Marginal Zone B-Cell Populations

Subjects: Cell Biology

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Marginal zone (MZ) B-cells are innate-like, and possess a polyreactive B-cell receptor (BCR) and several pattern recognition receptors (PRR). They are known to generate low-affinity first-line antibody responses against invading pathogens such as encapsulated bacteria. Unfortunately, deregulations affecting MZ B-cell populations have been reported in the context of Human Immunodeficiency Virus (HIV) and other chronic inflammatory conditions.

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1. Introduction

Marginal zone (MZ) B-cells are innate-like, and possess a polyreactive B-cell receptor (BCR) and several pattern recognition receptors (PRR) [1][2]. They are known to generate low-affinity first-line antibody responses against invading pathogens such as encapsulated bacteria [3]. Unfortunately, deregulations affecting MZ B-cell populations have been reported in the context of Human Immunodeficiency Virus (HIV) and other chronic inflammatory conditions [2][4][5]. In here, the MZ B-cell ontogeny and antibody responses will only be briefly discuss, as these topics have been reviewed elsewhere and are beyond the scope [1][2][3][6]. Examining the regulatory capacities of MZ and other B-cell populations sharing similar features will be concentrated. The importance of the B-cell activating factor (BAFF) and its analog A Proliferation-Inducing Ligand (APRIL) in shaping the MZ B-cell pool and Breg profile will be discussed. The deregulation of MZ B-cell populations and development of MZ lymphomas (MZL) in the context of HIV and other inflammatory diseases will also be addressed. Lastly, the possible therapeutic avenues that could be deployed to restore MZ B-cell immune competence will also be talked about.

2. Ontogeny of MZ B-Cells

The first B-cell progenitors can be found as early as 7 weeks post conception in the fetal liver [7]. However, the B lymphoid progenitor compartment differs between fetal and postnatal life, and herein, only postnatal ontogeny will be briefly concerned , as these topics are beyond the scope and have been thoroughly reviewed elsewhere [7]. As depicted in **Figure 1**, post-natal B-cell development originates in the bone marrow, first, with pluripotent hematopoietic stem cells and their differentiation into common lymphoid progenitors (CLP) [8]. During their development, B-cells will undergo rearrangement of their BCR heavy chains (during the pro-B stage) and their light chains (during the pre-B stage) via the action of the Recombination-activating genes 1 and 2 (*RAG1*, *RAG2*) [9]. Overall, during these recombination steps, positive and negative selection ensures that the new BCR is functional, yet not autoreactive [10]. After these selection processes, immature B-cells, which express the newly rearranged BCR of the IgM isotype on their surface, exit the bone marrow and migrate to the spleen or other secondary

lymphoid organs, where they complete their maturation and differentiation [10]. At this point, the immature B-cell is called transitional immature (TI); it will follow maturation steps comprising stages TI-1 to TI-2 and TI-3, and will commit to either the follicular (FO) or the MZ B-cell fates, depending on the signals it receives (see below) [11][12] [13]. Although this generalized sequence of events appears to be similar for the murine and human systems, several distinctions prevail [14]. One major difference is the fact that in the murine system, MZ B-cells are believed to arise mainly from TI-2 progenitors, which complete their maturation in the spleen, where they appear to be restricted in contrast to those observed in the human system where MZ B-cells recirculate [15]. Interestingly, recent studies in humans have demonstrated the existence of bone-marrow-derived TI-2 IgM^{lo} and IgM^{hi} progenitors, the latter of which share transcriptional features with MZ B-cells, express α4β7 and migrate to the gut-associated lymphoid tissue (GALT) [13]. This suggests that the GALT may be an important site for human MZ B-cell differentiation [14].
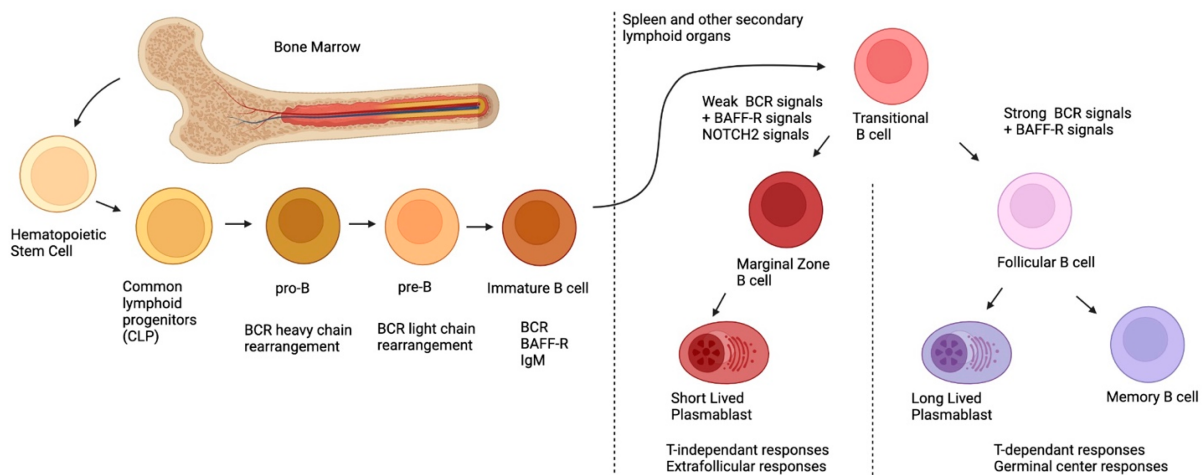

Figure 1. Ontogeny of postnatal B-cells.

FO and MZ B-cells are known as conventional B-cells or B2 cells [16]. Another subpopulation with innate-like properties has been identified in mice, and its cells are dubbed B1 cells. B1 and B2 cells differ in their ontogeny, as B1 cells come from a distinct lineage in the fetal liver and B2 cells originate from the bone marrow; moreover, B1 and B2 cells differ in their location, as B1 cells are most commonly found in the pleural cavity, unlike B2 cells [16][17]. Despite the fact that B1 cells are acknowledged in mice, their presence in humans, to date, remains controversial [17].

To date, at least three signals are involved in the FO versus MZ B-cell fate: *1.* via the receptor for BAFF (BAFF-R), fundamental for sending survival signals to TI B-cells and for activating the canonical nuclear factor kappa B (NF-κB) signaling path; *2.* signals resulting from the engagement of the newly expressed BCR; and *3.* Notch Receptor 2 (NOTCH 2) signals, the latter two being responsible for cell fate commitment [12]. When NOTCH2 binds to its ligand, delta-like 1 (DLL1) (expressed by a variety of cells in the spleen such as endothelial cells of the red pulp venule), in the context of weak BCR signaling, the former is internalized and translocated into the nucleus; there, it binds to DNA and allows the expression of genes involved in MZ differentiation [18]. However, strong BCR signaling will induce Bruton's tyrosine kinase (BTK) signals, which will inhibit the NOTCH2 signaling pathway, allowing for

the expression of genes involved in FO differentiation [19]. It is important to note that the level of BCR signaling required for MZ differentiation induces the expression of a disintegrin and metalloproteinase-containing protein 10 (ADAM10); this is required for the cleavage of NOTCH2, necessary for its nuclear translocation [20], implying that a complete absence of BCR stimulation will impede MZ B-cell differentiation. While BAFF itself is not a direct player in MZ differentiation, it can skew the TI B-cells into differentiating into MZ by upregulating NOTCH2 expression [12] [21][22].

