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# CD19 structure, expression, and signaling: From basic mechanisms to therapeutic targeting

Stéphane Schurmans [a,*], Bastien Moës [a,b]

[a] Laboratory of Functional Genetics, GIGA Institute, University of Liège, Avenue de l'Hôpital 11, 4000-Liège, Belgium
[b] Laboratory of Immunophysiology, GIGA Institute, University of Liège, Avenue de l'Hôpital 11, 4000-Liège, Belgium

A B S T R A C T

CD19 is a central regulator of B-cell biology, acting both as a lineage marker and a critical modulator of signaling thresholds that govern development, activation, and tolerance. Structurally, CD19 is a heavily glycosylated transmembrane protein whose cytoplasmic domain harbors multiple tyrosine motifs serving as docking sites for key signaling molecules, including PI3K. Its expression is tightly regulated by transcriptional, post-transcriptional, and post-translational mechanisms, as well as by interactions with CD21 and CD81 in surface complexes. Genetic studies in mice and humans demonstrate that CD19 acts as a molecular rheostat, with both deficiency and overexpression leading to profound immunological dysfunctions ranging from hypogammaglobulinemia to autoimmunity. Importantly, recent work has revealed an additional level of CD19 signaling regulation mediated by conformational control of the CD19 cytoplasmic domain. A basic CD19 cytoplasmic juxtamembrane region engages in ionic interactions with PtdIns(4,5)P2, thereby influencing CD19 activation state. Loss of the 5-phosphatase INPP5K increases PtdIns(4,5)P2 levels, leading to constitutive CD19 signaling, impaired B-cell development and hypogammaglobulinemia. This discovery underscores the role of lipid–protein interactions in restraining inappropriate CD19 activation. Clinically, CD19 has emerged as a validated therapeutic target, with CAR T cells, bispecific antibodies, and monoclonal antibodies achieving remarkable efficacy in B-cell malignancies and autoimmune disorders. Understanding the fine regulation of CD19 expression, structure, and signaling remains essential to optimize therapeutic strategies.

## 1. Introduction

CD19 is a transmembrane glycoprotein that functions as a central regulator of B-cell biology, integrating signals that shape development, activation, and tolerance. Expressed from the early pro-B (Fr.B) to mature stages but absent in plasma cells, CD19 amplifies signaling through its cytoplasmic tyrosine motifs and interactions within the $CD19^{-}CD21^{-}CD81$ complex. Genetic and structural studies have established CD19 as a molecular rheostat, with both deficiency and overexpression leading to immunodeficiency or autoimmunity. Beyond its physiological role, CD19 has emerged as a key therapeutic target, revolutionizing the treatment of B-cell malignancies and offering new opportunities in autoimmune disease management.

### *1.1. The human CD19 gene, transcripts and protein*

Official full name/symbol and synonyms.

The official name of the human gene is *CD19*, and its approved symbol is CD19. This gene is registered under the HUGO Gene Nomenclature Committee (HGNC ID: 1633), NCBI Gene (ID: 930) and Ensembl (ID: ENSG00000177455). CD19 is also known by several synonyms that have appeared in the literature, including B4 (from the first monoclonal anti-CD19 antibody), CVID3 (when

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* Corresponding author.
*E-mail address:* sschurmans@uliege.be (S. Schurmans).

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referring to disease-associated mutations causing Common Variable ImmunoDeficiency type 3), and MGC12802.

### 1.1.1. CD19 gene and transcripts

The history of the *CD19* gene unfolded in three stages: first, the discovery of the CD19 protein as a surface antigen, then the cloning and characterization of the cDNA, and finally the identification of the gene. In the 1980s, various laboratories were searching for specific markers for the B lymphocytes lineage. Monoclonal antibodies (such as B4 or the HD37 antibodies) made it possible to identify a membrane glycoprotein specific to B cells, which would later be designated CD19 at the 1st International Workshop on Clusters of Differentiation (Paris, 1982). The cloning of the human CD19 cDNA and the identification of the gene were published by Tedder's laboratory (Tedder and Isaacs, 1989; Zhou et al., 1992). The human *CD19* gene is located on the short arm of chromosome 16, at 16p11.2, and maps to 28,943,286–28,950,663 in GRCh37 coordinates. The gene contains 15 exons and the proximal *CD19* promoter lacks a TATA box. Two mRNA transcripts are usually described; both have an unusually short 5′-untranslated region.

