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Myeloid derived suppressor cells and autoimmunity.

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Running title: MDSC and autoimmunity

Key words: Myeloid derived suppressor cells; type 1 diabetes; rheumatoid arthritis, SLE; inflammatory bowel disease

Abbreviations: MDSC- myeloid-derived suppressor cells

T1D - type 1 autoimmune diabetes
RA - rheumatoid arthritis
SLE - systemic lupus erythematosus
IBD - inflammatory bowel disease
EAE - experimental autoimmune encephalomyelitis
AIH - autoimmune hepatitis
ROS - reactive oxygen species
PMBC - peripheral blood mononuclear cell
Abstract

Myeloid-derived suppressor cells are a heterogeneous group of immature myeloid cells with immunoregulatory function. When activated and expanded, these cells can suppress T cell functions via cell-to-cell interactions as well as soluble mediators. Recent studies investigated the involvement of MDSC in autoimmune diseases. Some papers have described beneficial effect of MDSC during the course of autoimmune diseases, and suggest a potential role as a treatment option, while others failed to detect these effects. Their contributions to autoimmune diseases are not fully understood, and many questions and some controversies remain as to the expansion, activation, and inhibitory functions of MDSC. This review aims to summarize current knowledge of MDSC in autoimmune disorders.
Introduction.

Myeloid-derived suppressor cells (MDSC) are a heterogeneous population of bone marrow-derived myeloid progenitors that fail to differentiate into mature myeloid cells. In steady state conditions, MDSC precursors reside primarily in the bone marrow (1). In a large variety of pathological conditions such as malignant tumors, infections, transplanted organs and inflammatory disorders including autoimmune diseases, MDSC populations expand and can be detected in the blood, peripheral lymphoid tissues, the spleen, cancerous tissues and inflammatory sites including different organs. After migrating from the bone marrow, MDSC inhibit other immune cells and normally prevent immune responses (2).

The frequency of MDSC can be closely associated with disease progression and clinical staging in some cancer patients and tumor bearing mice. However, their dynamics, function and effect on the immune response in other conditions are less well-understood. In vitro generation and expansion of MDSC has become possible, and the therapeutic applications of these cells are also being explored: the manipulation of MDSC is being considered as a potential strategy as an effective immunotherapy for cancer (3).

Contrary to cancer, only limited and sometimes contradictory information is available on these cells in autoimmune diseases; MDSC have been reported to affect autoimmunity in several ways. This review aims to present some current findings on MDSC in autoimmune conditions.
Phenotypic and functional characteristics of MDSC

Classification of murine MDSC was initially based on cell surface expression of CD11b and Gr-1. The CD11b^+Gr-1^− subgroup are now further divided into two groups, exhibiting either a monocytic morphology or a granulocytic morphology. Granulocytic MDSC (g-MDSC) display a CD11b^+Ly6C^{low} Ly6G^+ phenotype while monocytic MDSC (m-MDSC) are characterized as CD11b^+Ly6C^{high} Ly6G^− (4-7).

In humans, MDSC are characterized by an “immature” phenotype on the basis of expression of CD33, and the absence/low levels of HLA-DR. MDSC also express the common myeloid marker CD11b, found on granulocytes, monocytes, and macrophages. CD14 and CD15 have been suggested as markers for m-MDSC and g-MDSC, respectively: human MDSC could be categorized as granulocytic (CD15^+ or CD66b^+ cells showing polymorphonuclear morphology), and monocytic (CD14^+ cells showing mononuclear morphology) subsets. The two subsets are heterogeneous regarding nuclear morphology, and display differences in their suppressive capacity and functional mechanism depending on the actual disease (8-10) (Table 1).

MDSC require different signals for their expansion, activation and migration. The factors are responsible for driving the expansion of MDSC, trigger signaling pathways that support the proliferation in the bone marrow, and block their differentiation into mature cells. These include cyclooxygenase-2, prostaglandins, interleukin 6 (IL-6), macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon gamma (IFN-γ) and transforming growth factor beta (TGF-β) (11-14). Tumor necrosis factor (TNF) signaling drives MDSC accumulation in the periphery by promoting MDSC survival and inhibiting apoptosis (15). Cancer models have established an important role of IL-6, IL-1β, prostaglandin E\(_2\), and the calcium binding proteins S100A8 and S100A9 for the accumulation of MDSC at sites of inflammation (16).

