# Paraproteinemia and Related Disorders

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*This book is dedicated to our beloved families,*

*Samia, Ahmed, and Sherif*

*Antonia Vernoni, Diego, and Rita*

*Hanaa, Mariam and Quinn, Farah and Chance*

# Foreword

This book is devoted to paraproteinemia, i.e., the appearance of high concentrations of normal or abnormal plasma proteins resulting from an underlying pathologic condition, and its ensuing clinical effects. For the first time, in one book, the reader will find comprehensive analyses of the pathophysiological mechanisms responsible for paraproteinemias and exhaustive descriptions of their consequences.

The first chapters are devoted to the basic aspects of the diseases, focusing on the mechanisms involved in normal and abnormal B-cell activation.

Because B cells are a critical component of the adaptive immune system and mediate the production of immunoglobulins that target pathogens, they have been considered the major actors of humoral immunity. Since the initial description of B-cell functions, 60 years ago, we have learned that the roles of B cells are much more complicated and cannot be simply summarized as the production of antibodies: B-cell subpopulations have been identified and their actions described, and the interactions between B and T cells have progressively become better understood. Over the last decades, drugs targeting B-cell subpopulations have also become available; they have notable clinical impact and help treat diseases arising from B-cell involvement.

Paraproteinemia is characterized by the overproduction of a monoclonal immunoglobulin by plasma cells. That excessive paraprotein synthesis results in paraproteinemia. An excellent chapter on animal models describes the production of paraproteins and the deposition of light chains or whole immunoglobulins in different organs, mainly the kidneys. The clinician will find information on how to diagnose paraproteinemia and analyze monoclonal gammopathy patterns, which could indicate possible outcomes.

Chapters in the second part of the book describe the diseases caused by monoclonal gammopathy. The exhaustive list of those diseases highlights the different clinical manifestations and evolutions of the various paraproteinemias. For some chapters, like those on amyloidosis, the pathogenic mechanisms, classification, and diagnosis are addressed separately from clinical description and management. The most recent drugs, like transthyretin-interfering agents to treat amyloidosis, are given and, in the future, such treatments could revolutionize patients' outcomes.

Multiple myeloma is certainly one of the key entities treated in this book. Monoclonal gammopathy of unknown significance is a premalignant disease, characterized by a low-level plasma monoclonal protein; it has no clinical manifestations during periods which can last for years. Because protein electrophoresis is widely requested by many clinicians in developed countries, peaks of monoclonal gammopathy are quite frequently discovered fortuitously, mainly in elderly patients. For most patients, the outcome is favorable, with no clinical manifestations of malignant disease. For a minority of patients, around 1%/year, these lymphoproliferative diseases can have visceral manifestations, like peripheral neuropathy.

For decades, cytotoxic drugs have been the standard treatment of monoclonal gammopathies. They are still prescribed extensively and are effective, at least transiently.

New drugs are now available and several chapters focus on clone-directed therapies and non-pharmacological interventions, like plasmapheresis for hyperviscosity syndrome. The clone-targeting approach is probably not yet the optimal treatment to cure diseases that are still considered incurable. However, they are a real positive therapeutic advancement, which has improved patients' outcomes and prolonged survival. Treatment of these diseases usually combines new drugs, for example, the 26S-proteasome inhibitor, bortezomib, or/and the anti-CD38 monoclonal antibody, isatuximab, and autologous stem-cell transplantation. Many other monoclonal antibodies, new chemotherapies, and perhaps chimeric antigen-receptor (CAR) T cells might find a place among the future therapeutic strategies for multiple myeloma or malignant lymphoproliferative diseases with paraproteinemia.

This book will be of major interest for many specialists—hematologists, nephrologists, internists, rheumatologists, neurologists, cardiologists—and all other physicians caring for patients with paraproteinemia, its consequences and underlying pathologies.

Académie Nationale de Médecine
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Loïc Guillevin

# Preface

Dear readers

We invite you to join our expedition to explore the amazing universe of the paraproteinemias. Our team of editors and authors gathered from around the globe. Representing four continents and nine countries: Canada, Egypt, France, Greece, Italy, Lebanon, Taiwan, the United Kingdom, and the United States, in alphabetical order, they volunteered and cooperated to bring this book to light. It is the first of its kind to deal with paraproteinemias as one group and in one tome.