### 1.1.2. CD19 protein structure

The canonical CD19 protein of 556 amino acids (AA) (NP_001761.2) is the most studied, compared to the 557 AA variant protein. CD19 is a 95 kDa heavily glycosylated type I transmembrane protein composed of a signal peptide (AA 1–20), an extracellular N-terminus domain (AA 21–294), a single hydrophobic transmembrane domain (AA 295–317) and a long cytoplasmic C-terminus domain (AA 318–556). The extracellular domain contains two C2-type immunoglobulin-like domains. However, structure analysis indicates that, rather than a tandem of C2-type Ig folds predicted from the AA sequence, the CD19 extracellular domain exhibits an elongated β-sandwich formed by two Ig folds by swapping their C-terminal halves (Teplyakov et al., 2018). Five important N-linked carbohydrate sites ($N^{86}$, $N^{125}$, $N^{138}$, $N^{181}$ and $N^{265}$) have been identified in this domain (Billerhart et al., 2023; Teplyakov et al., 2018). CD19 glycosylation plays important roles for CD19 cell surface expression, $CD19^{-}CD21^{-}$CD81 complex formation, CD19 signaling and in the response to CD19-targeted immunotherapies. The main feature of the highly conserved CD19 cytoplasmic domain is the presence of 9 tyrosine residues. Three of them, murine $Y^{391}$, $Y^{482}$ and $Y^{513}$ ($Y^{402}$, $Y^{493}$ and $Y^{522}$ according to Ensembl, which correspond to human $Y^{409}$, $Y^{500}$ and $Y^{531}$), play an essential role: experiments have shown that substitution of phenylalanine for tyrosine at $Y^{482}$ and $Y^{513}$ leads to inhibited phosphorylation of the other seven tyrosines (Carter et al., 2002; Del Nagro et al., 2005; Haas and Tedder, 2005; Sato, 1999; Tedder and Isaacs, 1989). These phospho-Y are recruitment sites for p85/PI3K, VAV, LYN, LCK, FYN, GRB2, PLCgamma2, ABL and SH3BP2, playing thus an essential role in CD19 signaling (Tedder et al., 1997).

### 1.1.3. CD19 protein expression

CD19 was first identified as the B4 antigen on the surface of human B cells through the use of the anti-B4 monoclonal antibody. CD19 is specifically expressed on the surface of normal and neoplastic B cells, as well as follicular dendritic cells (Tedder, 2009; Haas and Tedder, 2005; Bradbury et al., 1992). In humans, CD19 expression starts at the early pro-B cell stage (Fr.B) and persists until and including the maturation and activation stages. During the terminal plasma cell differentiation, CD19 expression is lost (Tedder, 2009; Haas and Tedder, 2005). Expression of CD19 at the surface of B cells is a tightly regulated, multi-level process that integrates transcriptional programming, post-translational modifications, protein complex assembly, and dynamic cellular signals. First, at the transcriptional level, PAX5 (a master B cell transcription factor) directly binds the CD19 promoter and enhancer regions, enabling B cell-specific expression and B cell lineage commitment. In PAX5-deficient progenitors, CD19 induction fails and B-cell development is arrested at the early pro-B cell stage (Rolink et al., 2000; Horcher et al., 2001). Upstream epigenetic priming by factors such as E2A and EBF1 ensures accessibility of the CD19 locus before PAX5 occupancy, further orchestrating stage-specific expression during B-cell commitment (Walter et al., 2008). Second, proper maturation through the secretory pathway is essential: CD19 exists in two glycoforms: an immature, lower-molecular-weight, endo-H sensitive form retained in the endoplasmic reticulum (ER), and a mature, endo-H-resistant form indicative of passage through Golgi and reaching the cell surface (Shoham et al., 2003). The tetraspanin CD81 functions as a chaperone in this process: its absence drastically reduces the expression of mature CD19 glycoform and leads to decreased cell surface localization, without affecting mRNA levels (Shoham et al., 2003; Wang et al., 2012; Velasquez and Gottschalk, 2017). CD81 deficiency also impairs CD19-mediated calcium signaling, indicating that beyond expression, it contributes to receptor functionality (Tsitsikov et al., 1997). Third, CD19 participates in a surface complex with CD21 and CD81. CD21 presence inversely modulates CD19 levels: CD21-deficient mature B cells show increased CD19 surface expression (~19–36 %), suggesting a negative regulatory role for CD21 on CD19 cell surface density. Concomitantly, CD19 deficiency can slightly lower CD21 expression, highlighting reciprocal regulation within the coreceptor complex (Hasegawa et al., 2001). Fourth, pathological post-transcriptional alterations can affect CD19 surface presence, particularly in the context of immunotherapy resistance. Alternative splicing events that omit exons encoding the CAR T-cell epitope, or mutations disrupting CD19 splicing, lead to truncated or non-surface CD19 isoforms, underpinning antigen-negative relapses following CAR-T or bispecific antibody treatments (Sotillo et al., 2015; Aparicio-Pérez et al., 2023). Epigenetic changes and RNA-binding factors (e.g., PTBP1, SF3B4) also modulate splicing decisions and contribute to loss of CD19 expression in malignant contexts (Cortés-López et al., 2022).