To recapitulate, MZ B-cells originate from the bone marrow, where they will undergo BCR rearrangement. After expressing the newly arranged BCR and BAFF-R, they will migrate to the secondary lymphoid organs where they will complete their differentiation based on three signals: BAFF-R, BCR and NOTCH2. Weaker BCR signals coupled with NOTCH2 signals will dictate the differentiation towards an MZ profile, whereas strong BCR signals and a lack of NOTCH2 signaling will dictate the differentiation towards an FO profile.

In humans, MZ B-cells are usually found in the marginal zone, a strategic region surrounding germinal centers (GC). As such, MZ B-cells have been observed in the spleen and other secondary lymphoid organs such as tonsils, lymph nodes and the GALT, in areas such as in the sub-endothelial dome of the Peyer's patches [15][23]. Interestingly, as mentioned above, human MZs have the capacity to recirculate in blood, a trait that has not been identified in their murine counterparts. As such, in mice, MZ B-cells appear to be restricted to the splenic marginal zone, which is at the interface between the red and white pulps, and surrounding the follicular area of the spleen [24]. This difference contributes to fueling the controversy about the MZ's existence in humans, given that most studies on MZ B-cell biology were conducted in mice and restricted to the spleen. The spleen is one of the most irrigated organs, at any given time receiving around 5 to 10% of the total blood volume, which is huge considering its size and oxygen consumption under steady-state conditions [25]. One of the reasons for this lies in the fact that the spleen is involved in the "screening" of the circulatory system for bloodborne antigens [1]. Indeed, the marginal zone is placed strategically next to the blood entries in the spleen, allowing for MZ B-cells and other innate cells such as neutrophils, dendritic cells (DCs) and macrophages to act as first-line defenders, quickly responding to antigens found in the circulation [1][2].

The B-cell composition of the marginal zone area is heterogeneous, as populations such as B1, memory and MZ B-cells transit to, or reside within, that zone; this renders the characterization of such populations difficult, as they often share several markers. In humans, MZ B-cells are characterized by their high expression levels of the atypical major histocompatibility complex (MHC) class I molecule CD1c; the surface immunoglobulin (Ig)M and the complement receptor CD21; and the low and transient expression of CD23, a C-type lectin which is also the Fc receptor for IgE and is highly expressed by FO B-cells [1]. Interestingly, human MZ B-cells express the memory B-cell marker CD27, and their Igs present signs of somatic hypermutations (SHMs), even though these B-cells mostly produce extra-follicular T-independent Ig responses and, therefore, are not generated from typical T-dependent GC reactions, where Ig SHM and affinity maturation usually take place (discussed below) [26]. As such, MZ B-cells are often referred to as "antigen-experienced" cells [3][24][27]. However, there is some evidence of "memory-like" MZ B-cells that possess a more specific affinity for some bacterial antigens [26]. The fact that MZ B-cells express CD27, together with certain differences between human and mice, makes the classification of MZ B-cells in humans

controversial, where some authors consider these cells to be unswitched IgM memory B-cells [3][24][28]; although, several key differences between unswitched IgM memory and MZ B-cells have been documented [24]. The current tendency to track human B-cell populations—especially in blood in the context of inflammation, based on CD27 and CD21 expression levels—makes it difficult to identify innate-like populations such as MZs, as they are of low frequencies and fall into larger groups characterized in bulk. This is likely to preclude any contribution from such rarer populations. To this end, the usage of several markers should be more widely applied in order to identify such B-cell populations, whose contribution to inflammation is non negligible, as discussed further below.

3. MZ B-Cells and Their Antibody Responses

As first-line defenders, MZ B-cells possess several PRRs such as Toll-like receptors (TLRs) and C-type lectins. Given the polyreactive nature of their BCR, MZ B-cells bear a strong autoreactive potential [6][29][30]. They are known for their quick response against bloodborne pathogens, notably towards encapsulated bacteria [31]. Following their activation, mostly in a T-independent manner (discussed below), they differentiate into short-lived plasma cells that will mostly produce antibodies of the IgM isotype, providing a first level of defense while awaiting a more refined adaptive response from FO B-cells [32][33][34]. To this end, MZ B-cells have the potential to capture bloodborne antigens and then migrate from the marginal zone to the follicles (in a process known as shuttling); from there, they deliver immune-complexed antigens via antibodies through Fc receptors such as CD32, or via the complement system through complement receptors such as CD21 and CD35, to follicular dendritic cells (FDCs) [35]. This process has been found to be fundamental to the generation of GCs.

Briefly, GC reactions are sites of antigen-specific T-dependent—notably via CD40-CD40L signaling—FO B-cell differentiation and Ig affinity maturation [36]. Overall, there are two detectable phases in GC reactions: the dark phase where B-cells, having received signals for class switch recombination (CSR), stop expressing surface Ig and change their isotype into either of IgG, IgE or IgA, in order to gain effector functions (though CSR is not restricted to GC reactions) [37][38][39]. During this stage, B-cells (or centroblasts) proliferate and undertake SHM to increase antibody affinity for the antigen. Following the dark phase, the light phase allows for B-cells, or centrocytes, to express somatically mutated class-switched Ig on their surface with a view to being selected [39]. Notably, this differentiation scheme is not restricted to one round. The selection process is based on Ig affinity for the antigen presented at the surface of FDC, and on signals received by follicular helper T-cells (T_{fh}) [39]. B-cells with poor affinity will undergo apoptosis by neglect. This GC process is essential to assure the maturation and selection of memory B-cells and long-lived plasma cells, which guarantee the generation of high affinity antibodies endowed with refined effector potential [35].

As mentioned earlier, while MZ B-cells do not generate such high-affinity antibody responses, Ig produced by these cells have been shown (in humans) to bear low levels of SHM [24][40][41][42]. MZ B-cells also have the potential to undergo CSR from IgM to IgG or IgA following the binding of BAFF to the receptor transmembrane activator and calcium modulator and cytophilin ligand interactor (TACI), which is highly expressed at the surface of MZ B-cells [43][44]. However, these antibodies are considered of low-affinity and of a polyreactive nature, in contrast to those

produced through GC reactions. Nevertheless, antibodies produced by first-line populations such as MZ B-cells may be relevant in circumstances of microbial control and mucosal homeostasis, as will be discussed.

