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Highlights - Reviews

Updates on Toll-Like Receptor 10 Research

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ABSTRACT

Toll-like receptors (TLRs) are transmembrane proteins that share sequence similarity and biological function as they are responsible for the innate immune response to exogenous or endogenous molecular patterns. Distinct ligands are recognized by the leucine-rich repeats regions and trigger an inflammatory signal into the cell thanks to the TIR domain of TLR. TLR10 shares the same structural organization but shows a unique expression pattern and functional activity yet to be fully elucidated. In this review, we summarize the literature on TLR10 expression and cellular localization. Several polymorphisms were reported for the TLR10 gene that is present in most mammalians and arose from gene duplication of an ancestral TLR1-like gene. Accordingly, TLR10 was shown to act as TLR1 in terms of TLR2 interaction and TLR1/2 ligands recognition; however, in contrast to all the other TLRs it could also trigger anti-inflammatory signaling and was responsive to several unrelated microbial components. In this review, we will describe key steps and recent updates on TLR10 research highlighting common or divergent findings, in humans and animals.

1 | Introduction

Toll-like receptors (TLRs) are involved in the first sensing of pathogens or endogenous signals representing a primary line of defense of the organism [1, 2]. Their proper function results in successful fighting against invading microbes and tissue damage.

All the TLRs share a cytoplasmic C-terminal region which contains a conserved domain called TIR (Toll/interleukin-1 receptor/resistance protein) found also in the interleukin-1 receptor family members, and in the tobacco N resistance gene [3]. A single transmembrane domain is preceded by an N-terminal portion that contains multiple leucine-rich repeats [4].

TLR10 gene was cloned over 20 years ago, but many questions on the biology and regulation of this protein remain unresolved. We will herein review relevant literature focused on TLR10 research underlining key points and open issues on this receptor for which there is no agreed function yet. According to the Cluster of Differentiation nomenclature, TLR10 is known as CD290.

1.1 | TLR10 Cloning and Expression Pattern

Human TLR10 was identified in 2001 based on its sequence conservation and its similarity to TLR1 and TLR6 [5] (Figure 1). At that time, when the human genome sequence was not complete, the identification of novel genes was mainly based on the analysis of expressed sequence tags (EST) deposited in public and private databases. TLR10 was cloned using primers designed onto a specific EST and a cDNA library prepared from human spleen mRNA [5]. Initial gene expression analysis in humans confirmed the presence of high levels of the transcript in the spleen followed by other lymphoid tissues, B-cell lymphoma cell lines (Ramos and

