Chapter 4

Understanding B Lymphocyte Development: A Long Way to Go

Malavika Bhattacharya

Additional information is available at the end of the chapter

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Abstract

B lymphocytes play a significant role in both antigen-dependent and antigen-independent pathways. Although significant progress has been made in context of delineating the pathways that lead to their development, maturity and differentiation, their detailed mechanisms are yet to be dissected out completely. This chapter is aimed towards summarising the knowledge that has been gained till date and identifying the areas that need to be addressed in future research work. Overall, the chapter is planned in a sequential way to guide the reader through the processes of B cell development and the various latest findings that have improved our understanding of this vital physiological system.

Keywords: B lymphocyte, bone marrow, marginal zone, antigen, spleen, germinal centre

1. Introduction

B lymphocytes play vital role in maintaining the normal immunologic functions of the body. Their functions range from producing antibodies to presenting antigens. They are also involved with productions of several regulatory cytokines, such as IL-2, IL-4, IL-6, IL-10, IL-12, TGF-β1, TNF and IFN-γ. Each of these functions are further fine tuned by the fact that they are dependent upon several factors, including the B lymphocyte subsets, their location and the type of stimuli that is encountered by the specific B cell subset in that particular environment. Understanding all these components of B cell development is not only required for getting a better picture of B cell biology, but is also necessary for understanding various immunologic anomalies that lead to disorders. They are also important towards generating effective B cell based therapies. This chapter begins with explanation of the overall pathway

of B cell development and the organs that are involved in its various stages. This is followed by discussion on the role of gene rearrangements in the entire process. Subsequently, the role of various transcription factors has been addressed.

2. Steps in B lymphocyte developmental pathway

2.1. Bone marrow-dependent stages

During foetal life, B cells are generated in the foetal liver. Subsequently in the adults, they are produced by differentiation of haematopoietic cells (HSCs) in the bone marrow [1]. Most of the stages of B lymphocyte development take place in this primary lymphoid organ. The pluripotent HSCs gradually differentiate into progenitors, which have increasingly lower potency. Initially, they form a population of cells that are known as multipotent progenitors (MPPs). These progenitors, in turn, give rise to two main progenitor populations: common granulocyte/megakaryocyte/granulocyte progenitor (CFU-GEMM) and early lymphoid progenitor (ELP). CFU-GEMMs subsequently develop into cells that have either myeloid or erythroid potential. On the other hand, cells with lymphoid potential arise from ELPs. Thus, CFU-GEMMs are the primary source of those elements of blood that are non-lymphoid in nature, whereas the lymphoid elements originate from ELPs. Two major precursors arise from the ELPs, common lymphocyte progenitor (CLP) and early T-lineage precursor (ETP). Both Pre-NK cells and Pre-B cells develop from CLPs, which eventually give rise to NK cells and B cells, respectively. T cells derive from thymocytes, which are generated by differentiation of the ETPs. The CLPs give rise to early Pro-B cells first. They mature to form the late Pro-B cells, which eventually develop into Pre-B cells. Immature B cells arise from these Pre-B cells and they leave the bone marrow to enter into the secondary lymphoid organs. Subsequent stages of B cell development primarily continue in the spleen. During this entire period of maturation, the various B cell subpopulations are found to migrate within the bone marrow, keeping in touch with the stromal cells. Initially, the progenitor cells having highest potency lie in the endosteum. This region is located near the inner surface of the bone. As the B cell progenitors mature to give rise to cell types that have less potency and are more committed towards the B cell fate, they start migrating towards the central sinus of the bone marrow cavity. During this entire process, these maturing cell populations are reported to remain in contact with the reticular stromal cells, which are believed to provide indispensable signals for migration and maturation. This process continues till the developing cell reaches the stage of Immature B cell [2–4].