### 1.1.4. CD19 functions

CD19 is a pivotal regulator of B cell signaling, functioning to establish intrinsic signaling thresholds and to modulate both B cell receptor (BCR)-dependent and independent pathways (Fujimoto et al., 1998; Poe et al., 2012). CD19 is therefore essential for events as diverse as B cell development or B cell activation resulting from the stimulation of the surface immunoglobulin or other surface receptors, thus ensuring effective immune responses.

#### 1.1.5. Molecular mechanism of CD19 action

Molecularly, CD19 works in complex with the pre-BCR, the BCR or other surface molecules/receptors like IL-4R, FcgammaR or TLR4 to allow recruitment, binding and activation of various SH2 domain-containing cytosolic proteins on its phosphorylated cytoplasmic tyrosines (Zhou et al., 1992; van Zelm et al., 2006). The recruited proteins include p85/PI3K, VAV, LYN, LCK, FYN, GRB2, PLCgamma2, ABL, BTK and SH3BP2, and thus play an essential role in CD19 signaling. Thus, CD19 serves as a membrane docking protein to directly or indirectly recruit, bind and (further) activate cytosolic kinases, lipases as well as guanosine nucleotide exchange factors, in order to positively amplify signals generated from pre-BCR, BCR and other surface receptors.

#### 1.1.6. The CD19 complex on mature B cells

At the surface of mature B cell, CD19 can form a multimolecular complex with other membrane proteins, including CD21 (the receptor for the fragments of the third complement component (C3)), the tetraspanin membrane protein CD81, as well as CD225, which collectively lower the threshold for receptor-dependent signaling in B cells (Haas and Tedder, 2005; Carter et al., 2002; Tedder, 2009; Del Nagro et al., 2005; van Zelm et al., 2006; Tedder et al., 1997). Two models are classically present in the literature to explain this phenomenon. In the first one, the coligation of the CD19 and BCR complexes model, in which the opsonized antigen-C3d complex bridges the BCR - via the antigen and the surface immunoglobulin - and the CD19 complexes - via the antigen-bound C3d fragment and CD21 -, resulting in the amplification of the B cell response to the antigen (Del Nagro et al., 2005; Ishiura et al., 2010). In the second one, the self CD19 complex colligation model, in which the opsonized antigen-C3d complex bridges two or more CD19 complexes via multiple antigen-bound C3d fragments and CD21, resulting in decreased signaling thresholds that govern signaling events through other cell surface receptors, like IL-4R, FcgammaR or TLR4 (Del Nagro et al., 2005; Sato, 1999; Deaglio et al., 2007).