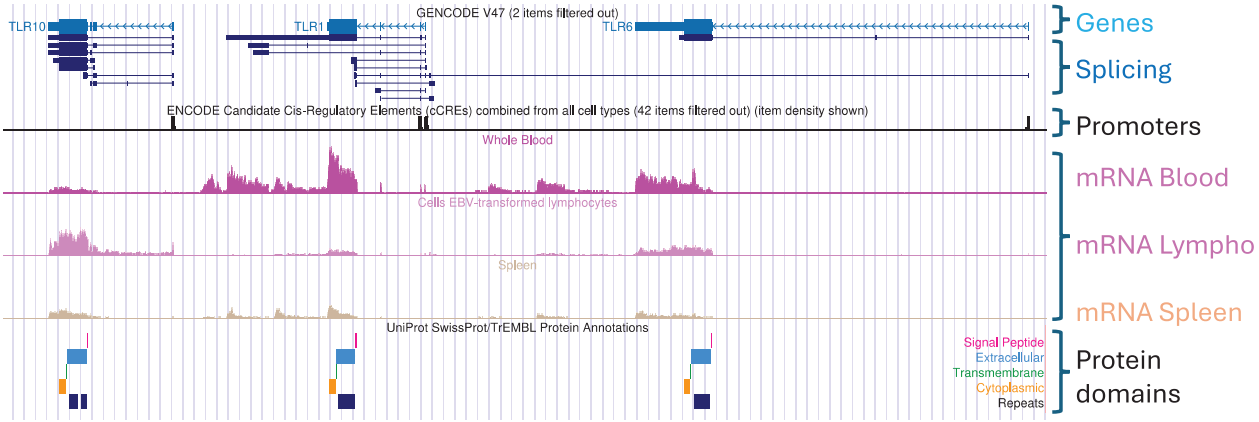

FIGURE 1 | Graphic representation of the TLR10 locus was created by using the USCS Genome Browser and the GRCh38/hg38 genome assembly [81]; dark blue graphs represent different mRNA isoforms for each gene (GENECODE V47 datasets filtered for gene symbol and splice variants; PMID: 36420896). Candidate promoter regions are shown in black (ENCODE dataset filtered for "promoter like signatures" and "DNAse/H3K4Me3"; PMID: 31713622). mRNA levels are reported in pink and brown (the GTEx V8 RNA-Seq dataset was filtered for whole blood, EBV-transformed lymphocytes, and spleen datasets; PMID: 32913098). The bars shown at the bottom indicate different protein domains (UniProt/SwissProt dataset; PMID: 22102590).

Raji), and to a lesser extent myeloid leukemia cell lines (HL60 and THP1) [5].

Soon after cloning, it was clearly shown that TLR10 has a peculiar expression pattern, somehow similar to TLR9, with high levels of transcripts found in B lymphocytes isolated from the peripheral blood or tonsil and peak levels in memory and activated B-cells; anti-CD40, SAC, anti-Ig and CpG stimulation in vitro can all induce TLR10 mRNA levels [6–8]. However, different from TLR9, TLR10 is enriched in B cells [9]; several public databases containing mRNA expression datasets clearly show an exquisite selectivity of expression in B lymphocytes (e.g., Human protein atlas: https://www.proteinatlas.org/ENSG00000174123-TLR10/single+cell) [10]. Further studies at protein levels confirmed the enrichment of TLR10 expression in circulating memory B-cells with lower but detectable levels in other B-cell subsets [11–13].

Nevertheless, TLR10 can be found also in other cell types and regulated by specific stimuli, although at generally lower levels. Human plasmacytoid dendritic cells express both mRNA and protein on the cell surface [9, 14, 15]; TLR10 mRNA was detected in a specific subset of DC derived from CD34+ progenitors that resemble Langerhans cells in the epidermis [15]. Langerhans cells and keratinocytes show detectable levels of mRNA although less as compared with blood DC [16]. A distinct expression of TLR10 on the surface of T-regulatory cells was attributed to the transcriptional control of FOXP3 in cooperation with NFAT [17]. Low TLR10 expression on the surface of primary human monocytes was increased after in vitro stimulation (BCG and *Streptococcus pneumoniae*) suggesting gradual enrichment of this receptor in the myelomonocytic lineage upon activation/differentiation toward macrophages [18]; this was further extended in microglial cells where TLR10 expression was upregulated upon polarization to an anti-inflammatory "M2-like" state [19].

The expression of TLR10 was further investigated in different animal species such as horses and cattle showing a similar pattern with high levels in lymphoid tissues (spleen, blood and PBMC, lymph nodes) and low levels in small intestine, lung, kidney, and liver [20, 21].

In addition to the expected cell surface expression, TLR10 was found enriched into the cytoplasm and endosomes of monocytes and neutrophils respectively [18, 22, 23]. In neutrophils, surface TLR10 expression was downregulated after LPS treatment while at the same time increasing in the cytoplasmic vesicles suggesting that its internalization may be mediated by lipid raft-related endocytosis [22]; accordingly, after longer incubation time, TLR10 was re-expressed on the cell membrane. TLR10 mRNA was also found to be expressed by intestinal epithelial cell lines [24, 25].

TLR10 expression was reported to be dysregulated in different human diseases and tumor types (see paragraph below for details on tumors). Monitoring TLR10 in distinct B-cell types, during disease activity or progression, highlighted increased expression in patients with rheumatoid arthritis but lower levels in patients with Sjogren's disease and lupus erythematosus [11]–[13]. TLR10 emerged significantly upregulated in *H. pylori*-infected gastric mucosa, both in vivo and in vitro [26]. TLR10 is increased in obesity, within adipose tissue interstitial regions enriched for macrophages (crown-like structures) [27].

