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MDSCs in infectious diseases: regulation, roles and readjustment

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Question	**Response**
Please provide one or two short sentences highlighting what makes your manuscript especially interesting. This précis is meant for our table of contents and must not exceed 250 characters, including spaces. Please include an identical précis in your manuscript text, following the abstract	We discuss the roles of MDSCs in acute and chronic infection, as well as strategies to modulate their dynamics to benefit the host.

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Re: ANSWERS TO REVIEWERS R2

Dear Dr. Pawelec,

We thank the Reviewers and the Editorial office for the positive reviews of our manuscript. We have now made additional corrections based on the suggestions of the reviewers and editorial office. These changes are highlighted in the new version of the manuscript. A point-by-point reply to each comment can be found below.

Yours sincerely,

on behalf of all authors,

Anca Dorhoi and Annabel Valledor

Reviewer #1: The review is substantially improved and addresses my previous concerns. There are still some slight grammar issues and there could be some edits for length (i.e. the second paragraph seems extraneous).

We have made additional changes to the English, including the table and figures. We have amended and shortened several sections, including the second paragraph, and hope it is now easier to read.

Reviewer #2: The authors have addressed the concerns by the review panel and the editorial office in a comprehensive and in-depth manner. There are no further critics.

Reviewer #3: The authors have made a very detailed and comprehensive revision to their review. I have no further comments.

We thank the reviewers for their positive comments.

Answers to Specific Comments from the EDITORIAL OFFICE:

5) Regarding your "Author contributions" section:
A) "Conceptualization and writing-original draft" should be corrected to "Conceptualization and writing of the original draft".
B) These words seem to be followed by all co-author names, without any exception. Is this correct? If so, please replace the long list with ": all authors." Then carry on with "Figure design …".
C) There is no need to explicitly write (!) all names. However, the section must cover all contributions of all (!) authors.
D) "Writing-review and editing" should probably be changed to "Revisions and editing".
E) It would be optimal if the section ended in something like: "All authors approved the final version of this paper." (see also below)

All these changes have been made in the "Author contributions" section.

6) We wrote in our previous decision e-mail:

We cannot publish a table with a reference list that includes more references than we recommend for Symposium-in-Writing papers as table in the middle of a text. [Please do not misunderstand: it is OK that your paper has more than 50 references, and it is also OK that your table has more than 50 references.].
We have 2 options:
OPTION 1: Integrate your table in your manuscript text. All references should go into the normal reference list (make sure not to duplicate references!). The table should go also into the manuscript text, at the very end of it, following the references. Changes (other than the update of reference numbers and formatting changes) should be highlighted.
OPTION 2: Change your table into a supplementary table. Prepare one perfectly formatted PDF including only Supplementary Table 1 [no cover page]. No changes highlighted.
IN ANY CASE: Reference numbers must be in square brackets, for example [55] instead of (55), and the table must be Table 1 or Supplementary table 1 (not: Table I), also when referring to it in your text.

You responded:
We chose OPTION 2 and made all the changes indicated here.

It looks as if our request was not quite clear and could be misunderstood; our apologies. It looks as if you somehow mixed the two options.
In your original submission the 2 reference lists were the problem: a reference list of your paper, and a different reference list just for your table, being even longer than the real reference list. This was not OK; we could not include these 2 reference lists in one paper.
A) The 2 options are as follows:
REGULAR TABLE OPTION (preferred):
- There is only 1 single reference list.
- There is a regular table, with references to that reference list.
- The text refers to "Table 1", and not to "Supplementary Table 1".
- The references to literature must be updated in the table with each change of the reference list.
- The table must be uploaded in Word.
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SUPPLEMENTARY TABLE OPTION (optional):
- There are 2 different reference lists.
- The regular reference list must only include the references which are cited in the main manuscript. It must not include the references which are cited only in the supplementary table.
- There is a supplementary table.
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- The "Supplementary Table 1" has its own reference list in the same file. That reference list must include all references cited in that table, i.e. it might partially duplicate references that are already included in the regular reference list.
- The "Supplementary Table 1" must be uploaded as PDF.
- The PDF must not include any highlighting.
- Any changes must be explicitly explained to the Reviewers.
B) We would prefer option 1 because your table is not too long to be a regular "Table 1". It is, of course, no problem that it refers to many publications, as long as there is no enormous second reference list.

We have now changed to a regular Table format, following all the recommendations for option 1. The table does not cite any additional references beyond the ones used in the main text.

7) Should there be any new abbreviations, please do not forget to define them and, if used also stand-alone, to include them in your list of abbreviations.

This has been done for one abbreviation that was missing from the list of abbreviations.

8) Before you resubmit, please check your paper for consistency. Example: Do the figure legends match the figures? If you have figure parts a, b, c – does the figure legend also have a, b, c? Do the references to figures in your manuscript text really match the figure parts they refer to? The same goes for tables and references to literature.

All this has been checked.

9) A) Please correct:
- (Acknowledgements) "University of Edimburgh" – you probably mean "University of Edinburgh".
- (Conflict of interest) "conflicts of interes." (typo)

We have made these corrections.

B) Regarding all changes (also shortening etc.) and regarding all manuscript parts which were not corrected before: Before resubmission, after having made all changes, please make sure that both the contents and the English of your entire paper (including all parts) are correct. Correct also typos and punctuation. If you are not a native English speaker: first check the contents, then have your paper corrected for the English, and last check that the language corrections have not altered your paper inappropriately.
C) The language editor should also have a look at your table and figures if this has not been done before. Examples:
- (Figure 1 and Figure 2) You vary between "virus" and "viruses" – correctly?
- (Figure 2) "Fungi" or "Fungus"? Please use what is correct.

We have made additional corrections to the English, including the table and figures.
Regarding the comment in 9C), for consistency, we have now used the plural forms of every type of pathogen for both figures: e.g. bacteria / viruses / fungi / parasites, independent of the number of pathogens used as an example in each category. We have also made some colour corrections to Figure 1 (not highlighted).

10) Your final, revised paper must be seen by all co-authors (according to our full, on-line Instructions for Authors). Ask them explicitly to also check the correctness of their name, their affiliation, their ORCID (if applicable), their conflict of interest, and their contribution in the "Authors´ contributions" section, if they have not done so before. Do not forget to highlight any last minute changes, and make sure that they are in correct English.

All the authors have seen the last version of the manuscript and agreed to it.

MDSCs in infectious diseases: regulation, roles and readjustment

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Abstract

Many pathogens, ranging from viruses to multicellular parasites, promote expansion of MDSCs, which are myeloid cells that exhibit immunosuppressive features. The roles of MDSCs in infection depend on the class and virulence mechanisms of the pathogen, the stage of the disease and the pathology associated with the infection. This work compiles evidence supported by functional assays on the roles of different subsets of MDSCs in acute and chronic infections, including pathogen-associated malignancies, and discusses strategies to modulate MDSC dynamics in order to benefit the host.

Keywords: Myeloid regulatory cells, MDSC, Infection, Immunosuppression, Oncogenic viruses, Mye-EUNITER

Précis: We discuss the roles of MDSCs in acute and chronic infection, as well as strategies to modulate their dynamics to benefit the host.

