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Toll-Like Receptors, Infections, and Rheumatoid Arthritis

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Abstract
Toll-like receptors (TLR) that belong to the group of protein recognition receptor (PPR) provide an innate immune response following the sensing of conserved pathogen-associated microbial patterns (PAMPs) and changes in danger-associated molecular patterns (DAMPs) that are generated as a consequence of cellular injury. Analysis of the TLR pathway has moreover offered new insights into the pathogenesis of rheumatoid arthritis (RA). Indeed, a dysfunctional TLR-mediated response characterizes RA patients and participates in establishment of a chronic inflammatory state. Such an inappropriate TLR response has been attributed (i) to the report of important alterations in the microbiota and abnormal responses to infectious agents as part of RA; (ii) to the abnormal presence of TLR-ligands in the serum and synovial fluid of RA patients; (iii) to the overexpression of TLR molecules; (iv) to the production of a large panel of pro-inflammatory cytokines downstream of the TLR pathway; and (v) to genetic variants and epigenetic factors in susceptible RA patients promoting a hyper TLR response. As a consequence, the development of promising therapeutic strategies targeting TLRs for the treatment and prevention of RA is emerging.

Keywords Rheumatoid arthritis · Toll-like receptors · Infections

Introduction

With a prevalence of 0.5 ± 0.2% in the general population and a twofold female predominance, rheumatoid arthritis (RA) represents the most common chronic systemic autoimmune rheumatism [1]. RA clinical presentation typically retrieves morning stiffness, fatigue, poly-articular pain, and joint and bone inflammation and destruction. A more severe evolution is encountered in RA patients presenting early bone erosion, an age at diagnosis lower than 50 years, and an elevated level of autoantibodies (Abs) targeting immunoglobulin G, referred to as rheumatoid factor (RF), and/or anti-cyclic citrullinated peptide autoantibodies (ACPA) [2, 3].

RA presents a strong environmental factor component in addition to genetic, epigenetic, and female bias risk factors [4]. Environmental risk factors include smoking, silica exposure, education level, vitamin D deficiency, obesity, change in microbiota, and infectious agents [5]. As reported in Fig. 1 and although the primary events are suspected to occur outside the joint at mucosal surfaces (mouth, pulmonary, gut), leading to a primary immunization in secondary lymphoid organs, there are consistent information from human and animal models supporting a critical role of the TLR (Toll-like receptor)/IL-1R (interleukin-1 receptor) pathway, at least as a second hit signal in the synovium. Indeed, the TLR pathway amplifies the abnormal crosstalk existing between antigen-presenting cells (APCs), T cells, and B cells, leading to production of high amounts of pro-inflammatory cytokines, the expansion of autoreactive lymphocytes, and local detection of Abs including ACPA and RF. After several months or years, persistent immune activation can lead to FLS (fibroblast-like synoviocyte) hyperplasia, neutrophil recruitment, complement activation resulting in cartilage destruction, bone erosion, and joint damage.