Finally, a recent report measured soluble TLR10 in the serum, and found it downregulated in patients with relapsing-remitting multiple sclerosis [28]; however, the biochemical mechanisms that may release this receptor from the cell surface (and/or from the endosomes) are still unknown.

1.2 | TLR10 Evolution

To analyze the evolution of TLR10, it is fundamental to introduce the origin and the evolution of TLR family members that are coded by a multigene family conserved from invertebrates to vertebrates [2]. TLR genes can be divided into six families based on the localization, the type of ligand, and DNA sequence: the TLR1 family includes TLR1, TLR2, TLR6, TLR10, TLR14, and

TLR15; the TLR7 group includes TLR8 and TLR9; the TLR11 group includes TLR11 and TLR12. Each TLR3, TLR4, and TLR5 represents an individual group [29].

The most accredited hypothesis suggests that all TLRs derive from an ancestral precursor that underwent a first series of ancient gene duplications followed by later gene duplication. During the second series of gene duplications, the TLRs acquired functional diversification and different patterns of expression [30]. The evolution of TLR members is highly complicated and is based on gene duplication combined with genetic selection and gene loss. In particular, the ligand binding domain of the TLRs seems to have evolved thanks to genetic drift and positive selection of duplicated genes, allowing for the generation of receptors able to bind to different molecular patterns [29]. On the contrary, the TIR domain could be evolved by gene conversion to preserve the signaling function and to coevolve with the adapter molecules such as MyD88 [29]. To further complicate the evolution of TLRs, gene duplication can be associated with purifying selection to maintain the TLR function and binding capability to specific and relevant PAMPs [31]. This last mechanism slowed down the evolution of TLRs [31].

TLR10 belongs to the TLR1 family due to the localization on the same chromosome, the sequence similarity, and the heterodimerization with the other members [31, 32] (Figure 1). This family arose independently from an ancestral gene in fish, birds, and mammals (eutherian and metatherian), whereas the other TLRs were already present before the divergence of vertebrates and some of them have been lost in specific lineages [33]. More in detail, an avian TLR1 precursor duplicated to originate TLR10 and TLR1/6 genes of mammalians. The latter gene is duplicated in mammals to give birth to TLR1 and TLR6 except in marsupials where the gene TLR1/6 is still present [34]. Confirming this hypothesis TLR10 is found in mammals, including marsupials, but not in birds and fish [34]. In a few animal species, TLR10 is present as a pseudogene such as a mouse, where the gene has been disrupted by two retroelements [15].

Several phylogenetic evidence in ungulates and cetaceans, koalas, pigs, cattle, and humans suggest that TLR10 is one of the less TLR subjected to positive selection and its evolution seems to be preferentially guided by purifying selection in order to preserve its function [34–38]. The phylogenetic analysis of the extracellular domain of TLR1, TLR6, and TLR10 clearly separates the orthologue genes into three different groups suggesting a specialization for the ligand binding of the three receptors; on the contrary, the phylogenetic analysis of the cytoplasmic region shows an elevated conservation between TLR1 and TLR6 that follow in the same group, whereas TLR10 form a separate clade. This could justify a different signaling pathway and a different function for TLR10 compared with the other members of the TLR1 family [39]. Moreover, TLR10 exhibits similar variability in the extracellular and intracellular portions despite the other TLRs that have more variability in the extracellular compared with the cytoplasmic region, confirming the peculiarity of TLR10 in the signaling pathway and selective pressure [20].

1.3 | TLR10 Polymorphisms and Splicing

A simple PubMed search identified more than 3500 publications on TLRs and polymorphisms underlying the complexity of this field of research. Concerning TLR10, several SNPs and variants were identified and investigated to highlight any possible association with infections and other diseases.

The rs11096957 (T>G) is a missense polymorphism located in the promoter region of the TLR10 gene. This variant has been associated with a predisposition to hip osteoarthritis likely due to a disfunction of TLR10, a reduced susceptibility to complicated skin and skin structure infection [40], and increased TBC susceptibility in association with a TLR6 SNP [41–43]. Moreover, rs11096957 together with other TLR10-TLR1-TLR6 gene cluster SNPs [44, 45] showed an association with a reduced risk of prostate cancer, also when the analysis was restricted to advanced prostate cancer. The functional response of PBMC isolated from 112 volunteers was analyzed with respect to the rs11096957 allele; the heterozygous and homozygous (N241H substitution) genotypes showed increased inflammatory cytokines production after the addition of TLR2 agonists in vitro [46].