2.2. Role of bone marrow cell populations in B cell development

In addition to HSCs, B lymphocytes (in various stages of development) and plasma cells (PCs), the bone marrow consists of specialised cells that have multiple roles in various stages of this developmental process. Together they form the “niches” that are vital for normal functioning of the different systems associated with the bone marrow. The most important components of these “niches” are stromal cells and regulatory T cells. Out of these, the stromal cells form an

extensive network of non-lymphoid connective tissue in the bone marrow [5, 6]. They serve dual functions of forming adhesive contacts with developing lymphocytes and providing cytokines/chemokines/growth factors to them as per requirement. In context of maintenance of plasma cells, earlier reports have indicated that they are provided with survival signals such as CXCL13, IL-6, APRIL and BLγS by the stromal cells [7]. In addition, it has been found recently that the regulatory T cells present in the bone marrow play vital role in maintaining plasma cell pool [8]. The dendritic cells (DCs), present as perivascular clusters in the bone marrow, have also been reported to provide signals that are vital for B lymphocytes [9]. Megakaryocytes [10], eosinophils [11] as well as basophils [12] resident in the bone marrow have also been found to play role in maintaining plasma cell pools.

2.3. Spleen-dependent stages

The immature B cell undergoes final stages of development in the spleen to form mature B cells. The spleen primarily consists of red pulp, white pulp and marginal zone. The red pulp is made up of large, blood-filled sinuses and serves as the blood-filtering system of the spleen. In addition, the splenic macrophages play important role in recycling of iron. The white pulp is organised in line with the lymph nodes and consists of lymphoid sheaths having distinct B-cell and T-cell compartments. The marginal zone is a layer of highly specialised cells that surrounds the white pulp [13]. It plays a very important role in immunity because those haematopoietic cells that remain in circulation (as part of the surveillance mechanism) need to be able to migrate through blood and lymphatic systems continuously. The marginal zone plays a vital role in this process due to its strategic location in the spleen. It has been observed that G-protein linked receptors are involved in the signalling process that is responsible for active transport of B- and T-lymphocytes to-and-from the white pulp [14]. The specialised cells that constitute the marginal zone include two subsets of macrophages, the marginal-zone macrophages and the marginal-zone metallophilic macrophages. The first subset is present as an outer ring and express SIGNR1 (a C-type lectin) [15–17] and MARCO (a type I scavenger receptor) [18]. The second subset is present as an inner ring, lies closer to the white pulp and expresses SIGLEC-I (an adhesion molecule) [19]. A specialised B-cell population, known as marginal zone B cell, and DCs are located in between these two rings of macrophages [20, 21]. **Figure 1** shows the major cell populations that are generated in the bone marrow and peripheral lymphoid organs during the process of B cell development.

It has also been reported that the antigens are encountered by the mature B cells in the lymphoid follicles. This process is aided by T cells present in the germinal centres. All the subsequent stages of B cell development, including generation of various Ig isotypes, class switching and somatic hypermutation, contribute towards diversification of the antibody repertoire [22].

On activation by cognate antigen, the activated B cell can either differentiate into antibody-secreting plasma cells/plasma blasts or get recruited into a specialised region known as the germinal centre (GC). Those activated B cells that enter the GC subsequently undergo several rounds of proliferation, class-switching and affinity maturation. Thereafter, the GC B cells that have completed these steps successfully give rise to either long-lived plasma cells or