Abbreviations

Arg, arginase
Arm, Armstrong
ATRA, *all-trans* retinoic acid
B. fragilis, *Bacteroides fragilis*
C. albicans, *Candida albicans*
C13, clone 13
CCR, C-C chemokine receptor

COST, European Cooperation in Science and Technology

EBV, Epstein Barr virus

ETBF, enterotoxigenic *Bacteroides fragilis*

FV, Friend virus

H. felis, *Helicobacter felis*

H. polygyrus, *Heligmosomoides polygyrus*

HbsAg, HBV surface antigen

HDT, host-directed therapy

IAV, Influenza A virus

iNKT, invariant NK T

JEV, Japanese encephalitis virus

K. pneumoniae, *Klebsiella pneumoniae*

L. major, *Leishmania major*

LCMV, lymphocytic choriomeningitis virus

LOX, lipoxygenase

Mφ, macrophage

M-MDSC, monocytic MDSC

M. tuberculosis, Mycobacterium *tuberculosis*

MR, mannose receptor

MRC, myeloid regulatory cell

mTOR, mammalian target of rapamycin

NADPH, nicotinamide adenine dinucleotide phosphate

NOS, NO synthase

P. aeruginosa, *Pseudomonas aeruginosa*

PcP, *Pneumocystis* pneumonia

PDE, phosphodiesterase

PGE2, prostaglandin E2

PMN-MDSC, neutrophil-like MDSC

ROS, reactive oxygen species

S. aureus, *Staphylococcus aureus*

SIV, simian immunodeficiency virus

T. crassiceps, *Taenia crassiceps*

T. cruzi, *Trypanosoma cruzi*

T. gondii, *Toxoplasma gondii*

TB, tuberculosis

Tfh, T follicular helper

Introduction

Myeloid cells recognize pathogens and orchestrate the development of antimicrobial immunity. The sensing of microbial cues initiates inflammatory responses during infectious diseases. These events contribute to the generation of effective adaptive immune responses, pathogen removal, and a return to homeostasis. However, if uncontrolled or unresolved, inflammation results in immunopathology. Pathogen-derived molecules and inflammatory mediators trigger expansion and/or activation of specific myeloid cell subsets with regulatory activities, termed myeloid regulatory cells (MRCs). This affects the disease outcome in different ways, depending on the type and stage of the infection. MRCs include MDSCs with either a monocytic (M-MDSC) or a neutrophilic (PMN-MDSC) phenotype, alternatively activated macrophages, and regulatory dendritic cells. Here, we focus specifically on the functions of MDSCs in acute and chronic infections, including diseases triggered by oncogenic microbes.

It is important to note that there are limitations to the ways in which the functions of MDSCs can be addressed experimentally. Knockout animals specifically lacking MDSCs do not exist, as MDSCs are generated during the development of myeloid progenitor cells into innate immune cells such as neutrophils and monocytes. However, the potential functions of MDSCs have been explored using correlative and adoptive transfer studies, *ex vivo* functional assays and drug-induced differentiation of MDSCs. The identification of MDSCs is based on phenotypic markers and the validation of suppressive activity by immunological assays [1, 2]. Here, we will discuss the interactions of MDSCs with selected pathogens using examples in which MDSC subsets have been characterized using functional assays and not by immunophenotyping techniques alone. We will highlight the relevance of MDSCs in the resolution of inflammation, their roles as reservoirs for persistent microbes, the microbial signatures and host pathways that regulate MDSC dynamics, the capacity of MDSCs to modulate immunopathology in chronic infections and the implications of this for microbial-induced carcinogenesis. Finally, we will address MDSC-targeted strategies and discuss how these could be employed to treat infectious diseases.

Pathogen and host factors drive MDSC dynamics during infection

Experimental infections and *ex vivo* assays have indicated that selected pathogen-associated molecular patterns trigger the expansion of MDSCs. In mice, bacterial lipopeptides that bind TLR2/6 [3], LPS [4], which engages TLR4, and flagellin [5], a TLR5 ligand, lead to local or systemic expansion of $Gr1^{+}CD11b^{+}$ MDSCs with proven immunosuppressive properties *ex vivo* and *in vivo*. Viral ligands of TLR2, including HCV core protein [6–9] and HBV surface antigen (HbsAg) [10], both of which are secreted from infected hepatocytes, as well as surface HIV-1 gp120 [11], induce increased numbers of M-MDSCs that are able to suppress T cell [6–8, 10, 11] and NK cell responses [9]. Such PRR ligands can also drive differentiation of monocytes into MDSCs [12]. In contrast to TLR2/6, 4 and 5 ligands which lead to expansion of MDSCs, TLR3, 7 or 9 ligands negatively regulate the functionality of MDSCs during infection with influenza A virus (IAV) [13, 14].

Fungal pathogens promote the accumulation of PMN-MDSCs by activating C-type lectin receptors, notably the dectin-1/Card9 pathway [15]. However, purified β-glucans, which are abundant in *Candida spp.* and *Aspergillus spp*. and represent agonists for dectin-1, were shown to restrict MDSC expansion in tumor models [16]. For this reason, the precise molecular mechanisms by which fungal pathogens promote MDSC genesis require further characterization. Some parasite glycans also increase MDSC frequencies in infected tissues. For instance, intraperitoneal injections with intact glycans purified from *Taenia crassiceps* (*T. crassiceps*) or schistosome oligosaccharides elicit myeloid cell populations that suppress T cell proliferation *in vitro* [17–19]. Some of these effects are independent of TLR4 and Th2-type cytokines [18, 19]. Moreover, immunization of mice with *Toxoplasma gondii* (*T. gondii*) oocyst lysate antigen leads to increased numbers of PMN-MDSCs in the lungs [20]. However, the host sensors that control MDSC accumulation in parasitic infections are unknown.

In addition to PRRs, many other host factors affect MDSC dynamics during infection. Several inflammatory mediators and growth factors, including VEGF, GM-CSF, G-CSF, IL-1β, IL-6, TNF-α and prostaglandin E2 (PGE2) have been identified as inducers of MDSC expansion and/or activation [21–23]. There appears to be a critical requirement for IL-6 and STAT3 signaling in expansion of MDSCs in several unrelated infections [3, 10, 24, 25]. For example, a significant reduction in accumulation of splenic MDSCs was observed in IL-6-deficient mice during *Trypanosoma cruzi* (*T. cruzi*) infection in comparison to wild type (WT) mice [24]. Similarly, mice with deficient hepatic expression of gp130, the common signaling receptor for the IL-6 family of cytokines, had reduced frequencies of MDSCs during polymicrobial sepsis [25]. Furthermore, the IL-6-induced hepatic acute phase proteins serum amyloid A and chemokine (C-X-C motif) ligand (Cxcl)1 cooperatively promoted mobilization and peripheral accumulation of MDSCs [25].

The growth factors GM-CSF and G-CSF control myelopoiesis in the steady state. Dysregulated myelopoiesis occurs when levels of these factors are increased long-term, particularly during chronic infections, and this leads to continuous activation of progenitors, promoting MDSC generation [23]. Recent findings indicate that GM-CSF drives the conversion of murine Ly6C^{hi} monocytes and human CD14^{+} monocytes into suppressor cells. This differentiation requires activation of the protein kinase B (PKB)/mammalian target of rapamycin (mTOR)/mTOR complex (mTORC)1 pathway by GM-CSF and subsequent signaling through the IFN-γ receptor/IFN regulatory factor-1 (IRF-1) pathway [26]. Anti-apoptotic molecules such as cellular-Flice-like inhibitory protein (c-FLIP) and myeloid leukemia cell differentiation protein (MCL-1) play a role in the generation of MDSCs during cancer [27], but their role in MDSC generation during infection has not been demonstrated. Overall, it seems that the growth factors and cytokines that are present during an infection may interfere with the physiological differentiation of hematopoietic progenitors and result in abnormal cell phenotypes, including MDSCs. The interaction of MDSCs with other immune cells during infection may also influence their frequency and suppressive capacity. An example is the increased expansion of MDSCs in mice deficient in invariant NK T (iNKT) cells compared to control mice during infection with IAV [13]. MDSC suppressive activity was abolished *in vivo* by adoptive transfer of iNKT cells, suggesting that the interaction between iNKT cells and MDSCs modulates MDSC suppressive activity, at least during IAV infection. Whether this pathway operates in

other infections remains to be determined. In summary, accumulating evidence suggests that particular pathogen sensors and inflammatory mediators mutually or independently activate pathways that lead to the expansion of MDSCs during infection. Additional regulators and processes that affect MDSC dynamics will presumably be uncovered as research into the biology of these cells in infection develops.