Two variants (rs10008492 and rs4833103) in the TLR10-TLR1-TLR6 gene cluster were significantly associated with non-Hodgkin lymphomas without differences among the histological subtype [47].

The variant rs4129009 (T>A, C, G) is a missense polymorphism located in the coding region of the TLR10 gene [48]. This SNP has been investigated in asthma development in young children after bronchiolitis in infancy resulting associated with the increasing risk of asthma [48]. The same variant was associated with the overall survival and infiltration level of urothelial cancer [49] and with autoimmune thyroid disease together with the other two variants of the same gene [50].

The variant rs11096955 (T>C, G) is a missense polymorphism located in the exon 2 of the TLR10 gene [44]. As previously mentioned, this variant is related to a reduced risk of prostate cancer in a cluster with other TLR10-TLR1-TLR6 SNPs [44, 45], to reduced susceptibility to complicated skin and skin structure infection [40], to Meniere's disease, a chronic disorder of the inner ear [51]. This SNP seems to be correlated with the progression of hearing loss in patients with bilateral Meniere's disease [51].

Rs11466653 (A>G) is a nonsynonymous variant located in exon 2 [44] that has been linked to small tumor size in patients affected by papillary thyroid carcinoma [52].

The two SNPs rs2101521 (G>A, T) and rs10004195 (T>A) were found to associate with autoimmune disorders such as rheumatoid arthritis, autoimmune thyroid disease, pediatric idiopathic uveitis and childhood IgA nephropathy [50, 53–55]. Moreover, rs10004195 showed a link with protection against Bacillus Calmette-Guérin osteitis after newborn vaccination [56] and with increased susceptibility to gastric carcinoma in *Helicobacter pylori* diseases [57].

A group of variants (rs6841698 G>A, T, rs10024216 G>A, T, rs4274855 C>G, T and rs7658893 G>A) was associated with Crohn's disease and specific measures of disease severity [58].

Finally, rs11466655 (C>T) is a missense polymorphism located in the exon 2 of TLR10 gene [44] that has been correlated, together with other variants of TLR10, with long-term graft function in recipients treated with tacrolimus before solid organ transplant [59].

Several other studies investigated the associations of TLR10 SNPs with infectious and noninfectious diseases for example chronic atrophic gastritis, Q fever, allergies, and pneumococcus infections with variable results.

In general, there are some limitations in the definition of a reliable association between an SNP and a pathological condition due to limited or too homogeneous populations analyzed and the inclusion or exclusion of minor allele frequencies; despite the limitations, all these publications provide interesting data sets which suggest an association between missense TLR10 SNPs and different diseases. However, further studies are needed to determine the relevance of the SNPs to specific diseases through functional studies that could elucidate the effect of the missense SNP in disease cell biology.

TLR10 SNPs have been investigated also in domestic and wild animals. In pigs and wild boars, 33 SNPs were identified and 20 resulted nonsynonymous. Interestingly, the frequency of the presence of SNP was higher in domestic pigs compared with wild boars, suggesting a different environmental microbiological pressure in wild and selected domestic animals (36). In this study, none of the SNP seemed to alter the gene function, and none of them was located in the hinge region unaffecting the binding capability of the receptor [36]. In a small population of Australian Koalas, the presence of SNPs was investigated in the TLR gene family. The authors observed that in their samples only TLR10 was monomorphic, whereas the other nine TLRs presented at least 2 alleles [34]. Genetic variability in some koala populations is very low due to the founder effect, but increasing the number of the population under study could allow us to find more SNPs.

Concerning possible different splicing isoforms, we retrieved two annotated mRNA variants at the NCBI gene database: the isoform "a" and "b" (link: https://www.ncbi.nlm.nih.gov/gene/81793) (Figure 1). Isoform "a" includes 4 exons, whereas the isoform "b" lacks an exon in the 5′ UTR and uses a different splice site which results in part of the 5′ coding region being absent, compared with variant "a"; the resulting predicted isoform "b" has a shorter N-terminus and is missing a potential signal peptide. No publications were found on the structure, expression, and function of the two different isoforms; it is tempting to speculate that differential intracellular localization of TLR10 may be regulated also by differential splicing.