Our team consists of world class experts and practitioners, both clinicians and researchers belonging to many disciplines. You are welcome to this exciting and hopefully fruitful journey throughout the chapters. Whether your discipline is Immunology, Rheumatology, Hematology, Oncology, Nephrology, Neurology, Cardiology, Internal Medicine or you are specialized in the field of Pathology, Radiology, Laboratory investigations, etc., we are confident that you will find interest in the content. It has been our objective to present our readers with the most comprehensive and updated knowledge on the topic.

Louis Pasteur (1822–1895) was quoted to have said "Science proceeds by successive answers to questions more and more subtle, coming nearer and nearer to the very essence of phenomenon." Our measure of success will be the degree to which we managed to incite more questions and to inspire more enthusiasm.

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# Part I
# Introductory Chapters

# Chapter 1
# The Phenomenon of Paraproteinemia


**Gaafar Ragab**

## Introduction

Paraproteinemia or dysproteinemia is characterized by the overproduction of an immunoglobulin by clonal expansion of cells from the B cells lineage which includes the plasma cells. The resultant monoclonal protein can be composed of the entire immunoglobulin or of its components [1]. The identification and categorization of the different representatives of this group of disorders have traveled a long distance. Amyloidosis, for example, which refers to a group of disorders in which protein fibrils accumulate in certain organs disrupting their tissue architecture and impairing the function of the affected organ [2] has for long been identified both clinically and pathologically. Other disease entities have a different history, for instance, the link of autoimmune pancreatitis with immunoglobulin G4 was only revealed in 2001 after a long series of observations [3]. We do not, however, understand the significance of their presence in other disease entities such as infections and autoimmune diseases [4, 5]. It is interesting that paleopathologists described cases of multiple myelomatosis (MM) in their excavations in the Old World, which they dated back to the Middle Ages, whereas in the New World, skeletons showing MM could be traced back to the pre-Columbian era [6].

MM is the second most common blood cancer [7], and the neuropathies associated with plasma cell dyscrasias are a major cause of morbidity for patients managed by medical oncologists [8].

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A population-based study from Minnesota showed that in individuals aged >50 years, the overall incidence of paraproteins is 3.2% and could be as high as 5.3% for those >70 years [9]. Paraproteins are therefore a common laboratory finding in an elderly population [10].

Recent advances have been introduced in the diagnosis, risk stratifications, and management of many members of this group of illnesses. The diagnostic list of investigations now includes serum protein electrophoresis, immunofixation, immunoglobulin quantification, serum-free light and heavy-light chain arrays, MALDI-TOF mass spectrometric methods, molecular technologies such as fluorescence in situ hybridization and next-generation sequencing, liquid biopsies, and novel immune biomarkers [11–13]. Novel agents (proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, etc.) and autologous stem cell transplantation have improved the outcome for many patients [1, 2]. These new scientific departures are paving the way to progress in two directions, the first is the expansion of personalized treatment that provides maximum benefit to a specific patient [12]; and the second is the growing tendency towards standardization and networking [14, 15].

To better understand the nature, significance, and characteristics of paraproteinemia, we need to group, classify, and describe its representatives.

## Approaching Paraproteinemia

Paraproteinemia is a phenomenon encountered in many diseases and disorders, and it may be detected in apparently healthy individuals, particularly the elderly [9, 10].

Why to group all this in one book and how to introduce them to the reader was our main concern? Exact and precise use of words is needed to describe clear and distinct ideas, and we need our ideas to be conceived very clearly and very distinctly. That is the lesson we learnt from Décartes [1596–1650], the father of modern philosophy [16, 17]. This entails resorting to semantics, the study of the meaning of words, phrases, or systems [18].

Let us now start with a proper description of the words used in this context.

## Definitions

In science, we use definitions for a clear and distinct description. Definition is derived from Latin; it is the act of defining an exact description of a thing by its qualities and circumstances or an expression which explains a term so as to distinguish it from everything else [19].

## Phenomenon

The Austrian-born German philosopher Edmund Husserl [1859–1938] stated that nothing is known to us except as a condition or a state of consciousness, as a phenomenon [20]. Philosophers and scientists used the term "phenomena" to refer to what appears from nature since some natural events may be unobservable. Following his lead, phenomenologists advised taking a fresh approach, as free as possible from previous presuppositions. They also advised describing a phenomenon as faithfully, or precisely, as possible to attain. They held that we could obtain insights into the essential structures and relationships of these phenomena on the basis of a careful study of concrete examples [21].