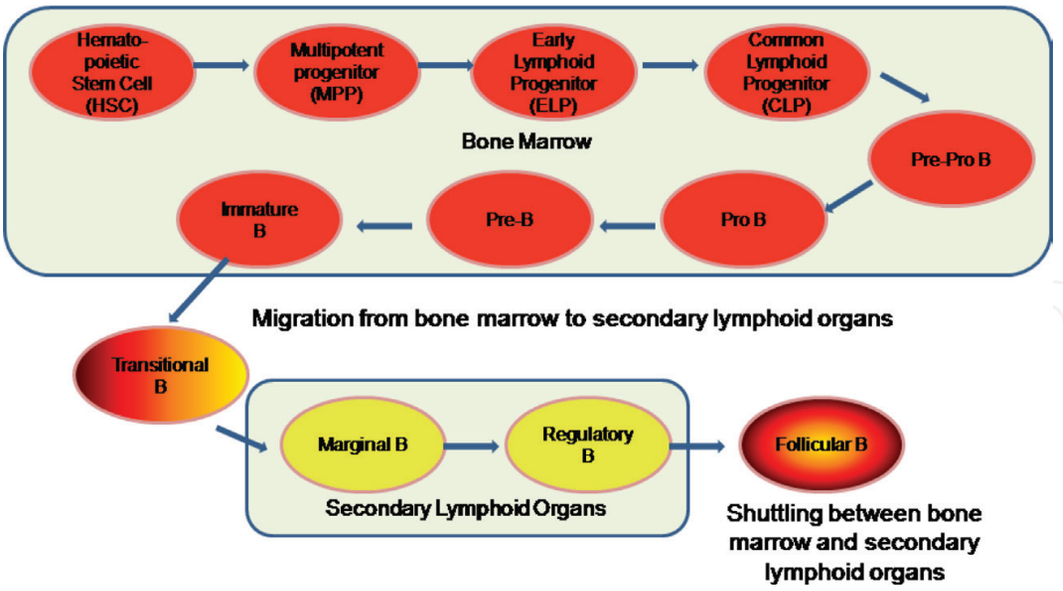

Figure 1. Major stages of B cell development.

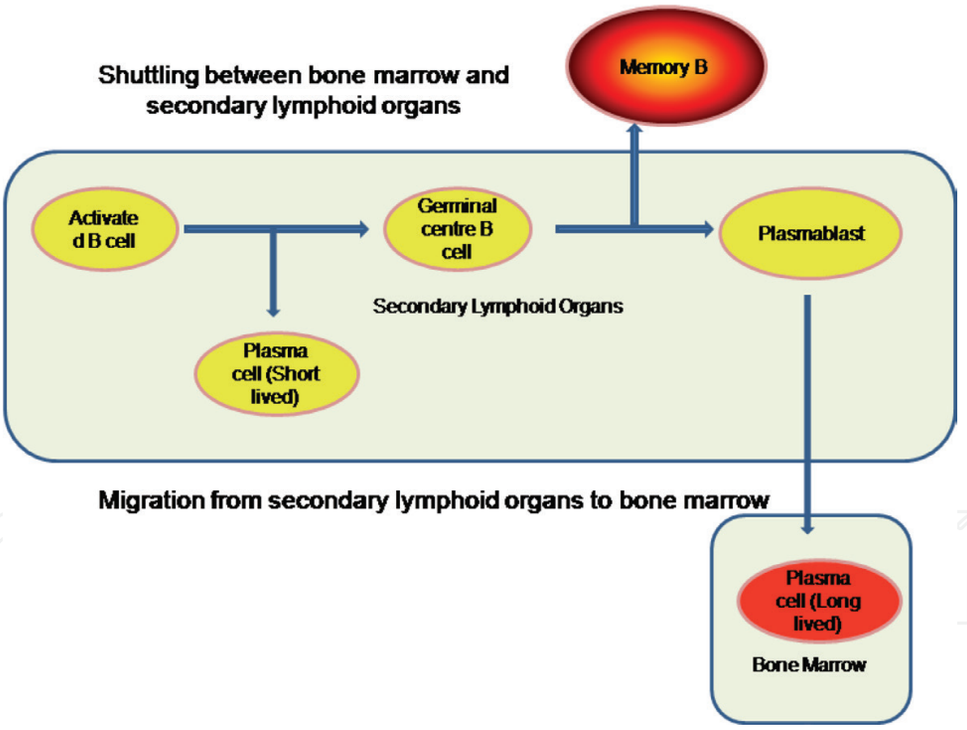

Figure 2. Major stages after activation of B cells.

memory B cells [23]. When the B cells undergo these changes in the GC, their transcriptional repertoire also undergoes huge transformation [24]. **Figure 2** shows the various stages that are developed after activation of B cells.

3. B cell subsets

In general, three subsets of B cells derive from naive B cells, B-1 B cells, follicular B cells and marginal zone (MZ) B cells. Furthermore, B-1B cells form two subsets, B-1a and B-1 b B cells [25]. All the subsets can be clearly identified on the basis of their surface markers. These surface markers can also be used to identify their progenitor populations. **Table 1** shows the various stages of B cell development and the most prominent cell surface markers that are used to identify them. Each one of these subsets maintains distinct location(s) and function(s). All these subsets of B cells produce functionally important antibodies. However, they vary in huge terms in reference to their origin and function [26–28].