1.4 | Human TLR10 Functions

Several complementary experimental approaches resulted in the identification of several potential ligands and functional roles of TLR10 (Figure 2). Due to the lack of an in vivo mouse model, the study of the biological activity of human TLR10 was, and still is, a challenging task that has been approached mainly by ectopic overexpression or protein knockdown with different and sometimes contradictory results depending on the cellular localization of the receptor and the cell type analyzed.

Chimeric receptors were developed to dissect the function of the intracellular or extracellular portion of TLR10. Signaling studies with reporter vectors suggested that TLR10 induces NFκB in a MyD88-dependent manner [15, 60], while another study reported that TLR10 failed to activate classic TLR-regulated NFκB-specific promoters (e.g., IL8 and IFNβ) [32]. Biochemical studies demonstrate that the TLR10 extracellular domain can dimerize with TLR2 as well as with the known TLR1/TLR2 ligands (e.g., PAM3CSK4 and Zymosan) [15, 32]. Moreover, TLR10 can also form homodimers [15].

Analysis of epithelial and myeloid cell lines supported a proinflammatory role of the intracellular TLR10 in the response to live infectious agents such as *Listeria monocytogens, S. pneumoniae*, or influenza virus [23, 24, 61]; however, the molecular mechanisms involved are ill-defined. HIV protein gp41 was also recognized as a TLR10 ligand, inducing NF-kB and IL8 after binding [62]. Intracellular dsRNA instead triggered a MyD88-dependent inhibitory response mediated by TLR10 that suppressed IFNβ production by competing with TLR3 [63]. In neutrophils, endosomal TLR10 positively controlled chemotaxis after LPS recognition by TLR4 colocalized with TLR10 [22].

On the other hand, surface TLR10 has been mainly involved in a novel anti-inflammatory pathway in response to Lipopeptides (i.e., PAM3CSK4) and other TLR2 ligands (e.g., *Borrelia burgdorferi*) acting as a negative regulator of both MyD88-dependent and MyD88-independent (but TRIF-dependent) TLR signaling [46, 64]. However, it was also reported a reduced proinflammatory role in TLR10 knocked down THP1 cells stimulated with different TLR ligands (e.g., FLS-1 and Flagellin) [65].

Distinct monoclonal antibodies were used to cross-link surface TLR10 with interesting results, but we should take into consideration the fact that the functional activity of these antibodies may be different from the "natural" ligands, and there is no direct evidence that the antibodies are blocking or activating although indirect tests suggest the latter [66]. These experiments supported again an anti-inflammatory role of TLR10 in different cell types including B-lymphocytes that express this receptor at most on their cell surface. The induction of the anti-inflammatory cytokine IL1RA, and the reduction of the DC-mediated adaptive immune response or the antibody-mediated immune response were all dependent on TLR10 [46, 66, 67]. Plasmacytoid DC (pDC) responded to anti-TLR10 antibody slightly different from monocytes-derived DC, with no impairment in T-cells stimulation capability; yet TLR10 engagement reduced levels of several proinflammatory cytokines after viral infection in vitro (DNA and RNA viruses) and induced a specific STAT3 signaling pathway with concomitant inhibition of IRF7 activation in pDC [14].

An interesting approach was used to force the endogenous TLR10 expression by CRISPR technology; A549 lung epithelial cells became less responsive to different TLR ligands in terms of inflammatory cytokine production (e.g., IL8 and IFN) while at the