MDSC suppress T cell functions via a number of different mechanisms involving both soluble mediators and cell-cell contact. G-MDSC usually inhibit T cell function through arginase-1 enzyme activity, while m-MDSC inhibit T cell functions via nitric oxide production. Activation by IFN-γ results in the upregulation of both arginase-1 and nitric oxide production. CD11b^+Gr-1^− cells were also shown to inhibit CD8^+ and CD4^+ T cell activity via nitric oxide- and IL-10-dependent mechanisms. Reactive oxygen species (ROS) represent another suppressor mechanism, and peroxynitrite was identified as a mediator of suppression of T cell function by MDSC (17-19). MDSC also facilitate the suppressive functions of regulatory T cell (Treg). In a mouse model of autoimmune diabetes, MDSC induced the antigen-specific expansion of Treg, and prevented the development of the disease (20). When MDSC mixed with islet allografts were transplanted into diabetic mice, allografts were protected without immunosuppression. This was associated with attenuation of CD8 T cells as well as marked expansion Treg in the grafts (21). MDSC- dependent expansion of Treg that promote of cardiac allograft survival in mice (22) as well as in kidney transplant patients (23) has also been reported.
Type 1 autoimmune diabetes

The role for MDSC in type 1 autoimmune diabetes (T1D) has been recently studied. Mouse studies demonstrated increased number of MDSC associated with B cell depletion treatment aimed to improve T1D. Further evidence is provided from a mouse model of T1D where non-diabetic NOD/SCID mice were injected with inflammatory T cells from diabetic NOD mice. Adoptive transfer of MDSC from mice with allogeneic tumor cells was found to delay the onset of hyperglycemia (21, 24). A recent study compared the number of CD11b<sup>high</sup> Gr-1<sup>int</sup> MDSC in the peripheral blood, spleen as well as in the pancreatic islets of prediabetic and newly diabetic NOD mice. The authors established that the onset of diabetes was associated with an expansion of MDSC in the peripheral blood while the number of MDSC in the islets significantly decreased. These changes were absent in prediabetic mice (25).

In humans, the frequency of MDSC in peripheral blood mononuclear cells (PBMC) of T1D patients using surface markers CD11b<sup>+</sup> CD33<sup>+</sup> within HLA-DR<sup>low/neg</sup> cells is increased. While healthy control subjects had a very low frequency, the number of MDSC was significantly increased in the peripheral blood of T1D patients. The cells were also characterized functionally, and were shown to suppress T cell proliferation (25).

Rheumatoid arthritis

Rheumatoid arthritis (RA) is progressive inflammatory autoimmune disease leading to the destruction of articular cartilage and bone. CD4<sup>+</sup> T cells, especially interleukin (IL)-17 producing T helper Th17 cells, are important in chronic inflammatory diseases. Th17 have been suggested as major effector cells participating in the pathogenesis of RA but the underlying mechanisms are not clearly known. Recent studies investigated the possible role of MDSC as well as the correlation with TH17 cells in both murine models of experimental autoimmune arthritis and in RA patients. MDSC with granulocytic phenotype were detected in the synovial fluid (SF) of mice with proteoglycan-induced arthritis (26). In a collagen-induced mouse model of RA, granulocytic MDSC were isolated from the spleens of arthritic mice. These cells had suppressive functions in vitro, and decreased the severity of joint inflammation upon adoptive transfer (27). Contrary to previous studies suggesting a protective role of MDSC in RA, a recent study has shown that expansion of MDSC corresponds with progression in mice with autoimmune arthritis. The authors also determined a positive correlation between MDSC numbers and Th17 cells in the spleen and affected joints. MDSC from arthritic mice did display a contact-dependent T cell suppressive capacity <i>ex vivo</i>, but were highly efficient in stimulating the differentiation of Th17 producing cells. Elimination of MDSC in these mice actually reduced disease severity and resulted in decrease levels of Th17 cells, and these effects could be reversed by adoptive transfer of m-MDSC (28).

Increased numbers of circulating MDSC were detected in the PMBC of RA patients when compared with healthy controls (HC). This study also investigated the number of Th17 cells as well as plasma levels of pro-inflammatory cytokines and Arg-1. The frequency of Th17 cells in RA patients was significantly higher than in HC but correlated negatively with the frequency of MDSC and plasma Arg-1. MDSC frequency and plasma TNF-α levels were negatively correlated (29).
A recent paper describing the presence of granulocytic MDSC-like cells in the SF of RA patients indicated that these cells are capable of suppressing the proliferation of autologous T cells in a non-specific manner (anti-CD3/CD28 Ab-induced) and in an allo-Ag-induced manner (30). In RA patients with high disease activity, elevated MDSC numbers were found compared with HC or patients with low disease activity. Furthermore, there was a positive correlation between MDSC infiltration and IL-17 levels in synovial fluid of patients. However, the frequency of MDSC in the peripheral blood was negatively correlated with the number of Th17 cells (28).

