3,4 The pre-engraftment phase is also characterized by T-cell depletion and can be associated with viral infections, such as Herpes-simplex virus (HSV) reactivation.1,2 The post-engraftment period starts with neutrophils counts recovery and extends to ∼100 d after transplantation, at the time when T-cell function starts to recuperate. This phase is characterized by the occurrence of acute graft-versus-host disease (mainly in allogeneic transplant recipients), which requires the administration of immunosuppressive drugs that further contribute to the impairment of T cell functions. This is also the time at risk for Cytomegalovirus (CMV) reactivation, which itself exerts some level of immunosuppression.5,6 During this phase patients are still at risk for invasive fungal infections, i.e., late-onset aspergillosis3,4 and Pneumocystis jirovecii pneumonia.1,2 The late risk period is mainly characterized by the occurrence of chronic graft-vs.-host disease, which further extends the period at risk for infection due to CMV,5,6 Pneumocystis and Aspergillus, and can also be characterized by infection due to Varicella-zoster virus (VZV) and pyogenic bacteria.1,2

While these phases are well characterized and the occurrence of corresponding infections quite reproducible at the population level, the pattern of infection at the individual level is difficult to predict. Despite similar
underlying conditions, similar age group and similar conditioning regimen, some patients rapidly or repeatedly develop severe infections with one or several pathogens, while other do not. An increasing number of studies have shown that individual susceptibility to infections in immunocompetent patients is influenced by genetic polymorphisms.\textsuperscript{7,10} By analogy, it has been hypothesized that susceptibility to infections in immunocompromised patients may also result, in part, from polymorphisms in immune genes. However, such investigations in strongly immunocompromised patients raise very specific questions.

First, HSCT represents an iatrogenic situation in which the infectious pattern is different from that observed in the general population, as infections are more frequent, more severe, and often due to different (so-called opportunistic) pathogens. On the one hand, the large number of infections within a limited number of patients may contribute to increase the statistical power to detect genetic associations. On other hand, HSCT patients represent a limited population, making it difficult to gather very large cohorts of patients as it can be done in a much easier way for common diseases. However, the iatrogenic condition may reveal genetic factors influencing hosts and pathogens interactions that have not been encountered during their long co-evolution. Second, because the phases of allogeneic HSCT are typically associated with specific risks, different prophylactic strategies have been developed to prevent the occurrence of frequent infections and/or to limit their consequences, which often differ depending on the center and local epidemiology. The extended use of anti-microbial drugs during these periods (either as prophylaxis or for the treatment of suspected or proven infections) can dramatically influence the type of infections and pathogens’ resistance patterns, thereby inducing major biases and limiting the ability to compare results from studies. Finally, allogeneic transplant recipients represent chimerical individuals in which a part of immunity is inherited from the donor (e.g. white blood cells), while another part comes from the recipient (e.g., epithelial cells, proteins produced in the liver), so that the polymorphisms responsible for susceptibility to infections may originate either from the donor or from the recipient, or both of them.

The correlation between single nucleotide polymorphisms (SNPs) and disease phenotypes can be assessed by performing association studies. Such studies can be conducted in a candidate genes approach, in which polymorphisms are selected based on the hypothesis that they can influence the function of a specific gene or group of genes and subsequent immune response to the pathogen (hypothesis driven approach). They can also be conducted in the genome-wide approach (genome-wide association studies, GWAS, or whole genome/exome sequencing) in which millions of polymorphisms throughout the entire genome are interrogated (hypothesis free approach).\textsuperscript{11,12} Up to now, to our knowledge, no genetic study exploring the association of polymorphisms within the whole genome with infectious phenotypes has been published in HSCT recipients. This may be due to the complexity and heterogeneity of the HSCT procedures, as well as the relative small number of patients presenting the phenotypes of interest. Even for candidate genes, the majority of association studies published so far are challenged by a small sample size, heterogeneous definition of cases and controls, differences in patients’ managements between different centers. Also, studies were restricted by the lack of replication and functional evaluation of associated polymorphisms, a restricted number of studied genes and SNPs, the lack of corrections for covariates and multiple tests. Despite