## Proteins, Paraproteins, and Paraproteinemias

Protein form the functional pattern of animal organisms and all the properties which mark animal organisms as organized units result from their protein constitution [22].

Stedman's Medical Dictionary in 1973, "defines" a paraprotein as an abnormal plasma protein, such as macroglobulin, cryoglobulin and myeloma protein, and paraproteinemia as the presence of abnormal protein in the blood [23]. The word begins with the prefix "para" denoting a departure from normal [23]. It also means "by" or "at the side of" [24].

The expanding knowledge in the field of immunology in general and of the B-lymphocyte line in particular directed the listing of a number of conditions including MM, Waldenstrom macroglobulinemia, primary amyloidosis, and the heavy chain disease in one group. They were given nomenclatures that are used synonymously: monoclonal gammopathy, paraproteinemia, plasma cell dyscrasias, and dysproteinemias [25]. Analysis of these nomenclatures reveals that they point to an abnormality or a disturbance in the proteins or their cell of origin.

## Disease and Disorder

The Oxford Advanced Learner's Dictionary defines disease as a medical problem or an illness affecting humans, animals, or plants, often caused by infection. Among the synonyms used for a medical problem, a disorder, which is rather formal and used to describe an illness that causes a part of the body to stop functioning correctly and is generally not an infection. When used to relate to physical problems, it is most often used with blood, bowel, and kidney which are commonly serious, severe, or rare. Normality and abnormality, however, cannot be fully explained by

statistical considerations. According to the statistical approach, normality is defined as that which is common, ignoring the fact that sometimes disease is common, and health is rare. Remember how malnutrition can be common for children in many parts of the world. Keeping all this in mind we need to appreciate that paraproteinemia or monoclonal gammopathy may be a common finding [4].

One school of thought considers illness as a deviation from normal biological functioning. Normal functioning does not refer to the common but to what a biological organism needs to thrive, reproduce, and sustain life [26].

We must have noticed that these terms are used broadly in different contexts.

## The Nature of the Problem

Earlier on, we discussed the importance of a precise choice of words. As we proceed to address the problem of how to present the phenomenon and its representatives, we have to answer some questions as follows:

- How should we group all the conditions associated with the presence of paraproteins?
  There were attempts by other investigators and experts to group these disorders on a smaller scale.

  Kanzaki and his group [27] recommended that the group of renal diseases attributed to deposition of monoclonal immunoglobulins or their components are arranged as one disease category in order to simplify the understanding of these complicated diseases in plasma cell dysplasia. The group led by Merlini introduced the concept of monoclonal gammopathies of clinical significance (MGCS). They identified their spectrum and classified them based on the mechanisms by which they cause tissue injury [4]. In emulation of this practical approach, we attempt to encompass the whole spectrum of the paraproteinemias in our textbook. This will have the dual benefit of offering the reader a panoramic view of this group of disorders and simultaneously keeping him/her focused on its individual representatives.

  Let us address some possible questions that are likely to arise in this context.
- How do paraproteins evolve and persist in the body and how can we imitate or reproduce this experimentally?
  This entails a review of the B lymphocyte line, as the cell of origin, the immunoglobulins as the protein molecules in question and the bone marrow, as the hotbed for their production. The Principle of the Uniformity of Nature tells us that similar phenomena occur when structurally similar systems are placed in similar situations. It is noteworthy that we are talking of similar and not identical systems [28]. Experimental animal models will also deserve an account as indispensable tools for research.
- When should the medical practitioner or the investigator suspect the presence of paraproteins when dealing with patients, samples, or images? How to detect them and report their findings?

– Since the phenomenon of paraproteinemia is not rare and may pass undetected with unfavorable consequences [4], physicians should be given clues for its early detection and once identified, the available diagnostic modalities should be employed meticulously.
– How to deal with the disorders in terms of understanding, diagnosis, and management?
  Medical science organizes all the knowledge and experience assembled by the careful study of individual patients and transmits it in a concise form through the publication of textbooks. Each disease or disorder is usually given an individual chapter the title of which is the disease name [26]. The conditions which are taking the established shape are better discussed as usual. Other conditions and associations still in the process of acquiring shape should be covered with our up-to-date knowledge based on observations and reports.
– What are the future prospects for therapy?
  As the field is experiencing an expanding horizon, there will be a need for a glimpse of the ongoing research for improving the therapeutic outcome of this group.