3.1. B-1 B cells

B-1 B cells have not been successfully studied in mammals, including humans [29]. Thus, most of the findings are based on studies performed in mice. The most interesting finding from these studies is that although the progenitors of B-1 a and B-1 b cells are distinct, they are found to occupy the same locations, namely the pleural and peritoneal cavities. In addition, it has been observed that the environment offered by these cavities plays a significant role in

Developmental stage	Mouse cell surface marker		Human cell surface marker	
	Positive	Negative	Positive	Negative
Pre-Pro B	CD43, B220, Flt3, CD93, CXCR4, IL7R	CD19, cKit^{low}	CD34, CD38, CD10	cKit^{low}
Pro B	CD19, CD43, B220, IL7R	Flt3, ckit^{low}	CD19, CD34, CD38, CD10, CD24, IL7/3R	ckit^{low}
Pre B	CD19, B220, IL7R, CD24, Siglec-G	CD43^{low}, ckit	CD19, CD10, CD20, CD24, CD38, IL3/4/7R	CD34, ckit
Immature B	CD19, CD43, B220, CD24	CD43, CD23	CD19, CD10, CD20, CD21, CD40, IL4R, CD24^{high}, CD38^{high}	ckit, CD27, IL7R
Transitional B	B220, CD19, CD24, CD93, CD21^{var}, CD23^{var}		CD5, CD2`1, CD19, CD20, CD24^{high}, CD38^{high}	CD27, CD10^{low}
Marginal Zone B	B220, CD9, CD1d, CD21^{high}, CD35^{high}	CD93, CD23	CD19, CD20, CD1c, CD21^{high}, CD27^{var}	
Regulatory B	CD19, CD5, CD24, TIM, CD1d^{high}	CD62L, CD93^{var}	CD19, CD5, CD21, CD1d^{high}, CD24^{high}	CD27^{var}
Follicular B	B220, CD19, CD23, CD38, CD22	CD93, CD1d^{low}, CD21/35^{low}	CD19, CD20, CD21, CD24, CD23, CD22	CD27, CD10, CD24^{low}, CD38^{low}
Activated B	B220, Flt3, CD27, CD80, MHC II^{high}	CXCR4, CD138	CD19, CD20, CD27, CD25, CD69, CD30, CD135	
Germinal Center B	CD19, CD20, Siglec2, GL7, CD37	CD93, CD38^{low}	CD19, CD10, CD23, CD27, CD20, CD38^{high}	CD24^{low}
Plasmablast	CD138, CD19, MHC II, CXCR4	Flt3, B220^{low}	CD19, MHC II, CD269, CD38^{high}, CD27^{high}	CD138, CD20
Plasma cell (short lived)	CD138, CD93, CXCR4^{high}	CD19, B220^{low}, CD38^{low}, MHC II^{low}	CD138, CD269, CD27, CXCR4, CD38^{high}	CD20, CD19^{low}, MHC II^{low}
Plasma cell (long lived)	CD138, CXCR4^{high}	CD19, B220^{low}, CD38^{low}, MHC II	CD138, CD269, CD27, CXCR4, CD38^{high}	CD20, CD19^{low}, MHC II
Memory B	B220, CD38^{var}, CD80^{var}, CD62L^{var}, CD95^{low}		CD19, CD40, CD20, CXCR4/5/7, CD27^{var}	CD38, CD23^{low}

Table 1. Most prominent cell surface markers used to identify various stages of B cell development.

shaping the functional characteristics of these B cell subsets. The milieu of these cavities also influences the functional characteristics of B-2 cells that reside there, although in low numbers [30, 31].

3.2. Follicular B cells

Several studies have shown that the naive, mature peripheral follicular B cells reside in two main niches during their circulation/recirculation through the bone marrow. Out of these, the "follicular niche" present in the spleen/lymph nodes/Peyer's patches is the main site that is occupied by these cells. These "follicular sites" are thought to play important role in those immune responses against protein antigens, which are T cell-dependent [25].

In addition, some follicular B cells have also been reported to home in the bone marrow [32]. The site of their homing has been termed as "perisinusoidal niche" and consists of a part of population of the same circulating follicular B cells that are found in the secondary lymphoid organs mentioned earlier. Interestingly, the follicular B cells residing in the bone marrow are involved in T cell-independent immune responses against microbial pathogens harboured by blood [33].