Interestingly, MZ B-cells have also been shown to migrate to T-cell zones of secondary lymphoid organs and activate CD4^{+} T-cells [45]. Additionally, MZ B-cells are able to present antigens to invariant natural killer T-cells (iNKT), a type of NKT-cell with a restricted TCR repertoire that can recognize lipidic molecules in the context of atypical MHC class I-like molecules of the CD1 family, widely expressed by MZ B-cells [46][47]. These MZ: iNKT cellular interactions confer activation, notably via the CD40-CD40L pathway [47].

4. MZ B-Cell Populations and Their Regulatory Potential

Bregs are involved in the maintenance of tolerance and homeostasis of the immune system. Bregs were originally defined as IL-10 producing B-cells (or B10) in mice [48]. Many groups have since identified different murine Breg subsets that possess anti-inflammatory suppressive mechanisms, mostly mediated by IL-10, such as T2-MZP-B-cells, MZ B-cells and B1a B-cells, amongst others (see **Table 1**). As in mice, human Breg subsets have been mostly identified based on their IL-10 production capacities [48]. Although IL-10 is an important regulatory cytokine, its production alone is not sufficient to qualify a B-cell population as Breg, since several human B-cell populations are capable of IL-10 production in the context of inflammation and upon stimulation [5][49]. However, in these populations, IL-10 production does not persist in time; therefore, these populations could be falsely identified as true Bregs. Unlike the expression of *Forkhead Box P3* (FoxP3), which is a shared feature of regulatory T-cell populations, there is no single marker reported to identify Breg populations to date [50]. As such, several immunoregulatory markers—such as IL-10, Programmed Death Ligand 1 (PD-L1), CD39 or CD73—have been associated with Breg potential and can help identify true Breg populations (see **Table 1**). Notably, the overlap of several markers used by different groups could imply that different Breg populations might in fact be more similar than expected.

Table 1. Characteristics of several Breg populations in mice and humans.

Species	Population	Phenotype	Mechanism of Suppression	References
Mouse	B10	CD19 + CD5 + CD1d^{hi}	IL-10	[51][52]
	MZ B-cells	IgM^{hi} IgD^{lo} CD21^{hi} CD23-CD1d^{hi}	IL-10	[53]
	T2-MZP	B220 + CD21^{hi} CD1d^{hi} IgM^{hi} CD23+	IL-10	[54]
	B1a	CD90-CD5+	IL-10	[55]
	Plasma cells	CD19 + CD138 + IgM+	IL10, IL-35	[56]
	Plasmablasts	CD138 + CD44^{hi}	IL-10	[57]

Species	Population	Phenotype	Mechanism of Suppression	References
	Tim-1 + B-cells	CD19 + Tim-1+	IL-10	[58]
	IL-35-Bregs	CD5 + CD1d^{hi} Fcγlib^{hi}	IL-35	[59]
	GITRL + B-cells	-	GITRL	[60]
	Killer B-cells	CD19 + CD5 + FasL+	FasL, TGF-β	[61][62]
	PD-L1^{hi} B-cells	CD19 + PD-L1^{hi}	PD-L1	[63]
	-	B220 + CD39 + CD73+	ADO, CD39 + CD73 + Extracellular vesicles	[64][65]
	GIFT-15 B-cells	B220 + CD21 + CD22 + CD23 + CD24 + CD1d + CD138 + IgM + IgD+	IL-10	[66]
Human	MZp	CD19 + CD1c + CD21^{lo} IgM^{hi} CD27 + CD10+	CD83, PD-L1, IL-10	[5][67]
	Transitional B-cells	CD19 + CD24^{hi} CD38^{hi}	IL-10	[68]
	Memory B-cells	CD19 + CD24^{hi} CD27+	IL-10	[69]
	Br1	CD25^{hi} CD71hi CD73^{lo}	IL-10	[70]
	TIM1 + B-cells	CD19 + TIM1+	IL-10	[71]
	Plasmablast	CD19^{lo} CD27^{hi} CD38^{hi}	IL-10	[72][73]
	IgA + B-cells	CD19 + IgA+	IL-10, PD-L1	[74]
	Exhausted B-cells	CD19 + CD95+	CD95	[75]
	Killer B-cells	CD19 + CD38 + IgM + FasL+	FasL	[76]
	PD-L1 B-cells	CD19 + PD-L1+	PD-L1	[62]
	CD39^{high}	CD19 + CD39^{high}CD73+	ADO	[77]
	iBreg	-	TGF-β, IDO	[78]

The phenotype and mechanism of suppression of different Breg subsets in mice and humans are summarized herein.

have been bears a CD19⁺IgM^{high}CD27⁺CD1c⁺CD21^{low}CD10⁺ phenotype [4][5][79]. Some recent research have shown that MZps possess strong regulatory potential due to the Breg molecules that they express (see **Table 2**). Indeed, besides their strong ex vivo IL-10 expression profile, MZps highly express the nuclear receptors (NR)4A1, NR4A2 and NR4A3, as well as the immunoregulatory molecule CD83 (see below) [5][67]. Furthermore, MZps also express the ectonucleotidases CD39 and CD73, as well as several molecules associated with Breg functions, such as Transform Growth Factor Beta (TGF-β), IL-35, TLR10, Human Leukocyte Antigen G (HLA-G) and PD-L1 [67].

Strikingly, it can be found that the Breg function of MZp was directly linked with signals involving CD83, and more recently with the PD-1/PD-L1 signaling path, as discussed below [67].

Table 2. The regulatory molecules expressed by human blood and tonsillar MZps.

mRNA Expression	Confirmed Protein Expression
NR4A1, NR4A2, NR4A3, CD83 CD39, CD73, TGF-β, IL-10, PD-L1, IL-10R, IL-27β, IL-12 p35, HLA-G	NR4A1, NR4A3, CD83, CD39, CD73, PD-L1, IL-10

Human blood MZps express high levels of mRNA transcripts of genes associated with a regulatory potential. A certain number of these regulatory transcripts had their protein expression confirmed, both in blood and tonsillar MZps [5][67].

4.1. Importance of NR4As

The NR4As are a family of orphan nuclear receptors, meaning that their endogenous ligand is unknown. There are three known transcription factors in this family: NR4A1 (or Nur77), NR4A2 (or Nurr1) and NR4A3 (or NOR-1), all of which possess a certain degree of homology and redundant functions [80]. Normally, a nuclear receptor must bind to its ligand in order to undergo a conformational change that allows for their DNA binding and subsequent gene transcription. However, it has been shown that the transcription factors of the NR4A family may not need such a ligand, since their natural conformation is constitutively active [80].