Indeed, answering the above four queries mandates the structure and organization of this text.

## The Structure of this Book

We preferred to use the term paraproteinemias for the book title as it describes a specific phenomenon which is the presence of certain proteins in the blood beside the normal proteins. It may be present in normal healthy people, especially the elderly [9, 10]. In certain other well-studied conditions, paraproteinemia is the focal point of attention as in MM since here they account for the pathophysiology, explain the manifestations, and stand as therapeutic targets. We can identify a third group in which the existence of paraproteins is not the center of attention. In the last group, they may represent an epiphenomenon, a transient finding, or a process in evolution. We also preferred disorders as it is more inclusive. Furthermore, blood is the "central stage" of this phenomenon.

This book is divided into three main parts:

**Part I:**

The introductory part which begins with this chapter deals with the origins of the paraproteins, their structure, and methods of diagnosis.

Chapter 2 describes the B cell lineage, being the cells that produce the paraprotein. Chapter 3 describes the structure and characteristics of immunoglobulins of which the paraproteins, or their fragments are constituted.

Chapter 4 discusses the bone marrow, the hotbed where plasma cells are actively producing paraproteins and also the importance of the matrix, the player that has recently attracted the attention of many researchers.

Chapter 5 deals with the experimental animal models of paraproteinemia with their central importance for understanding its pathophysiology and their significance as an indispensable tool for therapeutic innovations.

Chapter 6 is meant to raise the attention of medical practitioners and direct them to suspect the presence of that phenomenon and to guide their investigative procedures.

**Part II:**

This part includes Chaps. 7 through 21. It deals with the medical disorders associated with paraproteinemias. It starts with the conditions that have been studied and given the classical account. The list includes several conditions that have been given syndrome entities.

Usually, a chapter is structured as such: definition, causes (etiology and pathogenesis), clinical picture, prognosis, diagnosis, and treatment [26]. We followed this structure whenever possible, but to ensure the balance, the topic of AA amyloidosis is discussed in two successive Chaps. 7 and 8.

Chapters 17 through 20 discuss groups of diseases or disorders that are marked or associated with the existence of paraproteins. We tried to grasp the common features of the phenomenon in each group or class and simultaneously describe the distinctive features or characteristics of its representatives in each entity.

Chapter 18 which deals with infections as potentially causing paraproteinemias also serves as a practical guide to manage infections in the setting of paraproteinemias.

Chapter 21 is dedicated to reporting on a number of miscellaneous conditions and illnesses. We anticipate that some entities in this group will be further studied and elucidated in the future. We also expect the list to be continuously expanding with the discovery and reporting of new members that are likely to be added to our database.

**Part III:**

Finally, the last two Chaps. 22 and 23 are intended to offer a futuristic outlook on the new departures in the management of some representative diseases and disorders. We present a snapshot of experimental therapies (pharmacological and non-pharmacological) to highlight the current efforts of researchers in their endeavor to find new solutions and fill in many gaps.

## Conclusion

Paraproteinemia is a phenomenon that medical practitioners, investigators, and researchers encounter in their practice. Recent advances have been introduced in the diagnostic investigations, risk stratifications, and management of many members of this group with significantly improved outcomes for patients.

For a better understanding of the nature, significance, and characteristics of paraproteinemias, we need to group, classify, and describe its representatives.

This chapter describes the ethos and design of our textbook while adhering to a precise and exact use of terms and definitions.

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# Chapter 2
# B Cell in Health and Disease


**Marcella Visentini and Stefania Colantuono**

## Abbreviations

| | |
|---|---|
| BCR | B-cell receptor |
| BM | Bone marrow |
| BNHL | B-cell non-Hodgkin lymphomas |
| BTK | Bruton's tyrosine kinase |
| CD21 | Complemenr receptor 2 |
| CSR | Class switch recombination |
| CVID | Common variable immune deficiency |
| DLBCL | Diffuse large B-cell lymphoma |
| FO | Follicular |
| GC | Germinal center |
| HC | Heavy chain |
| HSC | Hematopoietic stem cells |
| Ig | Immunoglobulin |
| LC | Light chain |
| MS | Multiple sclerosis |
| MZ | Marginal zone |
| PC | Plasma cells |