3.3. Marginal zone (MZ) B cells

MZ B cells mainly home near the marginal sinus of the spleen. This process is facilitated by the molecules SIP 1 and SIP 3, which are receptors for sphingosine-1-phosphate [34–36]. These cells are mainly involved in T cell-independent immune responses against blood-borne microbes [34]. It has also been reported that these MZ B cells can transport pathogens from the marginal sinus to the splenic follicles, sites where the follicular B cells reside [21, 37]. Moreover, a few *in vitro* studies have shown that these MZ B cells might also be contributing towards T cell-dependent pathways of antigen recognition and subsequent immune responses. Some reports have demonstrated that they may have better capability than follicular B cells in context of activation of T cells [38, 39].

4. Contributions of various players towards B cell development and selection

4.1. Pathways involved in B cell maturation stages in bone marrow

As mentioned earlier, B cell development starts from haematopoietic stem cells (HSCs) in the bone marrow and continues either at the same site or in the peripheral sites. Two cellular pathways are believed to be involved in formation of mature B cells from T2-like cells, one in the bone marrow, and the other in the peripheral sites [25]. Thus, the population of mature B cells present in the bone marrow is heterogeneous in nature. It has been observed that one population of these cells is characterised by $sIgM^{high}$ IgD^{low} $CD23^{-}$, and do not respond either to BLγS/BAFF or multivalent antigens. In contrast, another population of these cells is $sIgM^{high}$

IgD^{high} $CD23^{+}$, and responds to both BLγS/BAFF and multivalent antigens [32, 40]. The exact mechanisms that are responsible for this differential developmental pathways and their significance is yet to be understood completely.

4.2. Pathways involved in B cell maturation at the peripheral tissues

Once immature B cells form, they generally migrate to the peripheral sites. These immature B cells have very short half-lives and on engagement with BCRs, they tend to undergo apoptosis instead of proliferation [41, 42]. The immature B cells are also referred to as "transitional B cells" and can be further subdivided into three subsets; T1, T2 and T3 [41, 43, 44]. CD93/AA4 (the B-lineage precursor marker) is expressed in all of these "transitional B cell" subsets. However, they display differential expression of IgM and CD23 on their surfaces that is exploited to identify them. T1 cells are characterised by IgM^{high} $CD23^{-}$, T2 cells by IgM^{high} $CD23^{+}$ and T3 cells by IgM^{low} $CD23^{-}$ [41]. All data till date suggest that T2-like cells give rise to mature B cells, either in the bone marrow or in the peripheral sites.

4.3. Tolerance and B cell development in peripheral sites

Tolerance to self-reactive antigens can take place by any of the existing three mechanisms: deletion, editing or anergy. In spite of significant number of studies addressing this aspect, it is not yet clear whether this tolerance is achieved by negative selection of self-reactive B cell clones or failure of positive selection. Several studies have suggested that local levels of BAFF may influence this decision [45, 46].

In humans, majority (around 55–75%) of immature B cells have been found to be self-reactive [47], indicating that clonal deletion may serve as one of the main mechanisms of elimination of these self-reactive cell populations. However, no such experimental data is available from mice. In addition, receptor editing has also been found to contribute towards elimination of such self-reactive immature B cells. The process of anergy, although a bit controversial, has emerged as the third mechanism involved in removal of self-reactive B cells [48].

4.4. Pathways involved in B cell maturation stages in the spleen

Spleen is the main site for positive selection of non-self reactive B cell clones. It has been reported that survival of the peripheral B cell populations is dependent upon continuous signalling through B Cell Receptor (BCR). It holds true for both populations, follicular B cells as well as marginal zone (MZ) B cells [49, 50]. Although a wide variety of V-gene segments are expressed by both follicular and MZ B cell populations, it has been observed that in IgH transgenic mice, those immature B cells that are specific for phosphorylcholine give rise to MZ B cells [51]. In another study, it has been observed that deletion of RAG2 in adult mice results in selective retention of MZ B cells over follicular B cells [52].

In addition to BCR, Notch2 signalling plays a significant role in MZ B cell development [53, 54]. Notch2 is a member of Notch family of receptors and ligands [55]. Interaction between Notch2 and DL1 has been found to be responsible for developing a unique MZB cell niche [54]. Moreover,

interaction of Notch2 with NF-κB pathway component p50 helps in maintaining MZ B cell pool, without affecting the pool of follicular B cells [56]. The NF-κB pathway may also work in synergy with the BAFF-BAFF-R pathway, both in context of survival of follicular B cells and generation of MZ B cells [57]. In addition, studies have indicated that BCR signalling and Notch2 signalling may work synergistically for development of MZ B cells [58].