### Table 1. Risk stratification of allogeneic haematopoietic stem cell transplant recipients.

| Phase after HSCT | Main risk factors | Infections | Recommended regimen for patients at risk |
|------------------|------------------|------------|----------------------------------------|
| Early pre-engraftment (up to 1 month) | Prolonged neutropenia, Mucosal damage from conditioning regimens, Central venous catheter, Prolonged empiric antibiotic therapy | Gram-positive and gram-negative bacteria, Hepatosplenic candidiasis, Invasive aspergillosis, HSV infection | Early empirical antibiotic therapy, Anti-fungal prophylaxis |
| Early post-engraftment (2-3 months) | Use of T-cell depleting agents, Grade II-IV of acute GVHD | CMV infection, EBV infection, Invasive aspergillosis, Pneumocystis jiroveci pneumonia | Anti-viral prophylaxis or empirical treatment, Anti-fungal prophylaxis |
| Late phase (>3 months) | Chronic GVHD, Treatment of GVHD, Alternate-donor allogeneic transplants | EBV infection, CMV infection, Invasive aspergillosis, Streptococcus pneumonia, Influenza | Anti-fungal prophylaxis |
these limitations, some associations seem to be relevant, because they have been replicated by one or several investigators, or are supported by strong functional evidence.

Because the innate immune system is at the interface of host and pathogen, most candidate gene studies focus on innate immune genes. The innate immune system is composed of physical barriers (skin and mucous membranes), cellular elements (monocytes, macrophages, neutrophils, dendritic cells, mast cells, natural killer [NK] cells) as well as soluble factors (cytokines, chemokines and other), which all contribute to contain the spread of infection. At the molecular level, pathogen-associated molecular patterns (PAMPs) are detected by specific receptors (PRRs), including toll-like receptors (TLRs), NOD-like receptors (NODs), c-type lectin receptors (CLRs) and RIG-I-like receptors (RLRs). Microbes can be neutralized by proteins of the complement system, thereby preventing their entrance into the cells, increasing the ability of immune cells to detect the pathogens (opsonization). Effective innate responses are very important for establishing adaptive immune mechanisms, including cytotoxic T-cell responses and B-cell differentiation which are responsible for microbial clearance and maintenance.

Bacterial infections represent an important problem in HSCT recipients, mainly during the pre-engraftment period. Neutropenic patients who develop fever require the immediate administration of broad-spectrum antibiotics, which are usually administered for long periods of time, even when the episode is neither clinically nor microbiologically documented. Thus, the development of bacterial infection is largely determined by environmental factors (e.g. previous administration of antibiotics for the prophylaxis or treatment of neutropenic fever), which may render the role of genetic factors more difficult to uncover. This may explain why only a limited number of studies identified polymorphisms associated with bacterial infections. To our knowledge, polymorphisms from 7 genes have been associated with bacterial infections in HSCT recipients (Table 2). Among them, 3 associations are relatively robust.

One of the most relevant associations was that of the promoter SNP rs2232582 in the gene encoding lipopolysaccharide-binding protein (LBP) with susceptibility to gram-negative bacterial infections in HSCT recipients. The polymorphic, risk allele was present in the recipient. It was discovered in a group of ~1200 patients and subsequently replicated in a smaller group of 230 patients. LBP binds to lipopolysaccharide (LPS), an essential component of gram-negative bacteria cell walls, and interacts with the surface pattern recognition receptor TLR4 (together with other molecules such as CD14 and MD2) to induce the NF-κB signaling pathways and subsequent production of pro-inflammatory molecules by innate immune cells. This association was further supported by the fact that patients carrying one or 2 copies of rare allele for rs2232582 SNP (a SNP that is in strong linkage disequilibrium with rs2232582) had higher circulating blood LBP levels before transplantation. A haplotypic combination of promoter variants in LBP (containing rs2232571) was associated with severe sepsis in immunocompetent individuals.