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| RA | Rheumatoid arthritis |
| SHM | Somatic hypermutation |
| SLE | Systemic lupus erythematosus |
| TLR | Toll-like receptor |
| XLA | X-linked agammaglobulinemia |

## Introduction

B cells are at the center of the adaptive humoral immune system and are responsible for mediating the production of antigen-specific immunoglobulin (Ig) directed against invasive pathogens. For a long time, humoral immunity has been considered pretty simple but in the last decades great effort in the field of B-cell biology revealed the complicated cellular and molecular pathways regulating the many B-cell functions, opening the way to still numerous major challenges that remain to be elucidated. Since the identification of B cells by Cooper in 1965, there has been tremendous progress in our understanding of B-cell development, maturation, and function and today different B cell subsets with specific functions have been identified [1]. B cells are not only responsible for antibody production but are also efficient antigen-presenting cells for CD4+ T cells stimulation and produce cytokines, notably interleukin (IL) 4, IL-6, IL-10, and tumor necrosis factor α, which have regulatory effects. Furthermore, B cells, pivotal actors of the adaptive immune response, also show innate-like features through the production of polyreactive IgM natural antibodies that bridge the innate and adaptive immune responses. These many B-cell activities are appropriately coordinated and tightly regulated and guarantee an efficient immune response. However, these same mechanisms underlying the complexity and integrity of B-cell immune response are tremendously error-prone and subject to repeated controls explaining the possible development of diseases characterized by B-cell dysfunction: (a) loss of B-cell tolerance results in autoimmunity with self-reacting B-cell clones able to produce autoantibodies; (b) loss of B cells, reduction or absence of serum Ig and/or loss of antibody function results in B-cell immunodeficiencies; (c) genetic lesion during B-cell development and activation results in malignant transformation of the B cell at a particular stage of differentiation raising the concept of "cell of origin" of a lymphoma (Fig. 2.1).

In this chapter, physiological B-cell development is described and a focus on the pathogenic mechanisms underlying the development of autoimmune diseases, immunodeficiencies, and B-cell lymphoproliferative disorders is provided.

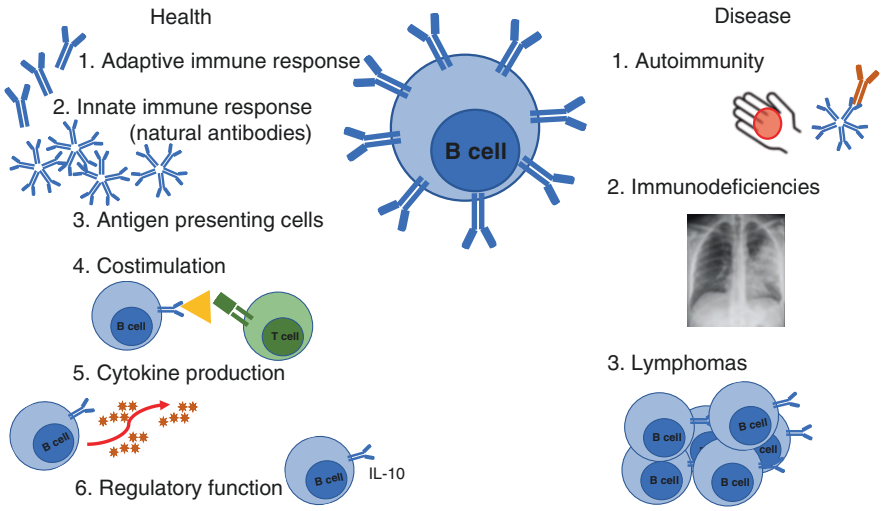


**Fig. 2.1** B cells in health and disease. B cells *in health* have different multifaceted roles that allow an efficient immune response. They are part of the adaptive immune system and responsible for its humoral arm through the production of a broad repertoire of antigen-specific antibodies. Marginal zone B cells are able to produce poly-reactive IgM natural antibodies that rapidly respond to blood-borne pathogens, bridging the innate and adaptive immune responses. Beside the well-known role in humoral immunity, B cells are efficient antigen-presenting cells for CD4+ T cells co-stimulation and produce different cytokines. The secretion of IL-10 and transforming growth factor β(TGFβ), that dampen T-cell-driven immune responses, gave rise to the concept of regulatory B cells that have an important role in maintaining peripheral tolerance. In *disease* defects in the mechanisms regulating these many physiological functions of B cells may be at the basis for its development. Loss of B-cell tolerance results in autoimmunity with self-reacting B cell clones able to produce autoantibodies. Loss of B cells, reduction or absence of serum Ig, and/or loss of antibody function results in B-cell immunodeficiencies, and a genetic lesion during B-cell development and activation results in malignant transformation giving rise to B-cell lymphoma development