5. Gene rearrangements during B lymphocyte development

The antibody responses demonstrated by the various subsets of B cells depend upon formation of the fully functional antibody having the required specificity. Each such fully functional antibody is constituted by two light chains (IgL) and two heavy chains (IgH). Each light chain, in turn, consists of variable (V), joining (J) and constant (C) domains. On the other hand, each heavy chain consists of variable (V), diversity (D), joining (J) and constant (C) domains. As mentioned earlier, mature B cells arise by stepwise development from Hematopoietic Stem Cells (HSCs). The genes encoding various domains of the heavy and light chains of the antibody also get progressively rearranged during these developmental phases [59, 60]. Finally, a specific group of genes encoding the various regions of the antibody get expressed [61, 62]. This remarkable process gives rise to the huge repertoire of antibodies, having infinite types of antigen specificities, from a limited pool of gene fragments encoding the various V(D)J domains. This process is known as V(D)J recombination, and is the hallmark of adaptive immunity [63]. The process of gene rearrangement begins in the heavy chain loci of the earliest progenitor cells that get fully committed to B cell lineage. Initially, μ gene rearrangement starts. If DH to JH recombination is successful, VH to DJH recombination follows. Formation of a productive μ gene on any one of the alleles results in expression of a functional immunoglobulin heavy chain μ (Igμ protein) on the cell surface and differentiation of the cell into precursor B cell (pre-B cell) [64, 65]. Once a successful recombination results in formation of a functional heavy chain, further rearrangements in remaining heavy chain loci cease. This newly formed functional heavy chain is stabilised by pairing with an invariant light chain. This heterodimer forms the pre-B-cell receptor (pre-BCR) in association with the signal transducing units, Igα and Igβ [66, 67]. In the next step, rearrangement in the immunoglobulin κ (Igκ) light chain gene locus begins for generating a successful recombination of its V and J fragments [68, 69]. This step of κ light chain gene rearrangement is stimulated by the newly formed Igμ heavy chain [70]. In case this rearrangement does not succeed, rearrangement begins in the immunoglobulin λ (Igλ) light chain gene locus for recombination of its V and J fragments to give rise to a functional λ light chain [71, 72]. If light chain gene rearrangement is successful, the light and heavy chains combine to form the functional IgM antibody molecule. This antibody is membrane bound and is expressed on surface of the B cell. Only those B cells which express a functional BCR as well as a functional IgM on their surface, progress to give rise to mature B cells.

The process of V(D)J recombination is never perfect. This imperfection allows development of diversity in the antibody structure. However, this imperfection also leads to formation of non-productive recombinations, which can be as high as two-thirds of the total number of recombinations. Several studies have shown that these non-productive rearrangements can be rescued by VH replacement [73–77]. Each of these gene segments is flanked by conserved sequences, known as Recombination Signal Sequences (RSS). The RSSs consist of a heptamer

(having the sequence CACTGTG) and a nonamer (having the sequence (GGTTTTTGT). They are separated by a spacer, which has a length of either 12- or 23-bp [78]. V(D)J recombination follows 12/23 rule. This rule refers to the fact that recombination is preferred between those gene segments that are flanked by RSSs of different spacer lengths. These RSSs are substrates for enzymatic activity of the products of recombination-activating genes (RAG-1 and RAG-2) [79–82]. This entire enzyme-substrate system is under tight regulation of systems that operate in tissue-specific and stage-specific manner. This ensures that they work in accordance with the lymphocyte developmental pathway [83].

6. Regulation of B lymphocyte developmental pathway: role of transcription factors and epigenetics

Transcription factors (TFs) play vital role during the entire process of B cell development and maturation from HSCs [84–86]. The entire process involves multiple changes both at the levels of transcriptional state as well as chromatin structure. They include at least four broad areas: (a) developing a localised chromatin state that will be favourable for gene activation through priming the enhancers in lineage-specific manner [87, 88]; (b) expressing TFs in lineage-specific manner [89]; (c) interaction between the various TF networks resulting in formation of extremely complex and fine-tuned regulatory networks that can activate various gene networks in lineage-specific manner [90]; and (d) activating TFs repression mechanisms to prevent development of alternative cell fates so that lineage-specific decisions and commitments do not get altered [91, 92].