The second relevant association was observed between the 3020insC frameshift mutation (known as SNP13 or L1007insC) within nucleotide-binding oligomerization domain containing 2/caspase recruitment oligomerization domain-containing protein 15 (NOD2/CARD15) and the development of sepsis in HSCT recipients. The risk allele was observed in both the donor and the recipient in an initial study of 430 patients, and in the donor (but not the recipient) in a subsequent, smaller study of 160 patients. NOD2 is a PRR that belongs to NOD-like receptor family. It is the detector of muramyl dipeptide, a component of the cell wall of both gram-positive and gram-negative bacteria. The presence of 3020insC in NOD2/CARD15 is predicted to result in production of a truncated NOD2 protein. In vitro HEK293T cells transfected with plasmids containing 3020insC NOD2/CARD15 mutant showed diminished relative NF-κB activity in response to LPS when compared with wild-type NOD2.

Another relevant association was found for haplotypes expressing low amounts of mannose-binding lectin (MBL2) and different types of bacterial infections in HSCT patients. MBL2 is a PRR involved in complement activation and subsequently opsonization and phagocytosis of invading pathogens as well as apoptosis. MBL2 polymorphisms are frequent in the human population and classically classified into groups of haplotypes/diplotypes that are strongly correlated with the serum levels (stratified into high, intermediate and low). Although these studies were limited by a relative small number of patients (e.g., < 150) and analyzed different phenotypes (bacterial infections due to gram-positive bacteria only, bacterial infections due to either gram-negative and gram-positive bacteria or bacterial sepsis) in different populations (autologous versus allogeneic HSCT), they provided relatively consistent results. Overall, low MBL2 expressing haplotypes in autologous and allogeneic HSCT recipient were or tended to be associated with an increased risk of infection.

Fungal infections are still associated with an important mortality and morbidity in HSCT recipients. The epidemiology of invasive fungal infections is influenced
by the use of antifungal prophylaxis (e.g. fluconazole, posaconazole, co-trimoxazole), which often differ according to the center, and influence the ability of investigators to detect genetic associations. To our knowledge, polymorphisms from 18 genes were significantly associated with invasive fungal infections among HSCT recipients, essentially with IA (Table 2). Among them, 3 associations are particularly robust, as they were performed in relatively large cohorts of patients, replicated by different groups and/or supported by in vitro experiments.27,29 (Fig. 1 and Table 2).

Two nonsynonymous SNPs in TLR4 (D299G and T399I) were associated with the risk of developing IA in HSCT recipients.27 The polymorphism at risk was identified in HSCT donors. The association was replicated in the initial study, and subsequently validated by others.30,31 TLR4 is a PRR essential for recognition of LPS from gram-negative bacteria as well as O-linked mannan from fungi. Functionally those 2 TLR4 polymorphisms were shown to affect lipopolysaccharide recognition by TLR4,32 however their impact on detection of the fungi has not clarified yet. From these studies and other emerged the concept by which the risk of developing invasive aspergillosis could be predicted before transplantation, by the identification of specific genetic polymorphisms together with other pre-transplant risk factors, such as CMV serostatus, both in HSCT donors and/or the recipients.27

A stop-codon polymorphism (Y238X) in CLEC7A, the gene encoding Dectin-1, was subsequently associated with IA in a cohort of ~200 HSCT recipients.28 A similar trend was observed in a cohort of ~180 HSCT recipients.33 In both studies, the risk was conferred by presence of the risk allele in either HSCT donors or recipients. Dectin-1 is a key PRR for β-glucan, an important component of fungal cell walls, and triggers inflammatory responses toward fungal pathogen, as well as their phagocytosis and killing.34-36 Different lines of experiments suggested an effective role for Dectin-1 in cells from both HSCT donors and recipients.28,33 SiRNA inhibition of CLEC7A in lung epithelial cells was associated with a diminished production of inflammatory cytokines after A. fumigatus stimulation, thereby suggesting an antifungal role for Dectin-1 in lung cells from the recipient.28 Human PBMCs and monocytes carrying the Y238X SNP produced lower amounts of inflammatory cytokines upon Aspergillus stimulation compared to WT cells, thereby suggesting that susceptibility to this infection may also depend from impaired Dectin-1 function in donor cells.28 A HSCT model of IA using different combinations of donor and recipient mice (WT and deficient in Dectin-1) further suggested a role for Dectin-1 in both donor and recipient derived cells in the immune response to Aspergillus.28