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is considered a prototypical systemic autoimmune disorder. Elevated levels of antinuclear antibodies (ANAs) and cellular infiltration of various organs, including the skin, heart, and kidney are the hallmarks of the condition which predominantly affects women. The dysfunction of many components of the immune regulatory network, mainly T cells, is central to the development of the disease. Lately, the possible involvement of MDSC in SLE associated organ injury has also been addressed. Using the lupus-prone MRL-Fas<sup>lpr</sup> mice, a study identified increased frequency of CD11b<sup>+</sup> Gr-1<sup>low</sup> cells during disease progression in both the affected kidney and peripheral blood. The cells were found to suppress CD4<sup>+</sup> T-cell proliferation <i>in vivo</i> through arginase-1 (31).

A recent article found cellular and functional differences in myeloid cells between male and female lupus-prone (NZB × NZW) F1 mice. Adjacent to the spleen’s B cell follicles, a set of Gr-1<sup>high</sup>Ly-6G<sup>+</sup>CD11b<sup>+</sup> myeloid cells increased in male (NZB × NZW) F1 mice compared with female mice. These cells directly inhibited cytokine-induced differentiation of naive B cells into antibody-secreting cells. Additionally, the administration of depleting anti-Gr-1 mAb resulted in increased production of antinuclear autoantibodies in male mice only. The authors offer a hypothesis of a male-driven inhibitory mechanism to control B cell pathogenesis, which delays/prevents the development of the disease in otherwise genetically predisposed male (NZB × NZW) F1 mice (32).

Another study using the similar model, evaluated the extracellular trap (ET) formation and the production of ROS. Both impaired expansion and functional defects of g-MDSC in the lymphoid organs of mice with established disease were observed. Increased elimination of g-MDSCs due to ET formation was mediated by cytokines from the proinflammatory microenvironment. Inhibition of ROS generation reduced ET release. The data suggest a likely contribution of g-MDSC to the mechanisms of the disease (33).

In humans, female patients with SLE showed a higher frequency of MDSC in PBMC and a higher level of tumor necrosis factor α (TNF-α) in serum compared with male patients. Additionally, estradiol level in the serum of female patients showed a positive correlation with the frequency of MDSC. The study also investigated the role of 17β-estradiol in mice; and found that 17β-estradiol may contribute to the accumulation of MDSC in blood by promoting TNF-α secretion, which increases the frequency of CD11b<sup>+</sup>Gr-1<sup>+</sup> (34).
Further support for a pathogenic role for MDSC in human SLE is suggested by a recent study. In the peripheral blood of patients with active SLE, a significant increase in the number of both CD14(+) CD66b(-) monocytic and CD14(-) CD66b(+) granulocytic MDSC was detected. The increase in numbers was positively correlated with serum Arg-1 activity, Th17 responses as well as disease severity. The authors also demonstrated, in a humanized SLE model, that MDSC induced renal injury via Th17 response in an Arg-1-dependent manner (35).

Inflammatory Bowel Disease

There are several studies suggesting a role for MDSC in experimental inflammatory bowel disease (IBD). In an IBD transgenic mouse model of enterocyte-specific expression of hemagglutinin (HA), repeated transfer of HA-specific CD8+ T cells resulted in expansion of MDSC. Isolated MDSC (CD11b+Gr-1+ cells) were protective and suppressed development of disease after the first transfer of CD8+ cells (36). Similarly, in a model of dextrane-sulphate sodium (DSS) induced colitis, adoptive transfer of splenic CD11b+Gr-1+ cells into DSS-treated mice proved to be beneficial (37). In mice with colitis induced by 2, 4, 6-trinitrobenzenesulfonic acid (TNBS) MDSC are detected in the spleen and colonic lamina. Adoptive transfer of MDSC from colitis mice into animals challenged with TNBS decreased intestinal inflammation, levels of IFN-γ, IL-17, and TNF, as well as percentage of spleen MDSC when compared with controls (38). Another study described that during chronic colitis; adoptively transferred Ly6C<sup>high</sup> monocytes are recruited into the colon and differentiate into inflammatory cells (39).

Hyperactivation of Signal Transducer and Activator of Transcription (STAT)3, a known regulator of MDSC expansion, has been associated recently with protection from experimental colitis. Acute and chronic colitis was induced in gp130(757F/F) mice as well as in mice with myeloid-specific STAT3-deficiency (LysMcre/STAT3(flox); gp130(757F/F) LysMcre/STAT3(flox). Cells obtained from spleen, mesenteric lymph node and colon were analyzed for different myeloid cell populations, and the function of MDSC and LPS-stimulated peritoneal macrophages were analyzed in vitro and in vivo. The resistance to colitis in gp130 (757F/F) mice was associated to myeloid-cell specific STAT3 activation, MDSC expansion and increased production of cytokines with suppressive and protective effects (40).