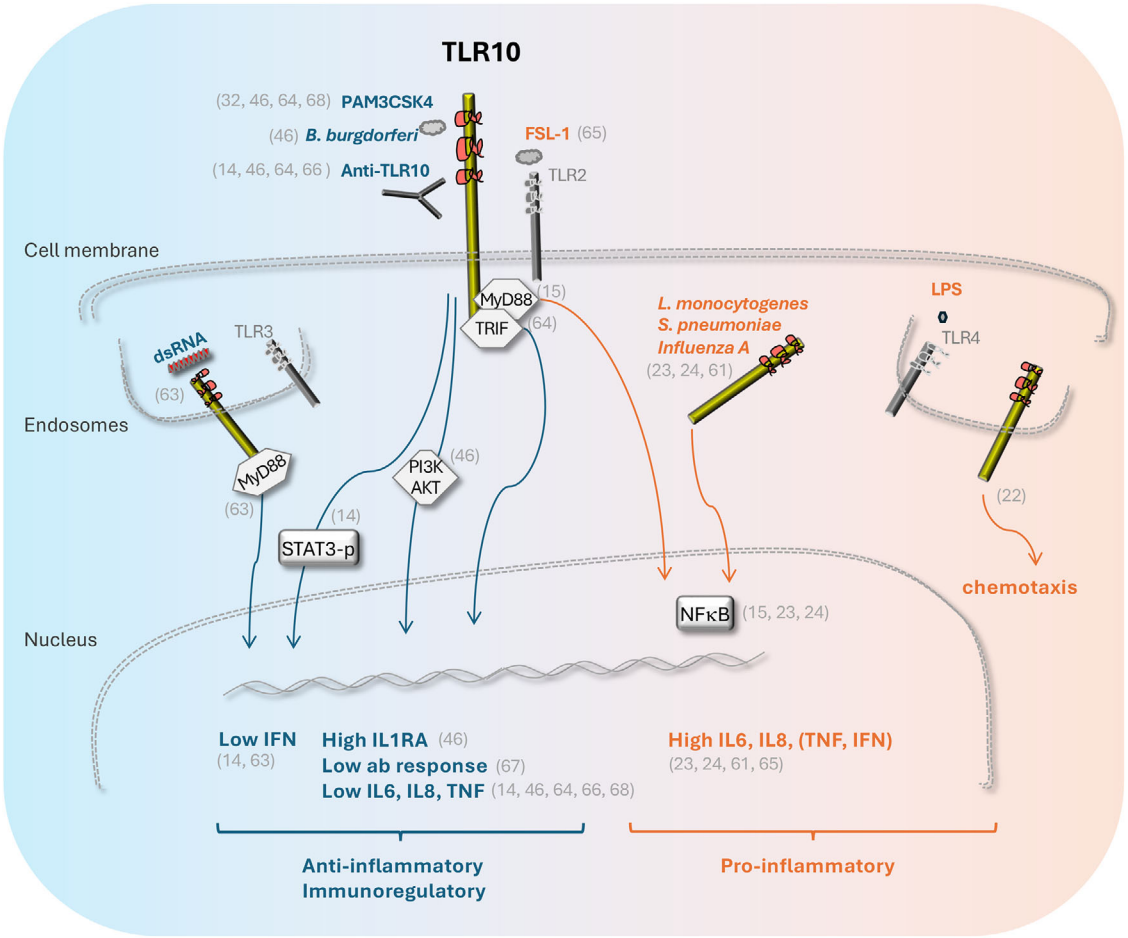

FIGURE 2 | Graphic representation of TLR10 protein on the cell surface or intracellular. All the ligands and the signaling pathways described in the text are schematically depicted and annotated with their corresponding references.

same time producing increased levels of IL10, suggesting again an anti-inflammatory role of TLR10 [68].

Transgenic mice overexpressing TLR10 were generated independently in two different laboratories with different constructs, yet in both cases TLR10 was "ubiquitously" expressed thanks to the use of constructs with strong promoters [46, 64]; in both cases, a broad anti-inflammatory effect was observed in vivo and ex vivo with decreased IL6 levels after TLR2, TLR3, and TLR4 agonist stimulation [46, 64]. Specific analyses to study diet-induced obesity revealed that TLR10-transgenic mice displayed reduced adipose tissue, but not body weight [69].

Later, a TLR10 knock-in mouse model was developed to analyze the function of "physiological" levels of this receptor [67]; hTLR10 expressed in splenic B-lymphocytes did not impact on B-cell development; however, it inhibited cell proliferation and IL6 secretion after anti-IgM/anti-CD40/CpG *ex-vivo* treatment. Accordingly, TLR10 transgenic animals were deficient in both T-dependent and T-independent antibody response [67].