The most relevant association between IA and genetic variant comes from the study showing the influence of donor haplotype in PTX3 (cluster of 281G and 734A SNPs) with IA in HSCT recipient.29 This association was discovered in a study of 268 HSCT recipients and replicated in another study of 330 recipients.29 The same haplotype was associated with IA in 2 cohorts of solid organ transplant recipients.37,38 PTX3 encodes long pentraxin 3, a soluble PRR that detects galactomannan from the fungi. PTX3 induces many immune processes such as pathogen opsonization, phagocytosis, complement activation, as well as clearance of apoptotic cells.39-41 Functional studies revealed the important role of the donor haplotype at risk in immunity to Aspergillus.29,42-44 The haplotype was associated with reduced PTX3 expression or production as well as reduced anti-Aspergillus phagocytic and killing activity of neutrophils.42 Different mouse models of IA (immunocompetent, neutropenic and HSCT) using PTX3-deficient vs. WT mice2,44 or wild type mice with/without complementation with soluble PTX3, respectively, further supported the role of PTX3 in protection from IA. The successful use of soluble PTX3 in animal models suggest that in the future, soluble molecules may be used in the clinical practice to complement defective immune functions in selected patients.38,43,45

Viral infections represent an important problem during HSCT, mainly during the pre- and post-engraftment period. They result from the reactivation of a pre-existing virus in the recipient or from the transmission of a new virus from the donor. As it is the case for bacterial and fungal infections, prophylactic and preemptive strategies have been developed to reduce the burden of viral infections in these high-risk periods, thereby complicating the interpretation of genetic association studies. To our knowledge, polymorphisms in 13 genes showed significant association with the presentation of viral infections in HSCT recipients, essentially with CMV infection (Table 2). Yet, only few of them were consistently replicated and/or supported by some level of functional evidence.

Several investigators reported associations between the expression pattern of killer immunoglobulin-like receptors (KIR) genes in allogeneic HSCT donors and the risk of CMV infection in the recipient. KIR are encoded by 15 distinct loci within a ~200kbp region in the leukocyte receptor complex (chromosome 19Q13.4) and interact with ligands from HLA class I molecules to regulate the immune function of NK cells.46 Some KIR exert an activating action on NK cells, while other exerts an inhibitory action. Individuals selectively express
### Table 2. Main pathogens causing infections after haematopoietic stem cell transplantation.

| Pathogen | Infectious phenotype | Incidence | Occurrence of infection | Genetic associations with infectious phenotypes after HSCT |
|----------|----------------------|-----------|-------------------------|---------------------------------------------------------|
| **FUNGI** |                      |           |                         |                                                         |
| Gram-negative | *Escherichia coli, Enterobacter, Klebsiella spp, Pseudomonas aeruginosa* | Bacteremia | Common | Pre-engraftment phase after HSCT | Loss of function: MBL2 (D/R) \(^{25}\), NOD2/CARD15 (D/R) \(^{16,26}\), FCGR3A (D) \(^{60}\) |
| Gram-positive | *Staphylococci, Enterococci, Streptococci, Clostridium difficile* | Bacteremia | Common | Pre-engraftment phase after HSCT | Loss of function: MBL2 (D/R) \(^{25}\), NOD2/CARD15 (D/R) \(^{16,26}\), FCGR3A (D) \(^{60}\) |
| **VIRUSES** |                      |           |                         |                                                         |
| CMV | CMV infection | Common | Post-engraftment or late phase after HSCT | Loss of function: TLR9 (D/R) \(^{56}\), DC-SIGN (R) \(^{57}\), IFNG (R) \(^{53}\), CD8 (R) \(^{58}\), FOXP3 (R) \(^{50}\), CTLA4 (R) \(^{58}\), KIR (D) \(^{51-53}\), MCP-1 (R) \(^{64}\), IFI1/4 (D) \(^{55}\), CCR5 (D) \(^{66}\) |
| HSV | HSV infection | Common | Any time after HSCT | Loss of function: NOD2/CARD15 (D/R) \(^{59}\), CCR5 (R) \(^{68}\) |
| VZV | VZV infection | Common | Late phase after HSCT | Loss of function: IFNG (R) \(^{67}\), CCR5 (R) \(^{68}\) |
| EBV | EBV reactivation | Less common | Post-engraftment or late phase after HSCT | No |
| HHV-6 | Post-transplant lymphoproliferative disease | Rare | Post-engraftment or late phase after HSCT | No |
| | HHV-6 infection | Rare | Post-engraftment or late phase after HSCT | Gain of function: CXCL12 (R) \(^{69}\) |
| Respiratory viruses | Influenza virus, parainfluenza, RSV | Pneumonia | Less common | Any time after HSCT | No |
| Adenovirus | Infection | Less common | Post-engraftment or late phase after HSCT | No |
| | Disease | Rare | Post-engraftment or late phase after HSCT | No |
| **FUNGI** |                      |           |                         |                                                         |
| Candida spp | Candida colonization invasive candidiasis | Common | Any time after HSCT | Loss of function: Dectin-1 (R) \(^{70}\) |