The outcome of MDSC expansion in acute infection

MDSC subsets appear to exacerbate certain acute infections (Table 1) (Figure 1). In viral diseases, expansion of MDSCs may favor immunosuppression and viral persistence. An example is the inhibition of T follicular helper cells (Tfh) and B cells by MDSCs that was observed during infection with a Japanese encephalitis virus (JEV) strain that causes acute encephalopathy [28]. Targeting MDSCs with retinoic acid reversed suppression and improved the survival of JEV-infected mice. In infection with Friend retrovirus (FV), which is able to persist lifelong in mice despite eliciting a strong acute immune response, expansion of both M-MDSC and PMN-MDSC populations during the late phase of acute infection correlated with $CD8^+$ T cell contraction. Of these MDSC subsets, experiments *in vitro* suggested that only PMN-MDSCs could suppress virus-specific $CD8^+$ T cell responses [29], although the specific contribution of this subset was not evaluated *in vivo*. Depletion of MDSCs rescued activated $CD8^+$ T cells and minimized viral loads. These observations suggest that MDSCs interfere with immune control of the viral load during acute infection, facilitating the subsequent establishment or maintenance of viral chronicity. The expansion of MDSCs during acute toxoplasmosis, a parasitic infection, has also been partly associated with immune hyporesponsiveness within the lung [30].

The expansion of MDSCs may also facilitate disease progression during sepsis. The number of circulating PMN-MDSCs in septic patients correlates with the disease severity and with plasma levels of IL-6 [31]. The type of infection may influence the dynamics of different MDSC subsets, as M-MDSCs were found in all sepsis patients included in a study cohort, whereas PMN-MDSCs expanded preferentially in sepsis caused by gram-positive bacteria. A $CD14^{low}$ PMN-MDSC population among the neutrophilic subset expressed IL-10 and suppressed T cell proliferation *in vitro* through the production of reactive oxygen species (ROS) [32]. In a recent study in which patients were enrolled from intensive care units, PMN-MDSCs were specifically expanded in individuals with sepsis and were responsible for increased arginase (Arg) 1 activity [33]. High initial frequencies of PMN-MDSCs, but not of M-MDSCs, were associated with subsequent nosocomial infections. Depletion of $CD15^+$ cells from PBMCs obtained from sepsis patients increased the rate of T cell proliferation *in vitro*, suggesting that PMN-MDSCs may have been largely responsible for the sepsis-induced immune suppression. The observations in murine models of sepsis diverge from those in the human studies. The expansion of MDSCs during polymicrobial sepsis induced by cecal ligation was found to be beneficial for the host [25, 34]. Murine MDSCs suppressed production of IFN-γ by $CD8^+$ T cells and contributed to sepsis-induced Th2 polarization *in vivo* [34]. Mice with reduced levels of circulating and splenic MDSCs as a consequence of hepatic gp130 deficiency showed decreased survival after induction of polymicrobial sepsis. The phenotype could be reverted by the adoptive transfer of a heterogeneous population of $Gr1^+CD11b^+$ cells comprised of 50% PMN-MDSCs [25]. Together, these

studies support a host-protective anti-inflammatory role for MDSCs during polymicrobial infections in mice. The discrepancy between observations emerging from humans and murine models may stem from the analyses of distinct phases of sepsis as well as from the distinct features of the MDSC subsets involved.

MDSCs may also be beneficial for the host in certain acute pneumonias and parasitic infections. During infection with *Klebsiella pneumoniae* (*K. pneumoniae*) tight control of inflammation is critical for pathogen clearance [35]. The accumulation of neutrophils in non-resolving pneumonia causes collateral tissue damage, resulting in acute lung injury. In mice infected with *K. pneumoniae*, MDSCs were recruited to the lungs several days post challenge and represented an important local source of IL-10, which correlated with the resolution of inflammation and recovery after infection [35]. MDSCs were shown to efferocytose apoptotic neutrophils, limit inflammation and prevent tissue damage, thereby facilitating the return to tissue homeostasis. In a murine model of Chagas disease, M-MDSCs exhibited protective roles as well. They were detected in myocardial lesions during the acute phase of *T. cruzi* infection and suppressed polyclonal T cell proliferation *ex vivo* through a NO-dependent mechanism [36]. Furthermore, higher numbers of MDSCs were detected in BALB/c mice compared to C57BL/6 mice during infection, along with lower levels of inflammatory cytokines, reduced liver injury and increased resistance to infection [24]. Moreover, decreased MDSC recruitment in IL-6-deficient mice and MDSC depletion both led to increased inflammation, higher parasite burdens and mortality [24]. Thus, MDSC-mediated modulation of the inflammatory response during *T. cruzi* infection allowed efficient parasite clearance while simultaneously limiting overzealous adaptive immune responses and excessive tissue damage. In humans suffering from chronic Chagas disease, increased tyrosine nitration was detected on $CD8^+$ T cells and heightened NO production was shown in peripheral leukocytes [37]. Characteristics of MDSCs such as activation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and production of NO and peroxynitrites can cause nitration of the TCR and may contribute to their suppressive activity in such conditions. However, whether MDSC expansion influences tyrosine nitration of $CD8^+$ T cells in humans with Chagas disease remains to be established. Overall, MDSC activity in acute infections can culminate in negative or beneficial outcomes, depending on the microorganism involved as well as the pattern and extent of inflammation. Deleterious effects could result from inability of the host to clear pathogens because of immunosuppression, whereas suppression of inflammatory responses that exacerbate tissue damage could be beneficial to the host.

The versatile roles of MDSCs in chronic infection

Many successful pathogens manipulate host immunity by suppressing T cell responses, thereby establishing chronic infections. Chronicity poses dual risks. Firstly, it requires prolonged therapy, which often leads to poor patient compliance and the development of antimicrobial resistance. Secondly, it leads to tissue remodeling and the development of microenvironments that favor pathogen persistence. Even when antibiotic therapy is effective and clears the pathogen, infected tissue often fails to reach *restitution ad integrum*, leading to the formation of tissue scars. Such tissue changes and non-resolving inflammation are reminiscent of the disease processes in cancer [38]. In fact, many types of cancer are associated with

infectious diseases, with several pathogens classified as Group 1 carcinogens so far [39–41]. We will discuss how MDSCs affect progression of various infections, including tuberculosis (TB), staphylococcal infections, viral hepatitis, immunodeficiency syndromes, chronic parasitic infections and fungal disorders (Table 1) (Figure 1). In addition, we will discuss examples in which MDSC-driven effects have been associated with pathogen-induced carcinogenesis.

An example of a chronic bacterial infection in which MDSCs play an important role is active TB, which results predominantly from inefficient T cell responses. Increased frequencies of MDSCs are present in pleural fluids from patients with pulmonary TB [42–44], and MDSCs isolated from the blood of TB patients suppress T cell function [42, 43], secrete abundant IL-1β and IL-6 [42], and correlate with high NO levels [42, 44]. Peripheral MDSCs increase in cases of recent, but not remote infection, and a reduction in their frequencies is observed after treatment [43, 44], suggesting that the expansion of MDSCs correlates with increased bacterial burdens. These findings have been recapitulated in the mouse model of TB, in which MDSCs are found in multiple tissues in infected mice [45, 46]. These cells harbor *Mycobacterium tuberculosis* (*M. tuberculosis*), and may thus provide a niche for *M. tuberculosis* survival. Furthermore, they release both pro-inflammatory (IL-6, IL-1α) and anti-inflammatory (IL-10) cytokines while exerting suppressive effects on T cells [45], including restriction of IFN-γ production via NO-dependent mechanisms [46]. MDSCs may thus support immune evasion by promoting T cell dysfunction and disease progression. Therefore, MDSCs are potential biomarkers of active TB and attractive targets for therapeutic intervention. Accordingly, different strategies used to deplete these cells during infection, either alone [45] or in combination with antibiotherapy [47], have resulted in improved disease outcomes in mice. MDSC depletion also improved disease outcome in *Staphylococcus aureus* (*S. aureus*) infection [48]. Gemcitabine delivery depleted PMN- and M-MDSCs and restored T cell responses. *S. aureus* is frequently associated with orthopedic biofilms that subvert immune-mediated clearance, and in murine models, MDSCs represent the main cellular infiltrate in biofilms. Their abundance inversely correlates with T cell activity and contributes to the chronicity of infection. Antibody-mediated depletion of biofilm MDSCs, which had increased Arg1, NOS2 and IL-10 expression compared to spleen cells, improved bacterial clearance by augmenting pro-inflammatory cytokine release by monocytes and macrophages [48].