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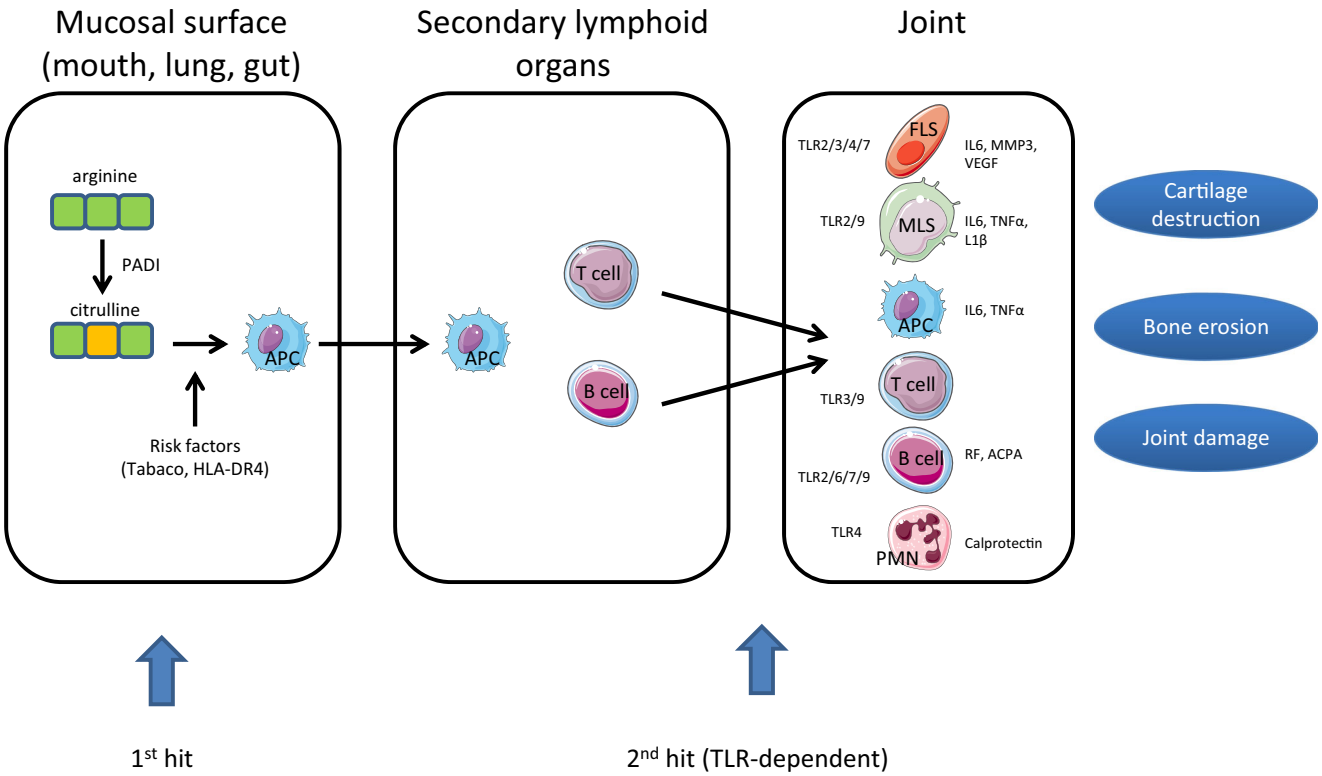

Fig. 1 A "two hits" model for the development of RA: critical role of TLRs. The first events for the occurrence of RA are supposed to take place outside the joint on the mucosal surfaces, leading to a primary immunization in secondary lymphoid organs. Nonetheless, a critical role of TLR/IL-1R as a second hit signal for the induction of an immune response directly inside the joint has to be taken into account, as a TLR-dependant second hit. Activation of TLRs induces a perpetual cycle of inflammation with the increased production of pro-inflammatory molecules like IL6, TNF alpha, or VEGF. A micro-environment is created within the joint, thanks to local (MLS, FLS) and immune-activated cells (monocytes, macrophages, B and T cells, PMN), inflammatory cytokines and death cell components, triggering a positive feedback for further TLR-mediated inflammation. PADI, peptidyl arginin deiminase; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide autoantibodies; FLS, fibroblast-like synoviocytes; MLS, macrophage-like synoviocytes; PMN, polymorphonuclear neutrophils

The TLR and IL-1 Receptor Signaling Pathway

The TLR family is evolutionarily conserved and, in humans, it is composed of 10 members, TLR1 to TLR10 [6]. TLR can be dichotomized into two groups based on their localization either on the cell membrane for TLR1/2/4/5/6/10, or on the membranes of intracellular compartments such as endosomes and endolysosomes for TLR3/7/8/9 (Fig. 2). TLRs are predominantly expressed by immune cells, as well as cells exposed to the external environment such as in the mouth, lungs, and gut (e.g., mast cells, epithelial cells) [7]. Their expression profiles vary among tissues and cell types (Table 1).