During embryogenesis, three SOXF factors (SOX7, SOX17 and SOX18) play regulatory role in development of haematopoietic system [93]. Out of them, SOX17 is directly involved in the process of expansion of foetal HSCs [94]. A very recent study has shown that SOX7 promotes formation and proliferation of early blood progenitors; and blocks lineage commitment and formation of B lymphocytes [95].

The adult haematopoietic system is established by the coordinated functioning of three TFs, c-myb, acute myeloid leukaemia (AML)-1 and SCL-Tal [96]. Another TF MEF2C is present in very high levels in CLPs and B lymphocytes in the bone marrow [97]. Recently it has been reported that this TF protects B cell progenitors and helps in their survival by enhancing expression of the factors that are involved in DNA repair and recombination [98]. Arid3a and Arid3b, members of the ARID (AT-rich interaction domain) family of TFs, are required for B cell development. However, HSC development can take place independent of Arid3b [99]. Three main TFs, E2A [100–102], Ikaros [103, 104] and PU.1 [105, 106] specify B lineage commitments in the progenitor populations of HSCs and MPPs. As a result, LMPPs are generated from them. The effects of some of these TFs work in dose-dependent manner. For example, levels of the TF PU.1 in the MPPs determine whether they will progress towards myeloid or B lymphoid lineage [107–109]. EBF (early B-cell factor) 1 is a known TF that plays vital role in B cell differentiation. In CLPs, E2A has been shown to regulate expression of this TF [110, 111]. In turn, EBF-1 acts in coordination with the TFs E2A and Foxo1 to regulate expression of Pax5 gene, which plays extremely important role in B cell development [112].

Thus it seems that a regulatory network of several TFs determines and regulates lineage commitment in a recurrent manner [113]. Other significant contributors to this regulatory network include Gfi1 [114, 115], members of NF-κB family [116–118], members of interferon regulatory factors (IRF-4/Pip and IRF-8/ICSBP) [119], T-bet [120], E47 [121], Krüppel-like factor 3 (Klf3) [122] and Fli-1 [123].

Epigenetic control plays a vital role in the entire process of lineage commitment and downstream B cell development. Tet (10–11 translocation family) enzymes, known to oxidise 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), are important regulators of somatic cell differentiation. Recent studies have indicated that at least two Tet enzymes, Tet2 and Tet3 are involved in the process of tissue-specific methylation of DNA essential for B cell differentiation [124]. Other studies have indicated the role of high mobility group (HMG) proteins, in particular HMGN, in the process of activation of naive B cells. This group of proteins was reported to act on the chromatin regulatory sites of the resting B cells [125]. Interestingly, the role of various TFs in regulating chromatin accessibility is also being observed. For example, a very recent study on EBF-1 has revealed that its C-terminal domain (CTD) is essential for gaining access to those regions of the genome that are least co-occupied by other TFs. This allows those regions of untouched chromatin to become accessible for structural modulations, such as demethylation. Subsequently, changes leading to B cell fate take place [126]. Earlier studies had shown that Ebf-1 deficient cells get stalled at the point where B cell lineage commitment gets implemented [127, 128]. Gain- and loss-of-function studies on EBF-1 have also shown that this TF upregulates genes that promote B lineage commitment and downregulates those genes that lead to commitment towards non-B lineages [129, 130], thus further confirming the regulatory role played by this TF.

7. Conclusions

B lymphocytes are key players in the immune regulation system. Thus, any alteration in their development or functioning is manifested in the form of a diseased state. Complete understanding of the pathways and the underlying molecular mechanisms of B cell development/functioning is vital as it may lead towards generating new medical interventions. Although we are yet to obtain a clear understanding of the intricacies that govern development of a specific a B cell type, a huge number of studies have contributed towards getting a better picture. Further research is needed for gaining better insight into these processes.

Conflict of interest

None declared.

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Notes

My sincere apologies go to all those researchers who are doing pioneering work in this field too, but whom I have not been able to quote in my article due to space constraint.

Author details

Malavika Bhattacharya

Address all correspondence to: malavikab@gmail.com

Department of Biotechnology, Techno India University, Kolkata, West Bengal, India

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