Members of the NR4A family are known for their regulatory, anti-inflammatory and pro-apoptotic actions. As a matter of fact, expression of all three known members of the NR4A family is essential for the maintenance of FoxP3 expression by Tregs; moreover, their deficiency converts Treg precursors into autoreactive T-cells, possibly due to the nature of Treg selection [81][82]. The expression of NR4As is quickly upregulated (they are "early induced genes") following several stimulatory engagements (such as after BCR and TCR stimulation, and even TLR signaling) to control unhindered immune responses, notably in the absence of co-stimulation. Moreover, they participate in the contraction of the immunological response by inducing clonally expanded lymphocytes to undergo apoptosis [83][84]. NR4As have been shown to be upregulated in exhausted T-cells in the context of cancer and chronic infection in mice, suggesting a contribution to the control of immune responses in the context of prolonged and/or excessive immune activation [85][86]. The NR4As are also important for monocyte differentiation, since NR4A1 is essential for the differentiation of intermediate and non-classical monocyte subsets, and monocyte derived dendritic cells (MoDC) are absent in NR4A3 knock-out (KO) mice [87][88][89][90]. Lastly, the NR4As are involved in the expression of immune checkpoint molecules such as PD-L1, further illustrating the immune regulatory function of these molecules [91]. Importantly, NR4As are a part of the cyclic AMP (cAMP) response elements (CREs), the expression of which is modulated by the cAMP binding protein (CREB) [92]. The CREB is involved in the expression of several immunoregulatory proteins and anti-inflammatory molecules such as IL-10, and it is activated by the accumulation of cAMP in the cytosol [93].

One of the molecules whose expression is directly controlled by the NR4A family is the immunoregulatory protein CD83 [94]. Accordingly, it can be shown that MZp express high levels of CD83 ex vivo, and their Breg function is related to this molecule, as the administration of a CD83 blocking antibody impedes MZp control of CD4+ T-cell

proliferation in vitro [67]. CD83 is a protein of the immunoglobulin-like superfamily, whose ligand is unknown. It can be found in a membrane-bound or a soluble manner, both of which seem to play different roles in immunity, with soluble CD83 (sCD83) being involved in immunoregulatory roles [95][96][97]. It has been suggested that, similarly to other B7 family members, it can interact with other CD83 molecules in a homotypic manner, a feat that was demonstrated in DCs [98][99][100]. CD83's expression and role has been shown in a wide variety of regulatory cell populations. Indeed, it has been shown that sCD83 inhibits monocyte differentiation into DC, DC maturation, and DC-mediated T-cell activation [97][98][101]. Tolerogenic DCs have also been shown to express CD83 in order to maintain mucosal homeostasis and the self- versus non-self-immunity control [95][100]. Furthermore, Treg generation seems to rely on sCD83 and indoleamine 2-3 dioxygenase 1 (IDO-1) production by DCs. Lastly, as is the case for NR4As, CD83 is essential for the maintenance of the Treg phenotype [102][103].

4.2. Importance of CD39 and CD73

It has previously shown that MZps express high levels of the ectonucleotidases CD39 and CD73, molecules involved in the adenosine (ADO) pathway [67]. As such, CD39 converts the extracellular ATP (highly inflammatory, and notably generated by cell death) into ADP and AMP, and CD73 converts the latter into ADO, an anti-inflammatory molecule [77][104]. Thus, CD39 and CD73 expression allows for the conversion of a pro-inflammatory milieu into an anti-inflammatory one. ADO production has been shown to induce a wide variety of anti-inflammatory responses [105]. For instance, the binding of ADO to the $A2_A$ receptor in FO B-cells impedes GC formation, BCR signaling and TLR responses [106]. In T-cells, ADO can promote Treg generation, which will express CD39 and CD73 [107]. Furthermore, $A2_A$ signaling (possibly autocrine or paracrine) in Tregs increases IL-10 and TGF-β production by these cells, further nourishing the anti-inflammatory environment generated by the ADO production [108]. As such, CD39 and CD73 expression was evaluated in a wide variety of contexts, including cancer, where these molecules and ADO have been found to contribute to the maintenance of the "cold", anti-inflammatory tumoral microenvironment [108]. CD39 and CD73 have previously been identified as regulatory molecules on T-cells and B-cells by different groups [105][107]. Indeed, some Breg populations were associated with CD39 and/or CD73 expression [77]. The binding of ADO to the $A2_A$ receptor activates adenylate cyclase, allowing for intracellular cyclic AMP (cAMP) production and accumulation, which will then inhibit the NK-κB response and the Janus Kinase (JAK)-Signal Transducer and Activator of Transcription (STAT) pathway, important for inflammatory responses [108]. ADO binding to the $A2_A$ receptor has been shown to upregulate NR4A expression in monocytes [84]. Given the importance of cAMP to CREB activation, and thus, to NR4A expression, a link between the adenosine pathway and NR4A expression is to be expected.

References

1. Cerutti, A.; Cols, M.; Puga, I. Marginal zone B cells: Virtues of innate-like antibody-producing lymphocytes. Nat. Rev. Immunol. 2013, 13, 118–132.

2. Palm, E.A.-K.; Kleinau, S. Marginal zone B cells: From housekeeping function to autoimmunity? J. Autoimmun. 2021, 119, 102627.

3. Weill, J.-C.; Weller, S.; Reynaud, C.-A. Human Marginal Zone B Cells. Annu. Rev. Immunol. 2009, 27, 267–285.

4. Fontaine, J.; Chagnon-Choquet, J.; Valcke, H.S.; Poudrier, J.; Roger, M.; the Montreal Primary HIV Infection and Long-Term Non-Progressor Study Groups. High expression levels of B lymphocyte stimulator (BLyS) by dendritic cells correlate with HIV-related B-cell disease progression in humans. Blood 2011, 117, 145–155.

5. Chagnon-Choquet, J.; Fontaine, J.; Poudrier, J.; Roger, M.; for the Montreal Primary HIV Infection and Slow Progressor Study Groups. IL-10 and Lymphotoxin-α Expression Profiles within Marginal Zone-Like B-Cell Populations Are Associated with Control of HIV-1 Disease Progression. PLOS ONE 2014, 9, e101949.

6. Martin, F.; Kearney, J.F. Marginal-zone B cells. Nat. Rev. Immunol. 2002, 2, 323–335.

7. Jackson, R.T.; Ling, R.E.; Roy, A. The Origin of B-cells: Human Fetal B Cell Development and Implications for the Patho-genesis of Childhood Acute Lymphoblastic Leukemia. Front. Immunol. 2021, 12.

8. Hardy, R.R.; Hayakawa, K. B CELL DEVELOPMENT PATHWAYS. Annu. Rev. Immunol. 2001, 19, 595–621.

9. Nishana, M.; Raghavan, S.C. Role of recombination activating genes in the generation of antigen receptor diversity and beyond. Immunology 2012, 137, 271–281.

10. Pieper, K.; Grimbacher, B.; Eibel, H. B-cell biology and development. J. Allergy Clin. Immunol. 2013, 131, 959–971.

11. Zhou, Y.; Zhang, Y.; Han, J.; Yang, M.; Zhu, J.; Jin, T. Transitional B cells involved in autoimmunity and their impact on neuroimmunological diseases. J. Transl. Med. 2020, 18, 131.