(Continued on next page)
## Table 2. (Continued)

| Pathogen | Infectious phenotype | Incidence | Occurrence of infection | Allogeneic | Autologous |
|----------|----------------------|-----------|-------------------------|------------|------------|
| **FUNGI** |                       |           |                         |            |            |
| *Aspergillus spp* | Invasive aspergillosis | Common | Pre- and post-engraftment phase after HSCT | Loss of function: TLR3 (D), TLR5 (R), Dectin-1 (D/R), MBL2 (D), FcγRIII (D), IL10 (R), CXCL10 (D), MASP2 (R), IL23R (D), TLR1 (R), TLR4 (D), IL4R (R), VEGFA (R), CCR6 (D), TLR6 (R), S100B (D), PLG (R) | | |
| Pneumocystis jirovecii | *Pneumocystis jirovecii* pneumonia | Rare | Post-engraftment or late phase after HSCT | No | No |

Notes. *D refers to the donor and R refers to the recipient.*

**The strongest associations with replication or functional assessment are presented in italic.**
different combinations of activating and/or inhibitory KIR genes (>50 haplotypes have been described so far), that have been shown to influence susceptibility to infectious diseases. Four small studies (≤230 subjects) were relatively consistent in showing that recipients of donor haplotypes expressing a high number of activating KIRs had a lower risk of CMV infection compared to recipients of those expressing a lower number; however, these studies used different cut-offs (>1 activating KIR gene versus <1, >5 vs. <5). Two studies showed that HSCT recipients of donor haplotypes containing the activating KIR2DS2 and KIR2DS4 genes had a reduced risk of CMV infection compared to those receiving other donor haplotypes.

The role of polymorphisms from 7 PRR genes on susceptibility to CMV infections has been investigated among HSCT recipients. Significant associations were observed for polymorphisms in 2 of them, TLR9 and dendritic cell-specific ICAM-3-grabbing non-integrin (DC-SIGN). TLR9 is a PRR recognizing unmethylated CpG motifs within viral DNA. Two TLR9 SNPs in HSCT donors (1174A/G and P545P SNPs, both in strong linkage disequilibrium) were associated with an increased risk of CMV infection in the recipients in 2 independent groups of HSCT patients (138 in the discovery study and 102 in the replication study). Furthermore the -1237C/T promoter polymorphism in TLR9 (that is not in linkage disequilibrium with the 1174A/G and the P545P SNPs) was associated with an increased risk of CMV infection in Caucasian HSCT recipients in a single study of ~220 subjects. DC-SIGN is a macrophage and dendritic cell specific PRR recognizing viral glycoproteins. The presence of 2 promoter polymorphisms in DC-SIGN (-139C/T and -939G/A) was associated with and increased risk of CMV infection and/or disease in another study of HSCT recipients (~130 subjects). Immature DCs from individuals carrying 2 copies of -139T and -939G alleles showed decreased expression of DC-SIGN as compared to DCs from individuals carrying 2 copies of -139C and -939A of those.