MDSCs may also support oncogenic transformation in chronic infections with bacterial pathogens that can cause colorectal and gastric cancer. In a murine model, infection with *Helicobacter felis* (*H. felis*) caused mobilization of PMN-MDSCs to the gastric mucosa and subsequent tissue metaplasia, a precursor of cancer [49]. PMN-MDSCs were also associated with intestinal metaplasia in human stomach tissue from *Helicobacter pylori*-infected individuals. Similarly, the gut commensal and candidate pathogen enterotoxigenic *Bacteroides fragilis* (ETBF) induced accumulation of MDSCs and colon carcinogenesis in a mouse model of colorectal cancer [50]. In this study, sorted M-MDSCs displayed higher immunosuppressive activity than PMN-MDSC in *ex vivo* assays.

In viral infections, MDSCs support the establishment of chronicity. This has been elegantly demonstrated in kinetics experiments with different strains of lymphocytic choriomeningitis virus (LCMV). Comparable

levels of MDSC expansion were observed during the first week of LCMV infection with the Armstrong (Arm) strain, which leads to acute resolving infection, and with clone 13 (C13), which develops into a chronic infection [51]. However, only C13 infection led to sustained high numbers of suppressive M-MDSCs in infected organs. C-C chemokine receptor (CCR)2-deficiency, which diminished the mobilization of monocytic cells, or antibody depletion of $Gr1^+$ cells led to enhanced LCMV-specific T cell cytokine responses in C13-infected mice, suggesting that expansion of suppressive M-MDSCs facilitated the establishment of chronicity [51]. A detailed analysis of MDSC during chronic infection with LP-BM5 retrovirus, which causes murine acquired immunodeficiency, has also provided evidence for M-MDSC-mediated down-regulation of $CD4^+$ T cell and B cell responses [52].

HIV induces concomitant immune-regulatory and inflammatory mechanisms that drive chronic viral persistence and disease progression [53, 54]. Several studies have quantified MDSC frequencies in different phases of HIV infection and investigated their interplay with anti-viral immune responses. In patients with primary or chronic HIV-1 infection, expansion of PMN-MDSCs with enhanced expression of PD-L1 was observed early during the primary immune response [55]. *In vitro*, PD-L1 blockade with specific antibodies attenuated the inhibitory function of patient MDSCs co-cultured with $CD8^+$ T cells, suggesting that PD-L1 forms part of their suppressive arsenal. Chronically HIV-1-infected patients showed increased levels of PMN-MDSCs that expressed IL-4 receptor alpha (IL-4Rα), and this positively correlated with the viral load, inversely associated with the $CD4^+$ T cell count and rapidly changed upon anti-retroviral therapy [56]. *In vitro*, MDSC inhibited the proliferation of $CD8^+$ T cells from both healthy donors and HIV-controllers (HIV-1-infected individuals able to control plasma viral load in the absence of therapy), and induced expansion of Tregs from HIV controllers. Another mechanism proposed for PMN-MDSC-mediated suppression in HIV-1 patients is their capability to inhibit CD3ζ expression by cell-to-cell contact [57]. Increased frequencies of M-MDSCs have also been detected in HIV-1 patients despite effective anti-retroviral therapy [58]. The suppressive activity of these cells is mediated by Arg1 and cell-to-cell contact, but their specific contribution to disease pathophysiology in HIV-1 infection remains elusive. The simian immunodeficiency virus (SIV)-macaque model recapitulates the pathogenesis of HIV infection in humans and is therefore widely used to study the physiopathology of AIDS. In a recent study, SIV infection induced the expansion of $CD14^{hi}CD16^{-}CCR2^{lo}$ M-MDSCs that efficiently suppressed proliferation of $CD8^+$ T cells, but not of $CD4^+$ T cells [59]. Like in humans, antiretroviral therapy of infected macaques led to contraction of MDSCs. Low copy numbers of SIV DNA were found in MDSCs of infected macaques, indicating that these cells could constitute a viral reservoir. In a follow-up study, PMN-MDSCs expanded after interruption of anti-retroviral therapy in the chronic phase of SIV infection. At all stages of infection, isolated PMN-MDSCs were able to suppress T cell proliferation [60]. Despite clear evidence that MDSCs are induced in HIV/SIV infection and that they can inhibit T cell responses, further studies are required to better characterize the dynamics and role of different MDSC subsets in the tissues where immune responses and inflammatory processes take place. Because of their immunosuppressive activity, MDSCs may constitute a reservoir for pathogens, and their permissiveness to HIV infection should be investigated.

M-MDSC frequencies are also significantly higher in patients with chronic HCV infection compared to healthy donors [6, 7, 61, 62] or patients receiving antiviral therapy [61, 62]. MDSC-induced suppression in HCV infection has often been associated with expression of IL-10 and Arg1 [6, 61, 62]. M-MDSC frequency was found to positively correlate with HCV RNA levels [7, 61, 62] and Treg expansion [7]. Despite strong evidence that MDSCs contribute to T cell impairment, which affects viral clearance in chronic HCV infection, one study has challenged this notion by reporting no differences in the frequencies of M-MDSCs and PMN-MDSCs between chronically infected HCV patients and healthy individuals and a lack of correlation between these cells and the viral load [63]. In chronic HBV infection, the M-MDSC population expands [10, 64] and M-MDSC frequencies correlate positively with HbsAg serum levels [10]. *In vitro*, MDSCs decreased HBV-specific $CD8^+$ T cell responses via PD-1-dependent secretion of IL-10 [64]. In a mouse model of chronic HBV infection, forced maturation of MDSCs by delivery of all-trans retinoic acid [ATRA] limited viral replication [10]. In this model, M-MDSCs were more effective at suppressing T cells than PMN-MDSCs [65]. Their accumulation in the liver was driven by γδ T-cells and led to $CD8^+$ T cell exhaustion [66]. In contrast to the findings in mice, higher PMN-MDSC and not M-MDSC frequencies were found in a chronic HBV cohort [67]. PMN-MDSCs transiently expanded in acute resolving HBV infection and contracted prior to acute liver injury. In persistent infection, Arg-expressing PMN-MDSCs increased predominantly in phases characterized by HBV replication without immunopathology and accumulated in the liver, suggesting that PMN-MDSCs may restrict liver inflammation [67]. MDSC expansion during HBV infection could therefore prevent immunopathology at the cost of promoting chronicity. Whether distinct MDSC subtypes drive such dual outcomes needs further investigation.