Finally, the TLR10 intracellular domain fused to PD1 was reported to enhance the antitumor efficacy of CAR-T [70].

All these experiments were instrumental in accumulating fundamental evidence on TLR10 function, and to build novel working hypotheses. Because TLR10 was reported to be both homodimerized and heterodimerized with other TLRs, different signaling capabilities may depend on the actual TLR10 complex that may be cell-type specific. Along this line of reasoning, TLR10 signaling may differ depending on the ligand/s specificity. However, no consensus has been reached yet, and more experiments are needed to provide the exact molecular framework of all the TLR10 activities.

1.5 | Human TLR10 Expression in Tumors

Mirroring the expression pattern observed in "healthy" cells and tissues, TLR10 mRNA was detected in several B-cell malignancies including chronic lymphocytic leukemia (CLL), splenic marginal zone lymphoma (SMZL), and multiple myeloma (MM) [71–74]. The only exception was glioblastoma in which TLR10 was overexpressed but specifically correlated with immune cell infiltration of B-lymphocytes [75].

TLR10 mRNA expression was first analyzed in CLL cells isolated from the peripheral blood of patients, in parallel to all the other TLRs: the expression pattern of TLRs in this mature B-cell neoplasia was similar to normal tonsillar B-cells [71]. A broader analysis of a large number of patients with CLL confirmed TLR10 mRNA expression in malignant B-cells and extended this

observation with surface TLR10 protein [72]; again, no significant differences were noted between B-cell isolated from healthy donors and leukemic cells isolated from the patients [76].

Different from CLL, primary SMZL cells (that can circulate in the peripheral blood), overexpress TLR10 protein as compared with B-lymphocytes isolated from healthy donors; however, the intraclonal difference was observed for the percentage of TLR10-positive cells [73]. Similar results were obtained when splenic tumor cells were analyzed [73].

In another study, mononuclear cells were isolated from the bone marrow of patients with MM or healthy donors, and TLR10 mRNA was detected in all the samples with no significant difference; however, after CD138-positive cells enrichment, TLR10 expression appeared higher in a small group of tumor versus normal samples that were almost negative [74]. A large cohort analysis confirmed high levels of expression of TLR10 in CD138-positive myeloma cells; TLR8 and TLR10 both correlated with the specific translocation t4:14 [77].

TLR10 transcripts emerged from different unsupervised screening analyses focused on lymphomas. Bromodomain and extra-terminal motif (BET) inhibitors shaped a specific gene expression profile characterized also by marked repression of TLR10 in diffuse large B-cell lymphoma and mantle cell lymphoma [78, 79]. On the contrary, the transformation of CLL into an aggressive lymphoma (Richter transformation) was characterized by overexpression of TLR10 among other genes [80].

Overall, these descriptive studies reported the expression of TLR10 in B-cell neoplasia; however, further investigations are needed to assess if the expression correlates with the pathogenesis and/or if TLR10 is functionally involved in the pathobiology of these tumors.

2 | Conclusion

Overall, the expression pattern and functional analysis of TLR10 suggest a novel unique role of this receptor in the B-cell context. No other member of the TLR family has such an expression selectivity while at the time showing promiscuity of exogenous ligands recognition. In fact, different molecules that have been shown to bind TLR10 on the cell surface share few if any molecular patterns, making it difficult to extrapolate the nature and common structure of any TLR10 ligands.

Several research questions remain including, but not limited to the following: (1) the identification of the cis-regulatory elements controlling the selective mRNA expression; (2) the identification of all its binding partners in the TIR domain and the extracellular portion; (3) the molecular mechanisms controlling its intracellular or surface expression and release in a soluble form; (5) its functional role in B-cell related diseases development and progression, including tumors.

The full biological and/or pathobiological role of TLR10 might not be fully understood until a natural ligand, either endogenous or exogenous has been studied in the B-cell context.

Author Contributions

Federica Riva and Marta Muzio contributed equally to all aspects of this study.

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Ethics Statement

No experiments using animals were conducted for this study. The manuscript does not contain human studies.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable as no new data were generated.

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