## B-Cell Development

B-cell development proceeds in an orderly fashion and is regulated by intrinsic genetic programs and by external cues such as cytokines, present in the specialized microenvironments of fetal liver, bone marrow (BM), and secondary lymphoid organs. In general, B-cell development can be subdivided into antigen independent, occurring in the BM, and antigen-dependent developing in the secondary lymphoid organs [2]. Each differentiation step is characterized by a specific structure of the B-cell receptor (BCR) and defects in each stage of the B-cell development and maturation pathways can lead to primary immunodeficiencies, autoimmune diseases, and even B-cell malignancies.

The major stages of B–cell development in the BM include the hematopoietic stem cells (HSC), the multipotent progenitor, the common lymphoid progenitor, the progenitor B cell (pro-B cell), the precursor B cell (pre-B cell), and finally the immature B cell [3].

One intriguing feature of B-cell development is that it is accompanied by Ig gene rearrangements [4]. Progenitor B cells rearrange their Ig heavy chain (HC) genes to differentiate into precursor B (pre-B) cells that express μ HCs. Pre-B cells then rearrange their Ig light chain (LC) genes to differentiate into immature $IgM^+$ B lymphocytes. Lack of a functional surrogate light chain acts as one of the first tolerance checkpoints and those cells carrying receptors with excessive high affinity for self-antigens undergo receptor editing to change the light chains. B cells that express a functional (and non-autoreactive) BCR exit the BM as transitional B cells [5] and differentiate into mature $IgM^+IgD^+$, naive B cells that will later further differentiate into a follicular (FO) B cell or marginal zone (MZ) B cell [6].

The initiation of the second phase, antigen-dependent development of B cells for an efficient humoral immune response, requires that mature, naive B cells get activated by antigen binding to the BCR. In T-cell-dependent immune responses, antigen-activated B cells undergo clonal expansion in structures called "germinal centers" (GCs) and their affinity to antigens is increased. These encounters predominantly occur in secondary (or peripheral) lymphoid tissues, including the spleen, lymph nodes, and Peyer's patches [7–9].

Upon binding antigen, signaling via the BCR initiates B-cell activation. The actual mechanism by which antigen binding activates the BCR remains an area of active investigation. One model proposes that antigen binding leads to clustering of BCRs on the membrane to initiate signaling [10]. Conversely, an alternative model is that BCR clusters preexist before antigen encounter, and antigen binding dissociates these clusters enabling signaling to occur [11]. A third variant of these models suggests that the mobility of the BCR, relative to co-receptor molecules, may be altered by antigen binding.

Complex antigens engage other receptors on the B cell in addition to the BCR. The ligation of some co-receptors, such as toll-like receptors (TLRs) or complement receptors 2 (CR2), leads to amplification and possibly qualitative modification in the BCR signaling [12, 13].

Upon encounter with an antigen, naive B cells become activated by the interaction with CD4+ T cells in the T-cell-rich area of the lymphoid tissues and aggregate into primary follicles to form GCs. In the GC, B cells are targeted by Ig gene remodeling processes, namely somatic hypermutation (SHM) and class switch recombination (CSR), in order to generate cells with the ability to produce high-affinity antibodies of different isotype classes. The GC structure consists of a dark zone, which almost exclusively contains highly proliferating B cells and a light zone in which B cells are intermingled with follicular dendritic cells, T cells, and macrophages. The dark zone is the site of B-cell division and SHM, whereas the light zone is where B cells undergo activation and selection on the basis of the affinity of their B-cell receptors [14]. Ongoing B-T interactions are critical for the maintenance of GCs. As B cells terminally differentiate into plasma cells, they initially continue

proliferating and are referred to as plasmablasts [15]. Once these cells cease dividing and fully mature, they become plasma cells (PCs). The factors that determine whether a B cell undergoes PC differentiation, becomes a GC B cell, or a memory B cell are being actively investigated. These differentiation states are influenced by a variety of signals, such as those from the BCR, co-receptors, and cytokines. PC development is tightly regulated by a panoply of transcription factors, most notably Bcl-6 and BLIMP-1. B cells with higher affinity for antigens give rise to a stronger PC response than B cells responding with lower affinity, and this reflects the strength of the plasmablast proliferative response [16].