Besides favoring chronicity, MDSC abundance correlates with the clinical outcome in several virus-associated malignancies. Epstein Barr virus (EBV) is the most growth-transforming pathogen in humans and, accordingly, is associated with human malignancies, mostly of B cell or epithelial cell origin [68]. In Hodgkin's lymphoma, which is EBV-associated, increased numbers of MDSCs in the blood were prognostic of a worse clinical outcome [69]. M-MDSCs were also found in EBV-associated extranodal natural killer NK/T cell lymphomas [70]. In this study, their suppressive function was dependent on NOS2, Arg1 and ROS activities and correlated with elevated expression of immune suppressive cytokines and an increase in Tregs. Several viral factors expressed by tumor cells may trigger expansion of functional MDSCs, as proposed in studies on EBV-associated nasopharyngeal carcinomas. For example, latent membrane protein 1-mediated glycolysis triggers the activation of p65 and the inflammasome, leading to the production of cytokines critical for MDSC expansion [71].

MDSCs also accumulate in chronic parasitic infections, which are commonly associated with the generation of Th2 and Treg responses [72]. *Schistosoma japonicum* antigens, for example, enhanced the expansion and suppressive activity of MDSCs [73]. In this model, immunosuppression was mediated through upregulation of NADPH oxidase subunits and ROS production. MDSCs isolated from *Heligmosomoides polygyrus* (*H. polygyrus*)-infected mice, in contrast, used an NO-dependent mechanism for immunosuppression [74]. Adoptive transfer of these cells promoted chronic infection with increased worm

burdens and egg production. Like macrophages, M-MDSCs may be both classically and alternatively activated depending on their exposure to Th1 or Th2 cytokines and many helminths induce mixed Th1/Th2 responses, at least in certain phases of infection [75]. Following implantation with the cestode *T. crassiceps*, IL-4/IL-13 signaling was critical for gradual expansion of MDSCs in the peritoneal cavity and acquisition of an alternatively activated phenotype. These cells suppressed T cell proliferation through mechanisms that switched from NO secretion at the early stages of infection to a combination of Arg activity, ROS production and generation of peroxisome proliferator-activated receptor gamma (PPAR-γ) ligands via 12/15-lipoxygenase (LOX) activity in the late phase of infection [76]. These results suggest that the mechanisms used by MDSCs to limit anti-parasitic adaptive responses may depend of the phase of infection.

The role of MDSCs in chronic infections with other pathogens such as protozoan parasites and fungi has also been investigated. During experimental leishmaniasis, resistant C57BL/6 mice accumulated MDSCs which suppressed parasite specific T cell proliferation, but not cytokine release [77]. MDSCs killed *Leishmania major* (*L. major*) parasites in an NO-dependent manner and enhanced parasite clearance in skin lesions despite decreased parasite-specific T cell proliferation, suggesting that MDSCs enhanced resistance to *L. major* [77]. In agreement with these observations, genetically susceptible BALB/c mice exhibited a reduced ability to recruit $CD11b^{+}Ly6C^{hi}$ cells to the site of *L. major* infection compared to resistant C57BL/6 mice [78]. Thus, genetic conditioning of MDSC function could contribute to disease resistance in murine inbred strains.

The fungal pathogen *Candida albicans* (*C. albicans*) induces a subset of PMN-MDSCs during infection in humans and mice [15]. *In vitro*, these cells inhibited T cell proliferation, and phagocytosed and killed fungi. In a mouse model of invasive *C. albicans* infection, adoptive transfer of PMN-MDSCs effectively dampened T and NK cell proliferation and improved mouse survival. Notably, different *Candida* species had differential capacities to induce *in vitro* PMN-MDSC expansion and subsequent suppressive activities [79]. *Aspergillus fumigatus* also elicited PMN-MDSCs [15], but adoptive transfer of MDSCs did not alter mice survival post-infection. The divergent effects of MDSCs in these fungal infections may have been due to the distinct animal models that were employed. *Aspergillus* infection was established in immunocompromised animals, whereas infection with *C. albicans* was performed in immunocompetent mice. MDSCs have also been studied in the context of *Pneumocystis* pneumonia (PcP), where they accumulated in the lungs of rodents upon infection and suppressed $CD4^{+}$ T cell proliferation *ex vivo* [80]. Their frequency correlated with the severity of disease, and adoptive transfer of these cells into healthy mice caused lung damage. ATRA treatment of PcP-infected rats and mice led to diminished MDSC numbers and an increase in alveolar macrophages [81]. Co-culture studies have suggested that MDSCs disable alveolar macrophage function through PD-1/PD-L1 signaling, indicating that MDSCs can also interact with other myeloid cells [82].

In summary, during chronic infection, MDSCs can contribute to microbial persistence and pathogens often trigger and benefit from MDSC expansion. However, MDSCs may also promote pathogen killing by

intrinsic effector mechanisms or prevent excessive tissue damage. Further investigations are required to determine the kinetics of MDSC subtypes and reveal how their compartmentalization to tissues or lesions influences the course of infections. MDSCs drive tissue metaplasia and are associated with a poor prognosis in cancer. Although it is poorly investigated, the genesis of MDSCs in such infections appears to be driven by prolonged inflammation, and possibly by microbial moieties. A comprehensive characterization of MDSCs in microbial-induced cancers is essential for the design of novel preventive and therapeutic strategies in this subgroup of malignancies.

Targeting MDSCs by host-directed interventions for infectious diseases

Various strategies to target MDSCs can be envisaged, depending on whether these cells have a beneficial or detrimental role in the infection concerned (Figure 2). In several chronic infections in which MDSC expansion limits protective immunity, depletion of MDSCs is able to reverse immunosuppression and improve disease outcome [45, 48]. In TB and SIV infection, such interventions may in addition remove pathogen reservoirs, as MDSCs can harbor these microbes [45, 83]. MDSCs can be targeted by (i) depletion, (ii) maturation-induced ablation, (iii) interfering with their production, and (iv) inhibition of their suppressive activities.

Antibody-mediated depletion of $Gr1^{+}Ly6G^{+}$ MDSC-like cells has proven successful in experimental models of TB [45, 84, 85], staphylococcal disease [3, 48] and viral infection [29, 51]. However, antibody depletion is impracticable in humans because MDSCs lack unique surface markers, and frequencies and functions of related myeloid populations could be affected. Drug-induced depletion of MDSCs using cytotoxic agents such as gemcitabine and denileukin diftitox, has been used in proof-of-principle experiments in murine models of *S. aureus* infection [86] and as a host-directed therapy (HDT) complementing canonical chemotherapy in TB [47]. Ablating MDSCs by inducing maturation is a more attractive option for therapeutically reducing the numbers of these cells. Various classes of drugs can induce differentiation or maturation of MDSCs. ATRA, for example, which induces MDSC differentiation into dendritic cells and macrophages, has been successfully employed in mouse models of TB. In these studies, ATRA ablated MDSCs and restricted bacterial replication [45], especially when given as adjunct to TB chemotherapy [87]. In a mouse model of HBV infection, ATRA promoted the maturation of HBV-induced MDSCs, restored proliferation and IFN-γ production of HBV-specific $CD4^{+}$ and $CD8^{+}$ T cells from chronically infected patients and prevented viral replication [10].

Alternatively, differentiation of MDSCs can be achieved by the delivery of β-glucan or low doses of cyclic diguanylate; strategies which have had beneficial effects in mouse models of cancer [16, 88]. A reduction in MDSCs can also be accomplished by the administration of ceramidase inhibitors, which induces apoptosis though ER-stress and interference with autophagy [89]. More recently, activation of liver X receptors has proven to be efficient in inducing apoptosis of MDSCs and has been employed in preclinical models and in human trials for tumor immunotherapy [90]. Interfering with enzymatic pathways relevant for MDSC-induced suppression represents a complementary intervention for targeting these cells.