By sensing highly conserved structural motifs known as PAMPs (pathogen-associated microbial patterns), which are expressed exclusively by microbial pathogens, or DAMPs (danger-associated molecular patterns) that are endogenous molecules released from necrotic or dying cells, TLRs play a critical role in the early innate immune response [8]. TLRs are type I transmembrane proteins characterized by an extracellular domain-containing LRR (leucine-rich repeats) and a cytoplasmic tail that contains a conserved region named TIR (Toll/IL-1 receptor) and able to recruit the adapter molecule MYD88 (myeloid differentiation primary response protein 88) after homodimerization or heterodimerization of the TLRs (e.g., TLR1/2 and TLR2/6) [9] (Fig. 3). The TIR domain is present on both IL-1R (interleukin-1 receptor) and all TLRs with the exception of TLR3. MYD88 carries a death domain which helps in interacting with IRAK1/4 (interleukin-1/4-receptor-activating kinase) [10]. Subsequently, IRAK4 activates IRAK2 by phosphorylation. After dimerization, both IRAK2 and IRAK4 leave the TLR-MYD88 complex to associate with TRAF6 (tumor necrosis factor-receptor-associated protein 6). As a consequence, the recruitment and phosphorylation of TAK1 (TGF-b activated kinase 1) and TRAF6 are ubiquitinated by interacting with Bcl10 and MALT1 [11]. In addition to MYD88, there are four other TLR adapters that can further orchestrate the inflammatory response: TRIF/TICAM1 (TIR domain-containing adapter molecule 1), TRAM/TICAM2 (TIR domain-containing adapter molecule 2), TIRAP (TIR domain-containing adapter protein), and Mal (MYD88 adapter-like protein); each of them interact with a specific set of TLR [12]. The TLR intracellular signaling is also controlled by endogenous inhibitors such as IL-1R8, a transmembrane molecule acting on TLRs, and the short-