Another factor that might influence the propensity to become a PC versus a GC cell is the chronic exposure to low avidity autoantigens. B cells exposed to such antigens show a downregulated expression of IgM and are in an "anergic" state, poorly responsive in vitro to antigen stimulation. However, when exposed to a cross-reactive multivalent antigen and T cell help, such anergic B cells preferentially enter the GC response where they undergo somatic hypermutation to mutate away from self-reactivity and develop increased ability to bind the foreign antigen in a process referred to as clonal redemption [17, 18]. The PCs arising in the early phases of B-cell responses, independently of GCs, typically remain within the peripheral lymphoid tissue and are short-lived PCs (SLPCs). In contrast, GCs give rise to long-lived plasma cells, many of which have a BM tropism and can live for months (Chap. 4).

In B-cell responses, memory may be maintained in two forms, first through the long-term production of antibody by long-lived plasma cells, and second by the generation of a pool of relatively quiescent memory B cells expressing mutated BCRs with enhanced affinities, persisting after antigen challenge and that can be reactivated by subsequent antigen exposures.

Upon re-exposure to antigen, memory B cells can differentiate into GC B cells or PCs, and specific subsets of IgM versus IgG memory B cells, defined by surface markers such as CD73, CD80, and PDL2, show different propensities to undergo particular differentiation programs. GC B cells are thought to give rise to a large fraction of the B-cell memory pool, yet GC-independent memory B cells have also been described to appear very early in the immune response [19, 20].

## B Cells and Autoimmunity

B cells play a key role in regulating the immune system by producing antibodies, acting as antigen-presenting cells, providing support to other mononuclear cells, and contributing directly to inflammatory pathways. Accumulating evidence points to disruption of these tightly regulated processes in the pathogenesis of autoimmune disorders. Although the exact mechanisms involved remain to be elucidated, a fundamental feature of many autoimmune disorders is the loss of B-cell tolerance and the inappropriate production of autoantibodies. Furthermore, B cells may contribute to autoimmune pathogenesis by presentation of autoantigen to T cells, or through production of proinflammatory cytokines.

These findings provide the rationale for B-cell depletion as a potential therapeutic strategy in autoimmune disorders and other disease states characterized by inappropriate immune responses [21, 22]. B-cell-targeted therapy focused on restoring normal B-cell function and eliminating pathogenic autoantibodies have been successful in treating rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and multiple sclerosis (MS).

A major pathway for immune activation and tissue damage for systemic autoantibodies is through formation of immune complexes that induce complement activation by both classical and alternative pathways and can lead to direct cell lysis and damage as well as recruitment of leukocytes to further enhance inflammatory responses. Immune complexes can activate Fc receptors that are expressed by a variety of cells, particularly by immune cells of the myeloid lineage. Autoantibodies have been shown to activate these immune cells through FcγR-dependent pathways or through direct modulation of signaling receptors on target cells [23].

Multiple self-tolerance checkpoints exist to remove autoreactive specificities from the B-cell repertoire or to limit the ability of such cells to secrete autoantigen-binding antibodies. These include receptor editing and deletion of immature B cells developing in the BM, competitive elimination of chronically autoantigen-binding B cells in the periphery, and a state of anergy that disfavors PC differentiation [24, 25]. Autoantibody production can occur due to failures in these checkpoints or in T-cell self-tolerance mechanisms.

However, despite this undisputed involvement of B cells, little is known about B-cell subpopulations with distinct immune functions that may play a role in the spectrum of autoimmunity. One distinct subset that is implicated in the autoreactive B-cell response are the innate-like MZ B cells.