MDSC or MDSC-like cells have been also detected in IBD patients. Significantly higher levels of CD14+HLA-DR-/low cells were found in the peripheral blood in patients with IBD compared with healthy subjects. Frequency of MDSC appeared to correspond with disease activity (41).

Experimental autoimmune encephalomyelitis

Experimental autoimmune encephalomyelitis (EAE) is a widely used animal model for multiple sclerosis (MS), and different studies have investigated the role of MDSC in EAE. Circulating Ly6C<sup>+</sup> myeloid precursors were shown to migrate to the CNS and maintain disease progression (42, 43), while other studies have demonstrated a possible regulatory role of Ly6C<sup>+</sup> myeloid precursors in the same model (44, 45). A detailed study described accumulation of CD11b<sup>high</sup> Ly6G<sup>-</sup>Ly6C<sup>-</sup> g-MDSC in the spleen of mice with EAE, prior to resolution of inflammation. Additionally, the authors found that in vivo transfer of g-
MDSC, purified from an autoimmune environment generated by the injection of a self-Ag plus adjuvant, reduced the expansion of autoreactive T cells and inhibited pathogenic Th1 and Th17 immune responses in a programmed death ligand (PD-L1)/IFN-γ–dependent pathway. Increased accumulation of g-MDSCs at the meningeal lesions of spinal cord was also observed, suggesting that, in addition to the peripheral lymphoid organs, the cells act at the target tissue as well (46). Other studies also demonstrated that the development of EAE in mice is accompanied with an expansion of CD11b⁺ Gr-1⁺ cells, which inhibit T cell functions in vitro. MDSC enhanced the differentiation of naive CD4⁺ T cell precursors into Th17 cells. Selective depletion of MDSC resulted in reduced severity of EAE correlated with reduced Th17 cells and inflammatory cytokines (IL-17A and IL-1β) in the lymphoid tissues and spinal cord, and adoptive transfer of MDSC restored disease progression (47).

MDSC are significantly increased in the peripheral blood of patients with active MS compared with patients in remission or healthy controls. Several patients were monitored over time, and a decrease in circulating MDSC numbers was associated with remission. Similarly to the mouse model, morphological analysis revealed a granulocytic phenotype. The sorted cells suppressed the activation and proliferation of autologous T cells in vitro (46).

Autoimmune hepatitis

Experimental hepatitis is a well-established animal model to study T-cell mediated hepatic injury resembling clinical conditions. MDSC accumulate in the liver during Concanavalin A (Con-A), as well as D-galactosamine (D-gal) and picryl chloride–induced hepatitis, and protect the liver from excessive damage (48, 49). Different studies identified that different subsets of MDSC may accumulate in the liver in these models, and the subsets use different suppressive mechanisms. Cannabidiol or IL-25 leads to increased numbers of hepatic CD11b⁺ Gr-1⁺ cells, and alters the ratio of g-MDSC to m-MDSC. T cell responses are inhibited in an arginase-dependent manner, dominantly by m-MDSC (48, 50). Treatment with sphingosine-1-phosphate receptor agonist FTY720 also recruits MDSC to the liver, but the suppressive function depends on iNOS and NO production (51). Another study in Con-A-mediated hepatitis described that, although the number of both MDSC subtypes increased; only m-MDSC were able to suppress T cell responses and decrease the extent of liver damage. Similar observation was made in TGFβ1⁻/⁻ mice with acute liver damage, where the number of both subtypes expanded in the liver with only m-MDSC suppressing T cells via iNOS (52).

In humans, data are limited. Early reports described increased numbers of CD11b⁺ cells in biopsies obtained from patients with active autoimmune hepatitis (53). A different study identified, in the peripheral blood, “highly activated” monocytes accompanying liver-antigen-specific T cells secreting IFN-γ (54).
Conclusions

The variety of activities and effects associated with MDSC in autoimmune models and diseases (summarized in Table 2) makes it difficult to offer a comprehensive hypothesis explaining the role of these cells in autoimmunity. MDSC display extraordinary heterogeneity and plasticity, have multiple phenotypes and may inhibit T cell responses by multiple mechanisms. Their differentiation, expansion and migration also are regulated by numerous factors. Complete characterization of these cells is not always possible, or simply lacking in some studies.