Phosphodiesterase (PDE) (i.e. PDE5) inhibitors block MDSC suppression by limiting Arg1 and NOS2 expression, and are beneficial as a HDTs in TB [91]. However, they may exhibit broad effects on other myeloid cells and additional pathways. Targeting the generation of MDSCs is possible with COX2 inhibitors, which block the synthesis of PGE2. This may explain the beneficial role of ibuprofen in a TB model characterized by increased MDSCs [92, 93]. In contrast to ablation, drug-induced generation of MDSCs has recently been reported. Delivery of finasteride boosts the genesis of suppressor cells [94] and may be employed in infections in which MDSCs are beneficial, for instance in acute sepsis or *Pseudomonas aeruginosa* (*P. aeruginosa*) infection [5, 25, 35]. Additional studies on the biology of MDSCs in infections are required to advance such HDTs into the clinic and to discover novel ways of targeting these cells therapeutically.

General conclusions and future perspectives

The roles of MDSCs in fine-tuning the interplay between host and pathogen are being increasingly recognized. Like most myeloid cell subsets, MDSCs are endowed with plasticity. One of the major challenges in dissecting the roles of MDSC subsets is that much of the research is based on a combination of correlation studies *in vivo* and functional assays *ex vivo*. In a study using genetically engineered mice in which either M-MDSC or PMN-MDSC were depleted, M-MDSCs were identified as the principle immunosuppressive MDSC population in the tumor microenvironment [27]. Before experiments using such genetic tools are performed in models of infection, including infections caused by tumorigenic microbes, current conclusions on the relative contributions of specific MDSC populations during infection need to be drawn cautiously.

MDSCs have nonetheless emerged as targets for HDTs for infectious diseases. The rapid development of antimicrobial resistance advances these cells in the pipeline for the development of novel therapies against drug-resistant microbes. Therapeutic targeting of MDSCs in infections with tumorigenic microbes, and the effect on tissue metaplasia, needs to be evaluated. Apart from their therapeutic potential, MDSCs have barely been investigated in the context of vaccination. Living organisms, PAMPs, adjuvants and inflammation trigger MDSCs generation. Thus, an understanding of whether and how MDSCs affect the success of immunizations is needed. This is particularly relevant for newborns and the elderly, as MDSC frequencies are raised in both age groups [95, 96]. Lastly, the value of MDSCs as biomarkers and their benefits for stratification of patients further justifies accelerating research focused on the biology of MDSCs in infection and pathogen-associated malignancies.

Author contributions

Conceptualization and writing of the original draft: all authors. Figure Design: Anca Dorhoi, Estibaliz Glaría, Thalia Garcia-Tellez and Annabel F. Valledor. Revisions and editing: Anca Dorhoi, Natalie E. Nieuwenhuizen, Cornelia Gujer and Annabel F. Valledor. Supervision: Anca Dorhoi and Annabel F. Valledor. All authors approved the final version of this paper.

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflicts of interest.

Ethical approval and ethical standards

Not applicable.

Informed Consent

Not applicable.

Animal source

Not applicable.

Cell line authentication

Not applicable.

Figure legends

Figure 1. Suppressive mechanisms of MDSCs in infection. MDSC subsets exhibit suppressive activities in various infections. Enzymatic pathways and secreted and cell-surface molecules controlling MDSC function are depicted in the context of specific pathogens. The target cells and consequences of MDSC

activities are indicated for each infectious agent. Suggested host-beneficial and -detrimental effects of MDSCs are displayed color-coded, in green and red color, respectively.

Figure 2. Targeting MDSCs as part of host-directed interventions against infection. Four different strategies have been envisaged for manipulating MDSCs: maturation-induced ablation, depletion, interference with their suppressive activity and altering their genesis. Specific drugs for each approach, as well as evidence from particular infectious diseases and the outcome of each immune therapy are summarized. *, successful method for depletion in mouse model.

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Table 1. The roles of specific MDSC subsets in acute and chronic infections. CFTR, cystic fibrosis transmembrane conductance regulator; HIF, hypoxia-inducible factor; hm, human; LP, lamina propria; mc, macaque; ms, mouse; Mφ, macrophage; ND, no data; PC, peritoneal cavity; PF, Pleural fluid; rd, rodents; Ref, references.

Pathogen / Disease	Host	Acute / Chronic	Location	MDSC Type	Phenotypic markers	Readouts of functional assays	Suppressive mechanisms	Outcome / Correlation	Interventions targeting MDSC	Ref
S. aureus	ms	Acute	Skin, LNs, spleen, blood, BM	MDSC	$Gr1^+CD11b^+$	↓T cell proliferation/ IFNγ production	Cell-cell contact, NOS2	Infection-induced suppression of dermatitis	Depletion (anti-Gr1 Abs)	[3]
		Chronic	Spleen, orthopaedic biofilm	PMN-MDSC	$CD11b^+Ly6G^{+/hi}$ $Ly6C^{lo/+}(Gr1^+)$	↓T cell proliferation/ activation;↓inflammation; ↑infection	Cell-cell contact; Arg1, NOS2, IL-10	Disease exacerbation; restricted biofilm clearance	Depletion (gemcitabine/anti-Ly6G Abs); MDSC transfer	[48, 86]
			Spleen	M-MDSC	$CD11b^+Ly6G^-$ $Ly6C^{hi}$					
P. aeruginosa	hm	Chronic	Blood	PMN-MDSC	$IL\text{-}4R\alpha^{int}CD33^{hi}$ $HLA\text{-}DR^{dim}CD66^{hi}$	↓T cell proliferation/ IL-17 production	ND	Correlation with active disease	ND	[5]
K. pneumoniae	ms	Acute	Lung	PMN-MDSC	$CD11b^+F4/80^+$ $Gr1^{int}Ly6G^{int}$ $Ly6C^{lo/-}$	Efferocytosis of apoptotic neutrophils	IL-10	Resolution of inflammation	ND	[35]
M. tuberculosis	ms	Acute	Lung	PMN-MDSC	$CD11b^+Ly6G^+$ $Gr1^{int}$	↓Splenocyte and $CD4^+$ T cell proliferation/ IFNγ production	IL-4Rα	Active disease and fatality	Ablation (ATRA); depletion (anti-Gr1 Abs); MDSC transfer	[45, 46]
		Acute / Chronic	Lung, BM, spleen, blood	M-MDSC	$CD11b^+Gr1^{dim/hi}$ $Ly6G^{-/dim}(F4/80^+$ $CD49b^+Ly6C^+$ $CD117^+CD135^+)$		IL-4Rα, NOS2; cell-cell contact			
	hm	Chronic	Lung, PF, blood	MDSC	$Lin^{-/lo}CD11b^{int/+}$ $HLA\text{-}DR^{-/lo}CD33^+$	↓T cell proliferation/ cytokine/CD69 expression	ND	Correlation with active disease	ND	[42, 43]
			Lung, blood	PMN-MDSC	$CD11b^+CD14^-$ $CD33^+CD15^+$ $HLA\text{-}DR^{lo/-}$	↓T cell proliferation	NO			[44]
H. felis	ms	Chronic	Stomach	PMN-MDSC	$Gr1^+CD11b^+$ $Slfn4^+Ly6G^+Ly6C^{lo}$	↓T cell proliferation	Arg1, NOS2	Correlation with metaplasia	ND	[49]
ETBF	ms	Chronic	Colon tumors	M-MDSC	$CD11b^+Gr1^{lo}$ $F4/80^{lo}CD11c^{-/lo}$ $MHCII^{-/+}SSC^{lo}$	Ag-specific $CD8^+$ T cell proliferation	NOS2, IDO1	Correlation with infection-induced colon carcinogenesis	ND	[50]