12. Pillai, S.; Cariappa, A. The follicular versus marginal zone B lymphocyte cell fate decision. Nat. Rev. Immunol. 2009, 9, 767–777.

13. Tull, T.J.; Pitcher, M.J.; Guesdon, W.; Siu, J.H.; Lebrero-Fernández, C.; Zhao, Y.; Petrov, N.; Heck, S.; Ellis, R.; Dhami, P.; et al. Human marginal zone B cell development from early T2 progenitors. J. Exp. Med. 2021, 218, e20202001.

14. Tiegs, S.L.; Russell, D.M.; Nemazee, D. Receptor editing in self-reactive bone marrow B cells. The Journal of Experimental Medicine. 1993. 177: 1009-1020. J. Immunol. 2011, 186, 1313–1324.

15. Spencer, J.; Finn, T.; Pulford, K.A.; Mason, D.Y.; Isaacson, P.G. The human gut contains a novel population of B lymphocytes which resemble marginal zone cells. Clin. Exp. Immunol. 1985, 62,

607–612.

16. Thomas, L.; Rothstein, D.O.; Griffin, N.E.; Holodick, T.D. Human B-1 cells take the stage. Ann. N. Y. Acad. Sci. 2013, 1285, 97–114.

17. Baumgarth, N. A Hard(y) Look at B-1 Cell Development and Function. J. Immunol. 2017, 199, 3387–3394.

18. Lechner, M.; Engleitner, T.; Babushku, T.; Schmidt-Supprian, M.; Rad, R.; Strobl, L.J.; Zimber-Strobl, U. Notch2-mediated plasticity between marginal zone and follicular B cells. Nat. Commun. 2021, 12, 1111.

19. Cariappa, A.; Tang, M.; Parng, C.; Nebelitskiy, E.; Carroll, M.; Georgopoulos, K.; Pillai, S. The Follicular versus Marginal Zone B Lymphocyte Cell Fate Decision Is Regulated by Aiolos, Btk, and CD21. Immunity 2001, 14, 603–615.

20. Hammad, H.; Vanderkerken, M.; Pouliot, P.; Deswarte, K.; Toussaint, W.; Vergote, K.; Vandersarren, L.; Janssens, S.; Ramou, I.; Savvides, S.N.; et al. Transitional B cells commit to marginal zone B cell fate by Taok3-mediated surface expression of ADAM10. Nat. Immunol. 2017, 18, 313–320.

21. Moran, S.T.; Cariappa, A.; Liu, H.; Muir, B.; Sgroi, D.; Boboila, C.; Pillai, S. Synergism between NF-κB1/p50 and Notch2 during the Development of Marginal Zone B Lymphocytes. J. Immunol. 2007, 179, 195–200.

22. Jia, W.; Poe, J.C.; Su, H.; Anand, S.; Matsushima, G.K.; Rathmell, J.C.; Maillard, I.; Radojcic, V.; Imai, K.; Reyes, N.J.; et al. BAFF promotes heightened BCR responsiveness and manifestations of chronic GVHD after allogeneic stem cell transplantation. Blood 2021, 137, 2544–2557.

23. Dono, M.; Zupo, S.; Leanza, N.; Melioli, G.; Fogli, M.; Melagrana, A.; Chiorazzi, N.; Ferrarini, M. Heterogeneity of Tonsillar Subepithelial B Lymphocytes, the Splenic Marginal Zone Equivalents. J. Immunol. 2000, 164, 5596–5604.

24. Weller, S. Human blood IgM memory B cells are circulating splenic marginal zone B cells harboring a prediversified immunoglobulin repertoire. Blood 2004, 104, 3647–3654.

25. Mebius, R.E.; Kraal, G. Structure and function of the spleen. Nat. Rev. Immunol. 2005, 5, 606–616.

26. Hendricks, J.; Bos, N.A.; Kroese, F.G. Heterogeneity of Memory Marginal Zone B Cells. Crit. Rev. Immunol. 2018, 38, 145–158.

27. Berkowska, M.A.; Driessen, G.J.A.; Bikos, V.; Grosserichter-Wagener, C.; Stamatopoulos, K.; Cerutti, A.; He, B.; Biermann, K.; Lange, J.F.; van der Burg, M.; et al. Human memory B cells originate from three distinct germinal center-dependent and -independent maturation pathways. Blood 2011, 118, 2150–2158.

28. Seifert, M.; Küppers, R. Human memory B cells. Leukemia 2016, 30, 2283–2292.

29. Janeway, C.A.Jr.; Medzhitov, R. Innate immune recognition. Annu. Rev. Immunol. 2002, 20, 197–216.

30. Bendelac, A.; Bonneville, M.; Kearney, J.F. Autoreactivity by design: Innate B and T lymphocytes. Nat. Rev. Immunol. 2001, 1, 177–186.

31. Guinamard, R.; Okigaki, M.; Schlessinger, J.; Ravetch, J.V. Absence of marginal zone B cells in Pyk-2–deficient mice defines their role in the humoral response. Nat. Immunol. 2000, 1, 31–36.

32. Martin, F.; Oliver, A.M.; Kearney, J.F. Marginal Zone and B1 B Cells Unite in the Early Response against T-Independent Blood-Borne Particulate Antigens. Immunity 2001, 14, 617–629.

33. Song, H.; Cerny, J. Functional heterogeneity of marginal zone B cells revealed by their ability to generate both early anti-body-forming cells and germinal centers with hypermutation and memory in response to a T-dependent antigen. J. Exp. Med. 2003, 198, 1923–1935.

34. Chappell, C.P.; Draves, K.E.; Giltiay, N.V.; Clark, E.A. Extrafollicular B cell activation by marginal zone dendritic cells drives T cell-dependent antibody re-sponses. J. Exp. Med. 2012, 209, 1825–1840.

35. Cinamon, G.; Zachariah, M.A.; Lam, O.M.; Foss, F.W.; Cyster, J.G. Follicular shuttling of marginal zone B cells facilitates antigen transport. Nat. Immunol. 2008, 9, 54–62.

36. Biram, A.; Davidzohn, N.; Shulman, Z. T cell interactions with B cells during germinal center formation, a three-step model. Immunol. Rev. 2019, 288, 37–48.

37. He, B.; Qiao, X.; Klasse, P.J.; Chiu, A.; Chadburn, A.; Knowles, D.M.; Moore, J.P.; Cerutti, A. HIV-1 Envelope Triggers Polyclonal Ig Class Switch Recombination through a CD40-Independent Mechanism Involving BAFF and C-Type Lectin Receptors. J. Immunol. 2006, 176, 3931–3941.

38. Roco, J.A.; Mesin, L.; Binder, S.C.; Nefzger, C.; Gonzalez-Figueroa, P.; Canete, P.F.; Ellyard, J.; Shen, Q.; Robert, P.A.; Cappello, J.; et al. Class-Switch Recombination Occurs Infrequently in Germinal Centers. Immunity 2019, 51, 337–350.e7.