#### 1.1.7. Control of CD19 signaling

After surface receptor activation (e.g. the cognate antigen binding to the surface immunoglobulin) or CD19 complex activation (CD19 antibody, antigen-C3d complexes, …), CD19 tyrosines phosphorylation is mediated by SRC family members (LYN, FYN, BLK) or by SYK. LYN is clearly the main initiator kinase which, for example, rapidly phosphorylates several CD19 tyrosines after BCR engagement. ABL and SYK may also contribute to CD19 tyrosines phosphorylation. By contrast, the protein tyrosine phosphatases PTPN6/SHP-1 and PTPRC/CD45 play a direct or indirect role in decreasing CD19 tyrosine phosphorylation, acting as a brake on or ending CD19 signaling. Interestingly, cell surface CD19 expression and density also play an important role in the control of CD19 signaling. A 20 % B cell surface overexpression of CD19 in humans and a 15–29 % overexpression in transgenic mice are associated with increased basal and BCR-stimulated CD19 signaling, as well as with autoimmunity features like autoantibodies production (Inaoki et al., 1997; Sato et al., 1996, 1997, 2000; Zhou et al., 1994). The mechanism leading to the constitutive CD19 phosphorylation and signaling activation when CD19 is overexpressed involves an enhanced LYN phosphorylation/activity due to the increased CD19 density at the B cell surface, followed by a processive amplification of CD19 phosphorylation (Fujimoto et al., 2000a, 2000b). Recently, we identify a novel mechanism which negatively regulates CD19 signaling through the control of its cytoplasmic domain conformation (Moës B, Mostafa A, Malempré R, Renson O, Piel G, Matagne A, Schurmans S, Mayer A, submitted for publication). Specifically, we showed that a positively charged basic amino acid region within the CD19 juxtamembrane cytoplasmic domain establishes ionic interactions with PtdIns(4,5)P2, influencing the proximity of the cytoplasmic domain to the plasma membrane and thus its conformation. In mice with reduced expression of the PtdIns(4,5)P2 5-phosphatase INPP5K, increased PtdIns(4,5)P2 levels within CD19 microclusters were observed. This was associated with an abnormal, high activation-prone conformation of the CD19 cytoplasmic domain, even in resting B cells. As a result, CD19 signaling and microcluster formation were constitutively elevated, leading to impaired peripheral B cell development and altered blood immunoglobulin levels. These findings demonstrate that INPP5K is essential for maintaining CD19 cytoplasmic domain conformation, thereby preventing constitutive activation of CD19 signaling and associated defects in peripheral B cell development, factors that may lead to autoimmunity. Furthermore, our findings may provide insight into why reduced INPP5K expression in naïve B cells from patients with systemic lupus erythematosus correlates with high disease activity.

### 1.2. Physiological functions in genetically-modified mice

#### 1.2.1. Human CD19 overexpression in transgenic mice

CD19 overexpression has been investigated in human CD19 transgenic (hCD19TG) mice (Sato et al., 1996, 1997; Zhou et al., 1994). Phenotypic analyses revealed that increased CD19 expression causes a profound (>80 %) reduction in peripheral B cells, largely due to impaired generation and maturation of immature precursors in the bone marrow. Despite this deficit, hCD19 TG B cells display gene dosage–dependent hyperproliferation in response to mitogens such as lipopolysaccharide (LPS). Homozygous mice exhibit markedly greater proliferation than heterozygotes, alongside with increased basal proliferation and extended survival without stimulation. Paradoxically, serum immunoglobulin levels are elevated by ~40 % despite reduced B cell numbers. This increase is isotype-specific: IgG2b is markedly elevated (168 %), IgG3 is strongly reduced (77 %), and IgA remains unchanged. These observations indicate that CD19 overexpression increases B cell sensitivity to transmembrane signaling and augments the overall susceptibility of B cells to induced differentiation. The data support a feedback model in which heightened CD19 density impairs precursor maturation but augments functional responsiveness of mature B cells.

#### 1.2.2. CD19 knockout mice

CD19 deficiency in mice primarily impairs later stages of B-cell maturation within the spleen and peripheral lymphoid tissues, while sparing early development in the bone marrow (Engel et al., 1995; Rickert et al., 1995; Sato et al., 1995, 1997). Although B-cell

morphology remains normal, CD19$^{-/-}$ mice exhibit profound reductions in peripheral and splenic B-cell numbers, particularly B1 cells, with altered immunoglobulin expression patterns. These mice display reduced proliferative responses to mitogenic stimuli and IgM cross-linking, though clonal expansion and plasma cell differentiation still occur at diminished rates. Unlike hCD19TG mice, CD19 deficiency leads to a uniform reduction across all immunoglobulin isotypes, with particularly severe decreases in IgG1 and IgG2a, reflecting impaired T cell-dependent B-cell responses. Additional defects include loss of splenic marginal zone B cells and reduced germinal center formation, resulting in compromised humoral immunity. Mechanistic studies confirm CD19's role as the central B-cell co-receptor, acting as a molecular rheostat that regulates signaling thresholds and maintains the balance between activation and tolerance.