**Figure 1.** The most relevant donor and/or recipient risk factors for invasive aspergillosis in HSCT recipients.
polymorphisms. Yet, so far, this association was not investigated by others. A study of 72 HSCT recipients reported associations between polymorphisms in 2 gene influencing T cells functions (CD28 and cytotoxic T-lymphocyte antigen-4, CTLA4) and CMV infection in HSCT recipients. CD28 is a co-stimulatory molecules constitutively expressed by naive T cells. CD28 can bind CD80 and CD86 molecules on antigen presenting cells (APC) to initiate signaling pathway important in T-cell activation. CTLA4 is a co-inhibitory molecule that is expressed by T-cells upon stimulation and compete with CD28 to bind to CD80 and CD86, thereby playing a key role in the regulation of adaptive immune responses by T lymphocytes. Both molecules are recognized as important factors determining the outcome of HSCT.

Conclusions/future standpoints
Increasing evidence from candidate gene studies suggest that polymorphisms in the donor and/or the recipient can influence susceptibility to bacterial, fungal and viral infections after HSCT. The identification of such markers may be useful in the clinical practice, as they may lead to the development of tailored strategies for the management of such patients. For instance, antimicrobial prophylaxes may be administered to patients undergoing a high risk to develop infections, thereby preventing the use of costly and sometimes toxic agents in patients who are at lower risk. However, many centers already use indiscriminate prophylaxis and/or preemptive treatment strategies that have proven to significantly reduce the infectious burden in this population. Alternatively, the use of immunosuppressive drugs after HSCT may be tailored to the individual risk, and/or novel immunomodulators (such as soluble pattern recognition receptors) may be developed to compensate for immune functions that are relatively deficient in selected individuals. However, studies have not translated into personalized approaches in the HSCT population. The major limitations include the fact that most studies identified genetic associations of a single polymorphism with a single pathogen. In the clinical practice, patients develop several infections either at the same time or sequentially, and each is influenced by a complex combination of demographic, clinical and genetic factors. The implementation of personalized approaches in the HSCT population would require the integration of these multiple factors within a global risk scoring system. Such approaches are currently limited by the relative small size of existing studies, the small number of available phenotypes as well as the limited number of genes and polymorphisms that have been tested. This goal could probably only be achieved with the implementation of very large cohorts of patients in several centers, with extensive clinical data and samples collection.

Abbreviations
CC chemokine (C-C motif) receptor
CMV Cytomegalovirus
CTLA4 cytotoxic T-lymphocyte-associated protein 4
CXCL CXC-chemokine ligand
D donor
DC-SIGN dendritic cell-specific ICAM-3-grabbing non-integrin 1
EBV Epstein-Barr virus
FCGRIIA Fc fragment of IgG, low affinity IIa receptor
FOXP3 forkhead box P3
GVHD graft-versus-host disease
HHV-6 human herpes virus 6
HSV haematopoietic stem cell transplant
HSV Herpes simplex virus
IFNG interferon gamma
HSV Herpes simplex virus
IFL3/4 interferon lambda 3/4
IL interleukin
IL23R interleukin 23 receptor
KIR killer cell immunoglobulin-like receptor
LBP lipopolysaccharide binding protein
MASP2 mannan-binding lectin serine peptidase 2
MBL mannose banding lectin
MCP-1 monocyte chemoattractant protein 1
NOD2/CARD15 nucleotide-binding oligomerization domain containing 2/caspase recruitment domain-containing protein 15
P2X7 purinergic receptor P2X7
PLG plasminogen
PTPN22 protein tyrosine phosphatase, non-receptor type 22
PTX3 pentraxin 3
R recipient
RAGE advanced glycosylation end product-specific receptor
RSV respiratory syncytial virus
S100B S100 calcium binding protein B
TLR toll-like receptor
VEGFA vascular endothelial growth factor A
VZV Varicella-zoster virus

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