39. Gatto, D.; Brink, R. The germinal center reaction. J. Allergy Clin. Immunol. 2010, 126, 898–907.

40. Weller, S.; Mamani-Matsuda, M.; Picard, C.; Cordier, C.; Lecoeuche, D.; Gauthier, F.; Weill, J.C.; Reynaud, C.A. Somatic diversification in the absence of antigen-driven responses is the hallmark of the IgM+ IgD+ CD27+ B cell repertoire in infants. J. Exp. Med. 2008, 205, 1331–1342.

41. Scheeren, F.A. T cell-independent development and induction of somatic hypermutation in human IgM+ IgD+ CD27+ B cells. J. Exp. Med. 2008, 205, 2033–2042.

42. Puga, I.; Cols, M.; Barra, C.M.; He, B.; Cassis, L.; Gentile, M.; Comerma, L.; Chorny, A.; Shan, M.; Xu, W.; et al. B cell–helper neutrophils stimulate the diversification and production of

immunoglobulin in the marginal zone of the spleen. Nat. Immunol. 2011, 13, 170–180.

43. He, B.; Santamaria, R.; Xu, W.; Cols, M.; Chen, K.; Puga, I.; Shan, M.; Xiong, H.; Bussel, J.B.; Chiu, A.; et al. The transmembrane activator TACI triggers immunoglobulin class switching by activating B cells through the adaptor MyD88. Nat. Immunol. 2010, 11, 836–845.

44. Treml, L.S.; Carlesso, G.; Hoek, K.L.; Stadanlick, J.E.; Kambayashi, T.; Bram, R.J.; Cancro, M.P.; Khan, W.N. TLR stimulation modifies BLyS receptor expression in follicular and marginal zone B cells. J. Immunol. 2007, 178, 7531–7539.

45. Attanavanich, K.; Kearney, J.F. Marginal Zone, but Not Follicular B Cells, Are Potent Activators of Naive CD4 T Cells. J. Immunol. 2004, 172, 803–811.

46. Marinkovic, D.; Marinkovic, T. Putative role of marginal zone B cells in pathophysiological processes. Scand. J. Immunol. 2020, 92, e12920.

47. Bialecki, E.; Paget, C.; Fontaine, J.; Capron, M.; Trottein, F.; Faveeuw, C. Role of Marginal Zone B Lymphocytes in Invariant NKT Cell Activation. J. Immunol. 2009, 182, 6105–6113.

48. Mauri, C.; Menon, M. The expanding family of regulatory B cells. Int. Immunol. 2015, 27, 479–486.

49. Mauri, C.; Bosma, A. Immune Regulatory Function of B Cells. Annu. Rev. Immunol. 2012, 30, 221–241.

50. Iizuka-Koga, M.; Nakatsukasa, H.; Ito, M.; Akanuma, T.; Lu, Q.; Yoshimura, A. Induction and maintenance of regulatory T cells by transcription factors and epigenetic modifications. J. Autoimmun. 2017, 83, 113–121.

51. Yanaba, K.; Bouaziz, J.-D.; Matsushita, T.; Tsubata, T.; Tedder, T.F. The Development and Function of Regulatory B Cells Expressing IL-10 (B10 Cells) Requires Antigen Receptor Diversity and TLR Signals. J. Immunol. 2009, 182, 7459–7472.

52. Yanaba, K.; Bouaziz, J.-D.; Haas, K.M.; Poe, J.C.; Fujimoto, M.; Tedder, T.F. A Regulatory B Cell Subset with a Unique CD1dhiCD5+ Phenotype Controls T Cell-Dependent Inflammatory Responses. Immunity 2008, 28, 639–650.

53. Huber, K.; Sármay, G.; Kövesdi, D. MZ B cells migrate in a T-bet dependent manner and might contribute to the remission of collagen-induced arthritis by the secretion of IL-10. Eur. J. Immunol. 2016, 46, 2239–2246.

54. Evans, J.G.; Chavez-Rueda, K.A.; Eddaoudi, A.; Meyer-Bahlburg, A.; Rawlings, D.J.; Ehrenstein, M.; Mauri, C. Novel Suppressive Function of Transitional 2 B Cells in Experimental Arthritis. J. Immunol. 2007, 178, 7868–7878.

55. Hsu, L.-H.; Li, K.-P.; Chu, K.-H.; Chiang, B.-L. A B-1a cell subset induces Foxp3− T cells with regulatory activity through an IL-10-independent pathway. Cell Mol. Immunol. 2015, 12, 354–365.

56. Fillatreau, S. Natural regulatory plasma cells. Curr. Opin. Immunol. 2018, 55, 62–66.

57. Matsumoto, M.; Baba, A.; Yokota, T.; Nishikawa, H.; Ohkawa, Y.; Kayama, H.; Kallies, A.; Nutt, S.L.; Sakaguchi, S.; Takeda, K.; et al. Interleukin-10-Producing Plasmablasts Exert Regulatory Function in Autoimmune Inflammation. Immunity 2014, 41, 1040–1051.

58. Ding, Q.; Yeung, M.; Camirand, G.; Zeng, Q.; Akiba, H.; Yagita, H.; Chalasani, G.; Sayegh, M.H.; Najafian, N.; Rothstein, D.M. Regulatory B cells are identified by expression of TIM-1 and can be induced through TIM-1 ligation to promote tolerance in mice. J. Clin. Investig. 2011, 121, 3645–3656.

59. Zhang, Y.; Li, J.; Zhou, N.; Zhang, Y.; Wu, M.; Xu, J.; Shen, C.; An, X.; Shen, G.; Yang, M.; et al. The Unknown Aspect of BAFF: Inducing IL-35 Production by a CD5(+)CD1d(hi)FcγRIIb(hi) Regulatory B-Cell Subset in Lupus. J. Invest. Derm. 2017, 137, 2532–2543.

60. Ray, A.; Basu, S.; Williams, C.B.; Salzman, N.; Dittel, B.N. A Novel IL-10–Independent Regulatory Role for B Cells in Suppressing Autoimmunity by Maintenance of Regulatory T Cells via GITR Ligand. J. Immunol. 2012, 188, 3188–3198.

61. Lundy, S.K. Killer B lymphocytes: The evidence and the potential. Agents Actions 2009, 58, 345–357.

62. Tian, J.; Zekzer, D.; Hanssen, L.; Lu, Y.; Olcott, A.; Kaufman, D.L. Lipopolysaccharide-Activated B Cells Down-Regulate Th1 Immunity and Prevent Autoimmune Diabetes in Nonobese Diabetic Mice. J. Immunol. 2001, 167, 1081–1089.

63. Khan, A.R.; Hams, E.; Floudas, A.; Sparwasser, T.; Weaver, C.T.; Fallon, P. PD-L1hi B cells are critical regulators of humoral immunity. Nat. Commun. 2015, 6, 5997.