EBV	hm	Chronic	Blood	M-MDSC	$CD11b^+CD33^+HLA\text{-}DR^-CD14^+$	$CD4^+$ T cell proliferation	NOS2, Arg1, ROS	Correlation with reduced survival	ND	[70]
IAV	ms	Acute	Lung	MDSC	$Gr1^+CD11b^+$	↓Ag-specific splenocyte proliferation	Arg1, NOS2	Suppression of IAV-specific immunity; high viral titers; increased mortality	Transfer of iNKT cells abolish MDSC suppressive activity	[13]
JEV	ms	Acute	Spleen	MDSC	$Gr1^+CD11b^+$	↓Tfh cell proliferation; ↓neutralizing Abs	ND	Reduced survival	Ablation (ATRA)	[28]
FV	ms	Acute	Spleen	PMN-MDSC	$CD11b^+$ $Ly6G^{hi}$ $Ly6C^{lo}$	↓Virus-specific $CD8^+$ T cell proliferation and granzyme B production	Arg1, NOS2, PD-L1, CD39	Increased viral load	Depletion (5FU/ anti-Ly6G Abs)	[29]
LCMV	ms	Chronic	Spleen	M-MDSC	$CD11c^-CD11b^+$ $Gr1^{lo}Ly6C^{hi}$ $F4/80^+SSC^{lo}$	↓Splenocyte/T cell proliferation; ↓virus-specific cytokine-producing T cells	ND	Chronic infection	Depletion (anti-Gr1 Abs); mobilization ($CCR2^{-/-}$ mice)	[51]
LP-BM5 retrovirus	ms	Chronic	Spleen	M-MDSC	$CD11b^+Gr1^+$ $Ly6C^+Ly6G^{-/lo}$	↓T- and B cell proliferation	NOS2	Susceptibility to infection	ND	[52]
HIV	hm	Primary response/ Chronic Chronic	Blood	PMN-MDSC M-MDSC	$HLA\text{-}DR^{lo/-}CD14^{-/+}$ $CD33^+CD11b^+$ $(CD15^+CD124^+)$ $HLADR^{-/lo}$ $CD11b^+CD14^+$ $CD33^{+/hi}CD15^-$	↓$CD8^+$ T cell proliferation/IFN-γ production; Treg expansion ↓T cell proliferation/ IFN-γ production	PD-L1, IL-4Rα, suppression of CD3ζ Arg1; cell-cell contacts	Positive correlation with viral load; negative correlation with $CD4^+$ T cell frequencies	ND	[55–57] [58]
SIV	mc	Acute/ Chronic	Blood Blood, spleen	M-MDSC PMN-MDSC	$CD14^{hi}CD16^-$ $CCR2^{lo}$ $CD3^-HLA\text{-}DR^-$ $CD11b^+CD66^+$	↓Inflammatory cytokines; ↓$CD8^+$ T cell proliferation ↓T cell proliferation	ND	Correlation with active disease	ND	[59] [60]
HCV	hm	Chronic	Blood, liver	M-MDSC	$HLA\text{-}DR^{-/lo}$ $CD14^+CD33^+$ $CD11b^{+/lo}$	Treg expansion; ↓T cell proliferation/IFN-γ production	IDO1, PD-L1, HLA-DR, IL-10, Arg1	Correlation with increased viral RNA and liver damage	ND	[6, 7, 61, 62]

HBV	ms	Chronic	Spleen, liver	M-MDSC PMN-MDSC	$CD11b^{+}Gr1^{+/dim}$ $Ly6C^{hi}Ly6G^{-/+}$ ($F4/80^{lo}CD80/86^{lo}$ $MHC\text{-}II^{lo}$) $CD11b^{+}Gr1^{hi}$ $Ly6G^{+}Ly6C^{lo}$	↓T cell proliferation, $CD8^{+}$ CTL function/ IFN-γ synthesis ↓T cell proliferation	NOS2, Arg1 (M-MDSC); CTLA-4/PD-1 on T cells	Chronic infection	Depletion (ATRA/anti Gr1 Abs); Arg inhibition; MDSC transfer to $TCR\delta^{-/-}$ mice	[10, 65, 66]
	hm	Chronic Acute/ Chronic	Blood Blood, liver	M-MDSC PMN-MDSC	$HLA\text{-}DR^{-/lo}CD33^{+}$ $CD11b^{+}CD14^{+}$ $CD11b^{hi}CD33^{+}$ $HLA\text{-}DR^{-}$ $CD14^{-}CD15^{+}$	↓T cell proliferation, IFN-γ production, CTL activity	PD-1-induced IL-10 synthesis Arg1	Positive correlation with viral load; negative correlation with liver pathology Correlation with infection without liver injury	ND	[10, 64] [67]
T. crassiceps	ms	Chronic	PC	MDSC	$CD11b^{lo}Gr1^{+}$ $F4/80^{lo}$	↓T cell proliferation; IL-4 induction	NOS2 (early stages); Arg, ROS, 12/15 LOX (late stages)	Correlation with disease progression	ND	[76]
H. polygyrus	ms	Chronic	LNs, spleen, LP	MDSC	$F4/80^{-}Gr1^{hi}$ $CD11b^{hi}Ly6G^{+}$ $Ly6C^{+}(CD11c^{-})$	↓Ag-specific $CD4^{+}$ T-cell proliferation/parasite-specific IL-4 secretion	NOS2	Exacerbation of infection	Transfer of $CD11c^{-}Gr1^{+}$ $CD11b^{+}$ cells	[74]
L. major	ms	Chronic	PC Skin	MDSC M-MDSC	$Gr1^{hi}CD11b^{hi}$ $CD11b^{+}$ $Ly6C^{hi}Ly6G^{-}$	↓T cell proliferation	ND NOS2	Enhanced resistance to infection	MDSC transfer; ablation (ATRA) ND	[77] [78]
T. cruzi	ms	Acute	Heart Spleen, liver	M-MDSC MDSC	$CD11b^{+}Ly6C^{+}$ $Ly6G^{-}$ $CD11b^{+}Gr1^{+}$	↓T cell proliferation	NO; L-arginine depletion NADPH oxydase; NO/ peroxynitrite	Protection from infection Reduced inflammatory cytokines/liver injury; resistance to infection	*In vivo* inhibition of NOS2; L-arginine supplementation Depletion (5FU)	[36] [24]
T. gondii	ms	Acute	Lung	MDSC	$Gr1^{+}CD11b^{+}$	↓Lymphocyte proliferation	NO	Correlation with defective lung responses	ND	[30]

C. albicans	ms	Acute	Spleen	PMN-MDSC	$CD11b^+Ly6G^+$	↓T/NK cell activation/Th17 and TNFα cytokine responses	ND	Increased survival and control of infection	MDSC transfer	[15]
	hm	Chronic	Blood	PMN-MDSC	$CD11b^+CD33^+$ $CD14^-CXCR4^+$ $CD16^+CD66b^+$	↓T cell proliferation	ND	ND	ND	
Pneumocystis	rd	Acute	Lung	MDSC	$Gr1^+CD11b^+$ (ms) $CD11bc^+His48^+$ (rat)	↓$CD4^+$ T cell proliferation Impaired alveolar Mφ activation/phagocytosis	Arg1, NOS2 PD-1/PD-L1 signaling	Increased severity of infection; lung damage	PcP MDSC transfer; ablation (ATRA)	[80–82]
Polymicrobial sepsis	ms	Acute	Liver, spleen, BM, blood, LNs	MDSC	$Gr1^+CD11b^+$	↓Ag-specific T cell IFNγ synthesis; ↑Th2-linked Abs; restrict Mφ IL-6/IL-12 and boost IL-10	Cell-cell contact	Increased survival; Th2 polarization	Depletion (anti-Gr1 Abs); MDSC transfer	[25, 34]
Sepsis	hm	Acute	Blood	PMN-MDSC	$CD11b^{+/hi}CD15^{+/lo}$ $CD66^+CD16^{int/hi}$ $CD45RO^+CD33^{-/+}CD14^{-/lo}$	↓T cell proliferation	Arg; ROS; alter T cell ζ-chain expression	Correlation with increased severity of infection, $Gram^+$ sepsis and subsequent infections	ND	[31–33]