### *1.3. Role of CD19 in human diseases*

#### *1.3.1. Immunodeficiency*

Diverse mutations in the human CD19 gene have been detected and associated with an immunodeficiency named Common Variable ImmunoDeficiency type 3 (CVID3) (https://www.omim.org/entry/107265) (van Zelm et al., 2006; Tedder, 2009). These CVID3 patients have very low to undetectable cell surface CD19 expression. Recurrent infections starting early in life are secondary to a mutated or truncated, non-functional CD19 protein, resulting in defects in B cell populations, poor B cell responses to antigens and impaired antibody production (hypogammaglobulinemia).

#### *1.3.2. Autoimmunity*

Cell surface CD19 overexpression was detected on B cells from patients with systemic sclerosis, a multisystem disorder of connective tissue with autoantibody production (Sato et al., 2000). CD19 density on blood B cells from systemic sclerosis patients was significantly (approximately 20 %) higher compared with normal individuals, whereas CD20, CD22, and CD40 expression were normal. These results, together with those from the analysis of CD19 overexpressing transgenic mice, indicate that modest changes in CD19 expression may shift the balance between tolerance and immunity to autoimmunity.

#### *1.3.3. CD19 as a target in B-cell malignancies and autoimmunity therapy*

CD19 is not only a B cell marker and a pivotal regulator of B cell signaling, it is also a validated therapeutic target for B-cell malignancies and some autoimmune diseases. Its near-ubiquitous expression on malignant B cells in diseases such as acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and various non-Hodgkin lymphomas renders CD19 a highly attractive therapeutic target. Indeed, CD19-directed chimeric antigen receptor (CAR) T-cells and monoclonal antibodies have achieved substantial clinical breakthroughs, producing high rates of complete remission and durable responses in patients with relapsed or refractory disease (Drokow et al., 2019; Yang et al., 2025). Beyond oncology, CD19 targeting also emerges as a promising strategy in autoimmune disorders such as systemic lupus erythematosus (SLE), wherein depletion of CD19-expressing B cells disrupts autoantibody generation and mitigates immune complex-mediated tissue injury (Mougiakakos et al., 2021; Schubert et al., 2023; He et al., 2025). Compared to strategies that target later B-cell stages (e.g. CD20), CD19-directed therapies potentially effect more profound depletion, including earlier B-cell subsets, thereby reducing reservoirs of autoreactive clones. Challenges remain, notably antigen escape or loss of CD19 expression, CAR T-cell exhaustion, and off-target effects, mandating combination approaches and next-generation CAR constructs.

## 2. Conclusion and perspectives

CD19 is a reference marker of B cells and serves as a pivotal co-receptor in these cells, integrating developmental and pathological functions while remaining a validated therapeutic target in malignancies and autoimmunity. Despite major advances, CD19 function is still poorly characterized, particularly when it comes to membrane events that regulates its signaling. Better understanding could help to mitigate pathologies associated with B cell alterations such as autoimmunity or immunodeficiency. In this sense, our recent discovery of a mechanism of CD19 conformational control, in which PtdIns(4,5)P2 interactions and INPP5K activity restrain CD19 signaling, highlights lipid–protein dynamics as critical safeguards of B cell development. This novel regulatory axis may not only participate in the aberrant activation in autoimmunity, but also offers opportunities for therapies that modulate CD19 function more precisely, guiding future strategies in both immunotherapy and immune regulation.

## CRediT authorship contribution statement

**Stéphane Schurmans:** Conceptualization, Funding acquisition, Investigation, Supervision, Writing – original draft, Writing – review & editing. **Bastien Moës:** Conceptualization, Funding acquisition, Investigation, Writing – review & editing.

## Declaration of competing interest

We have nothing to declare.

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## Data availability

The authors do not have permission to share data.

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