64. LeBleu, V.S.; Kalluri, R. Exosomes Exercise Inhibition of Anti-Tumor Immunity during Chemotherapy. Immunity 2019, 50, 547–549.

65. Kaku, H. A novel mechanism of B cell-mediated immune suppression through CD73 expression and adenosine pro-duction. J. Immunol. 2014, 193, 5904–5913.

66. Rafei, M.; Hsieh, J.; Zehntner, S.; Li, M.; Forner, K.; Birman, E.; Boivin, M.-N.; Young, Y.K.; Perreault, C.; Galipeau, J. A granulocyte-macrophage colony–stimulating factor and interleukin-15 fusokine induces a regulatory B cell population with immune suppressive properties. Nat. Med. 2009, 15, 1038–1045.

67. Doyon-Laliberté, K.; Chagnon-Choquet, J.; Byrns, M.; Aranguren, M.; Memmi, M.; Chrobak, P.; Stagg, J.; Poudrier, J.; Roger, M. NR4A Expression by Human Marginal Zone B-Cells. Antibodies 2019, 8, 50.

68. Blair, P.A.; Yassin-Noreña, L.; Flores-Borja, F.; Rawlings, D.J.; Isenberg, D.; Ehrenstein, M.; Mauri, C. CD19+CD24hiCD38hi B Cells Exhibit Regulatory Capacity in Healthy Individuals but

Are Functionally Impaired in Systemic Lupus Erythematosus Patients. Immunity 2010, 32, 129–140.

69. Jin, L.; Weiqian, C.; Lihuan, Y. Peripheral CD24 hi CD27 + CD19 + B cells subset as a potential biomarker in naïve systemic lupus erythematosus. Int. J. Rheum. Dis. 2013, 16, 698–708.

70. van de Veen, W.; Stanic, B.; Yaman, G.; Wawrzyniak, M.; Söllner, S.; Akdis, D.G. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. J. Allergy Clin. Immunol. 2013, 131, 1204–1212.

71. Gu, X.L.; He, H.; Lin, L.; Luo, G.X.; Wen, Y.F.; Xiang, D.C.; Qiu, J. Tim-1(+) B cells suppress T cell interferon-gamma production and promote Foxp3 expression, but have impaired regulatory function in coronary artery disease. Apmis 2017, 125, 872–879.

72. Mao, H.; Pan, F.; Wu, Z.; Wang, Z.; Zhou, Y.; Zhang, P.; Gou, M.; Dai, G. CD19loCD27hi Plasmablasts Suppress Harmful Th17 Inflammation Through Interleukin 10 Pathway in Colorectal Cancer. DNA Cell Biol. 2017, 36, 870–877.

73. Rybojad, M.; Hau, E.; Monfort, B.J.; Branchtein, M.; Michonneau, D.; Dessirier, V.; Socié, G. CD24(hi)CD27+ and plasmablast-like regulatory B cells in human chronic graft-versus-host disease. Blood 2015, 125, 1830–1839.

74. Fehres, C.M.; Van Uden, N.O.; Yeremenko, N.G.; Fernandez, L.; Salinas, G.F.; Van Duivenvoorde, L.M.; Huard, B.; Morel, J.; Spits, H.; Hahne, M.; et al. APRIL Induces a Novel Subset of IgA+ Regulatory B Cells That Suppress Inflammation via Expression of IL-10 and PD-L1. Front. Immunol. 2019, 10.

75. Wang, X.; Zhu, Y.; Zhang, M.; Wang, H.; Jiang, Y.; Gao, P. Ulcerative Colitis Is Characterized by a Decrease in Regulatory B Cells. J. Crohn's Colitis 2016, 10, 1212–1223.

76. van Rensburg, I.C.; Loxton, A.G. B-cells with a FasL expressing regulatory phenotype are induced following successful anti-tuberculosis treatment. Tuberculosis 2018, 108, 114–117.

77. Figueiro, F.; Muller, L.; Funk, S.; Jackson, E.K.; Battastini, A.M.O.; Whiteside, T.L. Phenotypic and functional characteristics of CD39high human regulatory B cells (Breg). OncoImmunology 2016, 5, e1082703.

78. Nouël, A.; Pochard, P.; Simon, Q.; Ségalen, I.; Le Meur, Y.; Pers, J.; Hillion, S. B-Cells induce regulatory T cells through TGF-β/IDO production in A CTLA-4 dependent manner. J. Autoimmun. 2015, 59, 53–60.

79. Sabourin-Poirier, C.; Fourcade, L.; Chagnon-Choquet, J.; Labbé, A.C.; Alary, M.; Guédou, F.; Roger, M. Blood B Lymphocyte Stimulator (BLyS)/BAFF levels may reflect natural immunity to HIV in highly exposed uninfected Beninese Commercial Sex Workers. Sci. Rep. 2016, 6, 32318.

80. Safe, S.; Jin, U.-H.; Morpurgo, B.; Abudayyeh, A.; Singh, M.; Tjalkens, R.B. Nuclear receptor 4A (NR4A) family—orphans no more. J. Steroid Biochem. Mol. Biol. 2015, 157, 48–60.

81. Sekiya, T.; Hibino, S.; Saeki, K.; Kanamori, M.; Takaki, S.; Yoshimura, A. Nr4a Receptors Regulate Development and Death of Labile Treg Precursors to Prevent Generation of Path-ogenic Self-Reactive Cells. Cell Rep. 2018, 24, 1627–1638.e6.

82. Bandukwala, H.S.; Rao, A. Nurrishing Treg cells: Nr4a transcription factors control Foxp3 expression. Nat. Immunol. 2013, 14, 201–203.

83. Ashouri, J.; Weiss, A. Endogenous Nur77 Is a Specific Indicator of Antigen Receptor Signaling in Human T and B Cells. J. Immunol. 2016, 198, 657–668.

84. Crean, D.; Cummins, E.P.; Bahar, B.; Mohan, H.; McMorrow, J.P.; Murphy, E.P. Adenosine Modulates NR4A Orphan Nuclear Receptors To Attenuate Hyperinflammatory Responses in Monocytic Cells. J. Immunol. 2015, 195, 1436–1448.

85. Wan, P.K.-T.; Siu, M.K.-Y.; Leung, T.H.-Y.; Mo, X.-T.; Chan, K.K.-L.; Ngan, H.Y.-S. Role of Nurr1 in Carcinogenesis and Tumor Immunology: A State of the Art Review. Cancers 2020, 12, 3044.

86. Hibino, S.; Chikuma, S.; Kondo, T.; Ito, M.; Nakatsukasa, H.; Omata-Mise, S.; Yoshimura, A. Inhibition of Nr4a Receptors Enhances Antitumor Immunity by Breaking Treg-Mediated Immune Tolerance. Cancer Res. 2018, 78, 3027–3040.