In contrast to FO B cells, which primarily express mono-reactive BCRs and give rise to highly specific, high-affinity antibodies, the innate-like MZ B cells express poly-reactive BCRs and rapidly produce low affinity antibodies with self-reactivity to clear pathogens and apoptotic cell debris [26]. MZ B cells are strategically located at the interface between the circulation and the white pulp of the spleen, where they provide a first line of defense by rapidly producing IgM and class-switched IgG antibodies in response to infections by blood-borne viruses and encapsulated bacteria. MZ B cells have a lower activation threshold than follicular B cells, which permits the rapid initiation of IgM production and of IgG- and IgA-inducing (CSR) in the absence of CD40-dependent help from T follicular helper cells. This T-cell-independent pathway requires dual BCR and TLR engagement by conserved microbial antigens together with co-stimulatory signals from dendritic cells, macrophages, and neutrophils via various cytokines, including BAFF, a proliferation-inducing ligand (APRIL), interleukin-6 (IL-6), IL-10, IL-21, interferon-α (IFNα), IFNβ, and CXC-chemokine ligand 10 (CXCL10).

MZ B cells share the feature of being "innate-like," meaning they exist in a "pre-activated" state and differentiate into antibody-secreting cells very rapidly (within 1–2 days) following antigen encounter. They have a B-cell repertoire enriched with specificities that recognize carbohydrate and lipid moieties present on various life-threatening microbes [27].

Unlike their murine counterpart, human MZ B cells carry mutated BCRs [28]. It was recently suggested that they complete their maturation not in the spleen, but rather in gut-associated lymphoid tissue [29]. Here they can interact with gut bacteria, mutate, and then be selected for (self-/) poly-reactive-binding abilities before circulating back to the spleen. Thus, the microbiota may play a crucial role in shaping the MZ B-cell compartment in humans. This may be one of the mechanisms whereby the microbiome, influenced both by genetics and diet, can play a significant role in the pathogenesis of several autoimmune conditions, for example, SLE, systemic sclerosis, and RA [30].

Another important feature of MZ B cells and other innate-like B cells is the production of natural antibodies [31, 32]. Natural antibodies can be produced in germ-free contexts although their composition is shaped by the microbiota. Natural antibody provides a first line of defense against a range of pathogens and, through opsonization, augments the follicular B-cell response. In general, natural antibodies are characterized by their low affinity, high avidity, and broad/multi-reactivity against self-antigens, but some have the ability to recognize evolutionarily conserved epitopes occurring in foreign antigens. A subset of B cells in mice, named B-1 cells, was recognized as the main source of natural antibodies. B-1 cells are found in various tissues of adult mice, including the peritoneal cavity, pleural cavity, spleen, bone marrow, lymph nodes, and blood and are considered an innate like B-cell population. In humans B1 B cells have not been identified and the main producers of natural antibodies are MZ B cells. Natural antibodies have a key role in the first defense against bloodborne pathogens but also in maintaining the immune homeostasis through the clearance of apoptotic cells and regulation of inflammatory, autoimmune, and allergic responses. Interestingly, natural antibodies seem to have potential functions in the pathogenesis and progression of other chronic inflammatory condition, such as atherosclerosis. It was demonstrated that oxidation-derived epitopes on apoptotic cells and oxidized low-density lipoproteins are recognized by the phosphorylcholine-specific natural antibody that seem to play a protective role in atherosclerosis [33].

Another recently identified B-cell population with a possible role in autoimmune and chronic infectious diseases is a subset of B cells characterized by low expression of the complement receptor 2 (CD21), the so-called $CD21^{low}$ B cells. These B cells have been found expanded also in aged female mice, have an increased expression of the transcription factor T-bet and of CD11c, and were named ABCs (aged B cells) or $T\text{-}bet^{+}CD11^{+}$ B cells. Their formation and expansion rely on TLR7 or TLR9 signals in the context of Th1 cytokines [34]. $CD21^{low}$ B cells are enriched in the peripheral blood of patients with pathogenic infections (malaria, tuberculosis, HIV) as well as in several autoimmune conditions including SLE, RA, common variable immunodeficiency, primary Sjögren's syndrome, hepatitis C virus-associated mixed cryoglobulinemia [35, 36], and MS, but their role in disease development or progression remains elusive. Functionally, this memory subset demonstrated altered responsiveness to stimuli compared to conventional memory B cells, express low or no CD27, and are therefore atypical memory B cells with features of innate-like B cells. It is possible that chronic BCR stimulation due to exposure to self-antigens