Figure 1

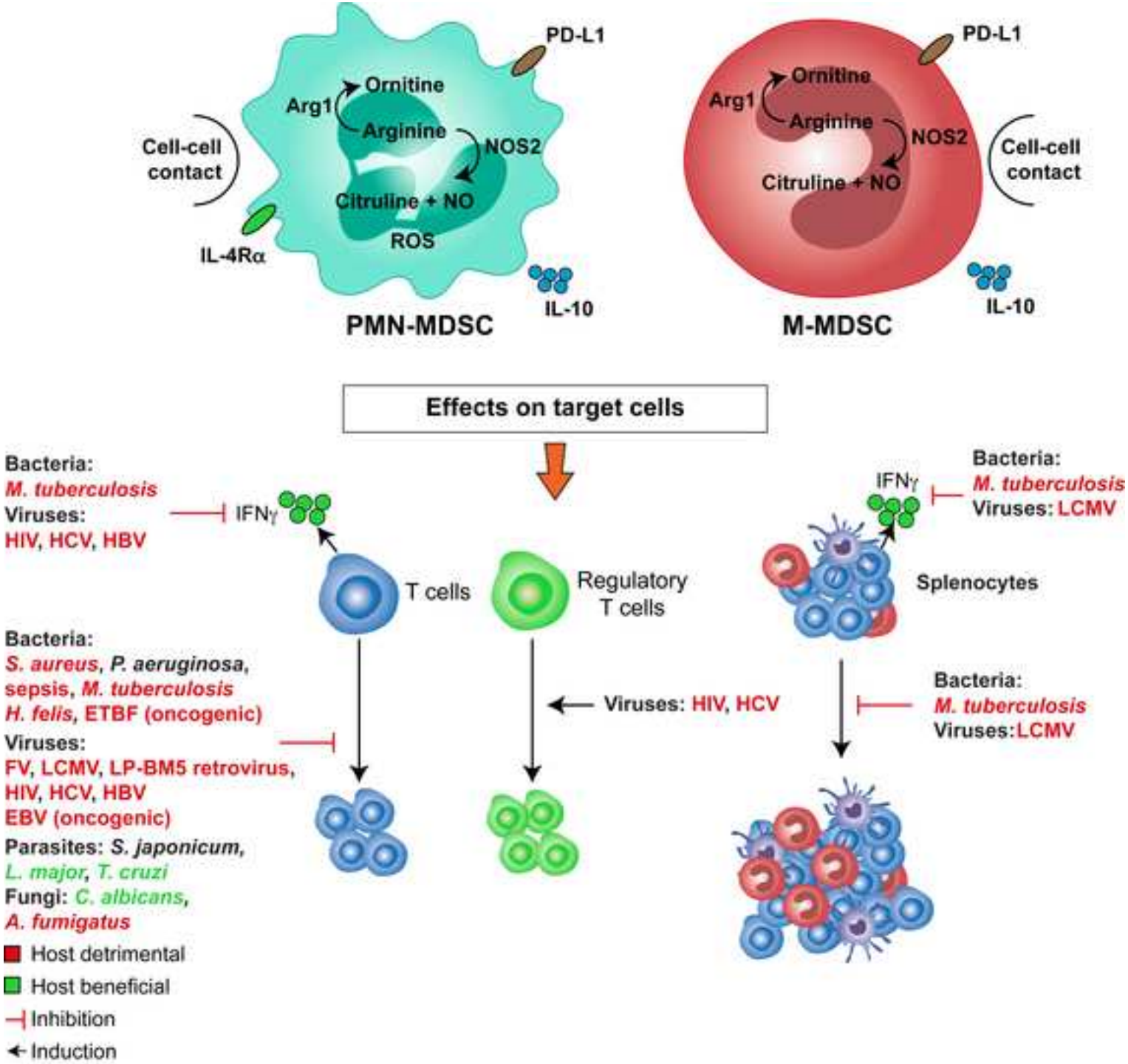

Figure 2

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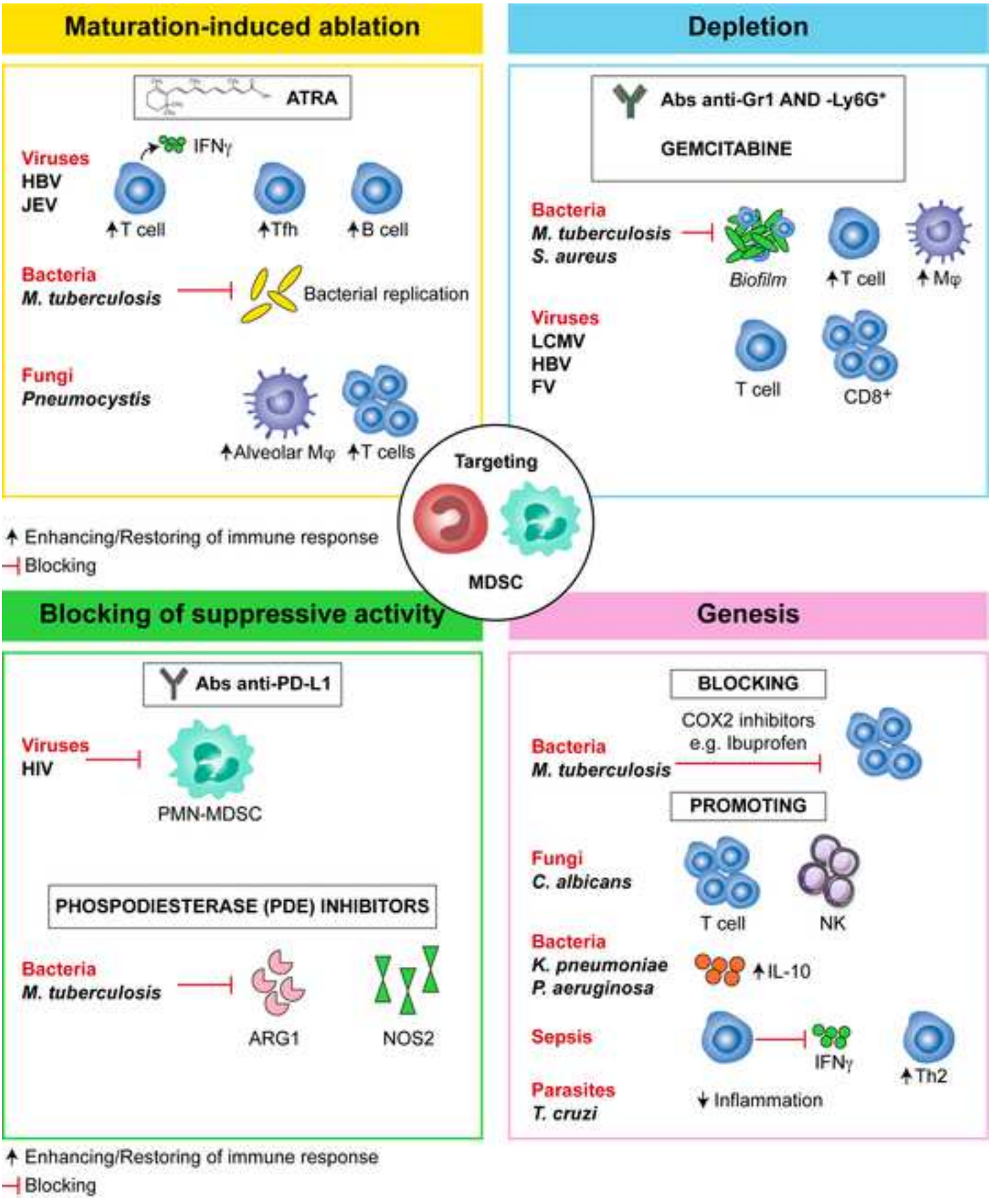

Note from the Editor (to be published, do not change, do not delete)

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