87. Boulet, S.; Daudelin, J.-F.; Odagiu, L.; Pelletier, A.-N.; Yun, T.J.; Lesage, S.; Cheong, C.; Labrecque, N. The orphan nuclear receptor NR4A3 controls the differentiation of monocyte-derived dendritic cells following microbial stimulation. Proc. Natl. Acad. Sci. USA 2019, 116, 15150–15159.

88. Mildner, A.; Schönheit, J.; Giladi, A.; David, E.; Lara-Astiaso, D.; Vivas, E.L.; Paul, F.; Chappell-Maor, L.; Priller, J.; Leutz, A.; et al. Genomic Characterization of Murine Monocytes Reveals C/EBPβ Transcription Factor Dependence of Ly6C—Cells. Immunity 2017, 46, 849–862.e7.

89. Hanna, R.N.; Carlin, L.M.; Hubbeling, H.G.; Nackiewicz, D.; Green, A.M.; Punt, J.A.; Geissmann, F.; Hedrick, C.C. The transcription factor NR4A1 (Nur77) controls bone marrow differentiation and the survival of Ly6C− monocytes. Nat. Immunol. 2011, 12, 778–785.

90. Tel-Karthaus, N.; Kers-Rebel, E.D.; Looman, M.W.; Ichinose, H.; De Vries, C.J.; Ansems, M. Nuclear Receptor Nur77 Deficiency Alters Dendritic Cell Function. Front. Immunol. 2018, 9.

91. Karki, K.; Wright, G.A.; Mohankumar, K.; Jin, U.-H.; Zhang, X.-H.; Safe, S. A Bis-Indole–Derived NR4A1 Antagonist Induces PD-L1 Degradation and Enhances Antitumor Immunity. Cancer Res. 2020, 80, 1011–1023.

92. Bridi, M.S.; Hawk, J.D.; Chatterjee, S.; Safe, S.; Abel, T. Pharmacological Activators of the NR4A Nuclear Receptors Enhance LTP in a CREB/CBP-Dependent Manner.

Neuropsychopharmacology 2016, 42, 1243–1253.

93. Wen, A.Y.; Sakamoto, K.M.; Miller, L.S. The Role of the Transcription Factor CREB in Immune Function. J. Immunol. 2010, 185, 6413–6419.

94. Duren, R.P.; Boudreaux, S.P.; Conneely, O.M. Genome Wide Mapping of NR4A Binding Reveals Cooperativity with ETS Factors to Promote Epigenetic Activation of Distal Enhancers in Acute Myeloid Leukemia Cells. PLoS ONE 2016, 11, e0150450.

95. Ge, W.; Arp, J.; Lian, D.; Liu, W.; Baroja, M.L.; Jiang, J.; Ramcharran, S.; Eldeen, F.Z.; Zinser, E.; Steinkasserer, A.; et al. Immunosuppression Involving Soluble CD83 Induces Tolerogenic Dendritic Cells That Prevent Cardiac Allograft Rejection. Transplantation 2010, 90, 1145–1156.

96. Lan, Z.; Ge, W.; Arp, J.; Jiang, J.; Liu, W.; Gordon, D.; Healey, D.; Debenedette, M.; Nicolette, C.; Garcia, B.; et al. Induction of Kidney Allograft Tolerance by Soluble CD83 Associated With Prevalence of Tolerogenic Dendritic Cells and Indoleamine 2,3-Dioxygenase. Transplantation 2010, 90, 1286–1293.

97. Lin, H.; Liang, S.; Zhong, Z.; Wen, J.; Li, W.; Wang, L.; Xu, J.; Zhong, F.; Li, X. Soluble CD83 inhibits human monocyte differentiation into dendritic cells in vitro. Cell. Immunol. 2014, 292, 25–31.

98. Bates, J.M.; Flanagan, K.; Mo, L.; Ota, N.; Ding, J.; Ho, S.; Liu, S.; Roose-Girma, M.; Warming, S.; Diehl, L. Dendritic cell CD83 homotypic interactions regulate inflammation and promote mucosal homeostasis. Mucosal Immunol. 2014, 8, 414–428.

99. Li, Z.; Ju, X.; Silveira, P.A.; Abadir, E.; Hsu, W.-H.; Hart, D.N.J.; Clark, G. CD83: Activation Marker for Antigen Presenting Cells and Its Therapeutic Potential. Front. Immunol. 2019, 10, 1312.

100. Wild, A.B.; Krzyzak, L.; Peckert, K.; Stich, L.; Kuhnt, C.; Butterhof, A.; Seitz, C.; Mattner, J.; Grüner, N.; Gänsbauer, M.; et al. CD83 orchestrates immunity toward self and non-self in dendritic cells. JCI Insight 2019, 4, e126246.

101. Sénéchal, B.; Boruchov, A.M.; Reagan, J.L.; Hart, D.N.J.; Young, J.W. Infection of mature monocyte-derived dendritic cells with human cytomegalovirus inhibits stimulation of T-cell proliferation via the release of soluble CD83. Blood 2004, 103, 4207–4215.

102. Bock, F.; Rössner, S.; Onderka, J.; Lechmann, M.; Pallotta, M.T.; Fallarino, F.; Boon, L.; Nicolette, C.; Debenedette, M.A.; Tcherepanova, I.Y.; et al. Topical Application of Soluble CD83 Induces IDO-Mediated Immune Modulation, Increases Foxp3+ T Cells, and Prolongs Allogeneic Corneal Graft Survival. J. Immunol. 2013, 191, 1965–1975.

103. Doebbeler, M.; Koenig, C.; Krzyzak, L.; Seitz, C.; Wild, A.; Ulas, T.; Baßler, K.; Kopelyanskiy, D.; Butterhof, A.; Kuhnt, C.; et al. CD83 expression is essential for Treg cell differentiation and stability. JCI Insight 2018, 3, e99712.

104. Saze, Z.; Schuler, P.J.; Hong, C.-S.; Cheng, D.; Jackson, E.K.; Whiteside, T.L. Adenosine production by human B cells and B cell–mediated suppression of activated T cells. Blood 2013, 122, 9–18.

105. Antonioli, L.; Pacher, P.; Vizi, E.S.; Haskó, G. CD39 and CD73 in immunity and inflammation. Trends Mol. Med. 2013, 19, 355–367.

106. Minguet, S.; Huber, M.; Rosenkranz, L.; Schamel, W.W.; Reth, M.; Brummer, T. Adenosine and cAMP are potent inhibitors of the NF-kappa B pathway downstream of immunoreceptors. Eur. J. Immunol. 2005, 35, 31–41.

107. Dwyer, K.M.; Deaglio, S.; Gao, W.; Friedman, D.; Strom, T.B.; Robson, S.C. CD39 and control of cellular immune responses. Purinergic Signal. 2007, 3, 171–180.

108. Allard, B.; Allard, D.; Buisseret, L.; Stagg, J. The adenosine pathway in immuno-oncology. Nat. Rev. Clin. Oncol. 2020, 17, 611–629.

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