Because of the exceptional diversity, sometimes incomplete or inherently limited nature of data such as in human studies, comparison among reports is challenging. The difficulties of these studies and the apparent need of harmonizing MDSC phenotyping are underlined by findings of a new report. Comparing immunophenotyping profiles of the same sets of MDSC performed in over 20 laboratories disclosed high inter-laboratory variance for all MDSC subsets. The main cause associated with variance was heterogeneous gating strategy. A detailed analysis, using harmonized marker combinations and gating parameters is important in different clinical settings, and would greatly facilitate evaluating results of different studies (55). In addition to identifying phenotypical and functional characteristics, the interactions of MDSC with other cell types also need to be explored.

Despite the contradictions, it is apparent that mouse CD11b\(^+\)Gr-1\(^+\) cells isolated from target site/inflammatory environment are capable of inhibiting T cells in vitro, using different mechanisms including production of NO, induction of T cell apoptosis and arginase-1. Endogenous MDSC in vivo, however, were found in several systems ineffective at alleviating the signs and symptoms of autoimmune diseases. CD11b\(^+\)Gr-1\(^+\) cells may be pro-inflammatory, and possibly can even aggravate the disease as reported in EAE. Exogenously expanded MDSC on the other hand can clearly improve tissue damage as suggested by results in mouse models of IBD or T1D.

These contrasting findings between the activities of endogenous and exogenous MDSC have not yet been resolved. It is possible that the differentiation and activation of these cells locally is inhibited or incomplete due to certain components from the inflammatory microenvironment, resulting in the absence of suppressive function. Intrinsic dysfunction of MDSC in vivo may also be a contributing factor to autoimmune tissue damage. MDSC expand and accumulate in response to local inflammation, but as the dysfunctional cells are unable to inhibit the T cell response, further broadening of the inflammatory process and additional recruitment of MDSC may ensue. Isolating the MDSC from the inflammatory site probably restores function by eliminating the inhibitory environment, and the now “exogenous” cells are suppressive both in vitro and upon adoptive transfer.

The obvious ability of exogenously applied MDSC to inhibit autoimmune tissue damage in murine models may offer a promising opportunity for the treatment of human autoimmune diseases. As several methods have been developed to expand MDSC in vitro from different cellular sources (peripheral blood, bone marrow and embryonic/hematopoietic stem cells), large scale production of MDSC seems feasible (56-58). Nonetheless, certain risks associated with such treatment remain to be considered. These in vitro expanded cells would not be specific for T cells recognizing autoantigens, and
may also inhibit protective immune responses. Administration of MDSC may result in release of inflammatory mediators. Additionally, it would also be difficult to control the migration and accumulation of the injected cells. The full utilization of MDSC as cellular therapy in human autoimmune diseases remains hindered by these concerns and by our still incomplete understanding of their phenotype, differentiation, functions, and interactions with the inflammatory microenvironment.
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### Table 1. Major phenotypic markers of MDSC

<table>
<thead>
<tr>
<th>Marker</th>
<th>Mouse M-MDSC</th>
<th>Mouse G-MDSC</th>
<th>Human M-MDSC</th>
<th>Human G-MDSC</th>
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<td>CD11b</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>n/a</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CD39</td>
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<td>n/a</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD66b</td>
<td>n/a</td>
<td>n/a</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>GR-1</td>
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<td>bright</td>
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<td>n/a</td>
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<td>n/a</td>
<td>low/-</td>
<td>-</td>
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<td>n/a</td>
<td>n/a</td>
<td>-</td>
<td>-</td>
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n/a: not applicable
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<tr>
<th>Disease</th>
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<th>Origin of cells</th>
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<td>proinflammatory</td>
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<tr>
<td></td>
<td>Human</td>
<td>CD11b&lt;sup&gt;+&lt;/sup&gt; CD33&lt;sup&gt;+&lt;/sup&gt; HLA-DR&lt;sub&gt;low/neg&lt;/sub&gt;</td>
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<td>25</td>
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<td>RA</td>
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<td>suppressor</td>
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<td>suppressor</td>
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<td>IBD</td>
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<td>suppressor</td>
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<td>G-MDSC</td>
<td>adoptive transfer</td>
<td>suppressor</td>
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<td>CNN</td>
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<td>adoptive transfer</td>
<td>suppressor</td>
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<tr>
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<tr>
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<td>liver</td>
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<td>M- and G-MDSC</td>
<td>liver</td>
<td>suppressor (M)</td>
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</tr>
</tbody>
</table>

T1D - type 1 autoimmune diabetes; RA - rheumatoid arthritis; SLE - systemic lupus erythematosus; IBD - inflammatory bowel disease; EAE - experimental autoimmune encephalomyelitis; AIH - autoimmune hepatitis