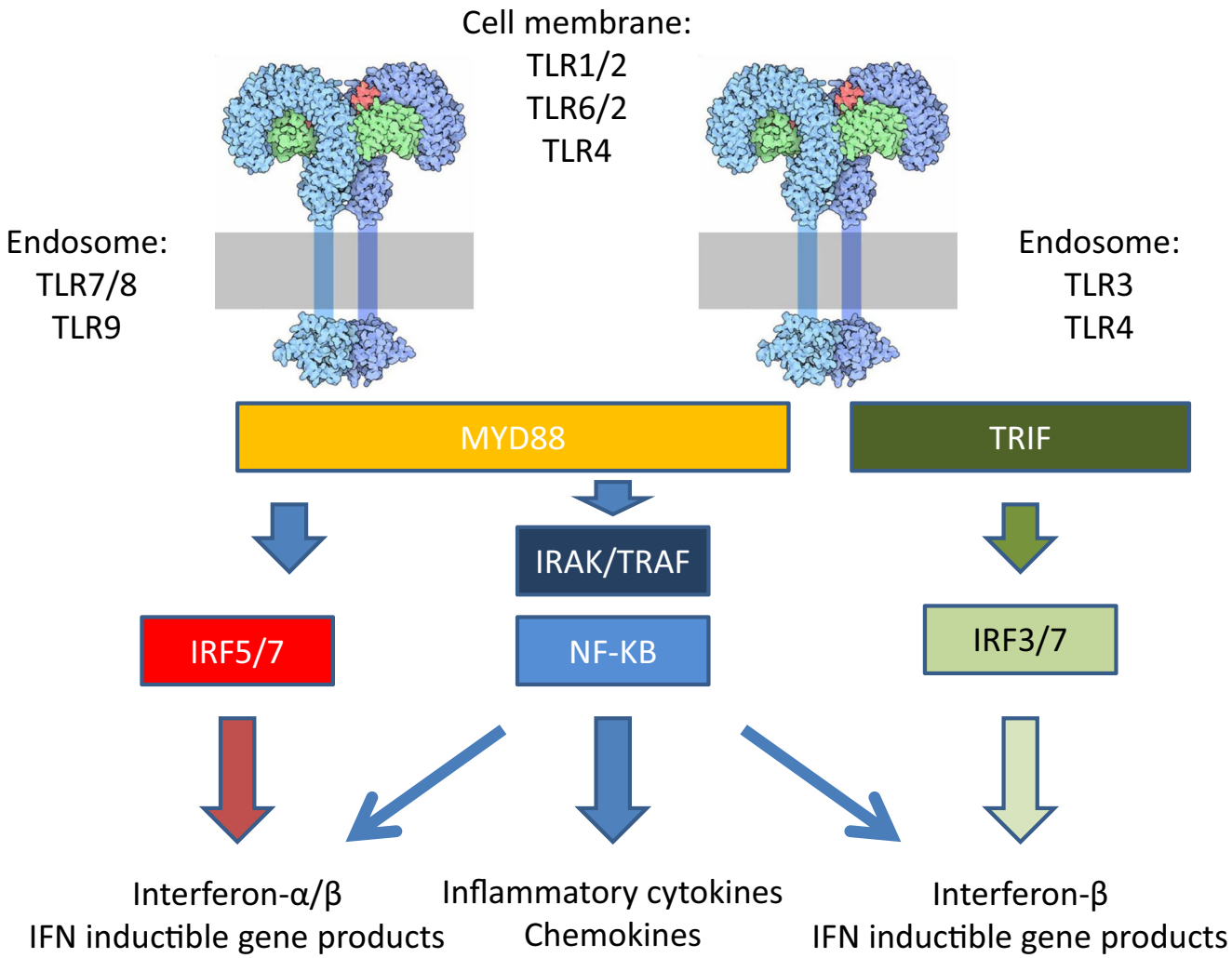

Fig. 2 The TLR family and signaling pathway. TLRs are activated through the binding of exogenous or endogenous ligands. Each of the ten members of the TLR family is classified into extracellular or intracellular subtypes. MyD88 (myeloid differentiation primary-response protein 88) and TRIF (Tir-domain-containing adapter protein inducing IFN-beta) are the two main adapter pathways for the transduction of TLR signaling. Predominantly, receptor activation leads to the association of MyD88. Therefore, two major downstream signaling pathways are induced: the NF-KB and IRF (interferon regulator factor) pathways. Regarding the NFKB pathway, the MyD88 fixation causes the phosphorylation of IRAK (interleukin-1-receptor-associated kinase), which results in the recruitment of TRAF (TNF receptor-associated factor). Some TLRs, like TLR3 and TLR4, can produce a MyD88-independent signal. Upon activation, TRIF protein is associated, enabling IRF3 and IRF7. All of these activating pathways promote the production of inflammatory proteins like interferons or inflammatory cytokines

MYD88, acting on MYD88 [13]. TLR4 presents several characteristics and, in particular, the necessity to recruit the adapter MD2 (myeloid differentiation protein-2) and the accessory molecule CD14 in order to form a complex with LPS leading to a MYD88-dependent pro-inflammatory signal. The second particularity is related to the capacity of the TLR4/MD2/CD14 complex to translocate from the plasma membrane to the endosomes, which is associated with recruitment of TRIF, as observed with TLR3, which triggers production of IFN-β in an MYD88-independent manner [14].

Stimulation of TLRs by the corresponding PAMPs or DAMPs initiates MYD88 dependent signaling cascades leading to the activation of TAK1 which in turn phosphorylates the IKK complex (IκB kinase, IKK-α, IKK-β, and IKK-γ) that leads to activation of the NF-κB (nuclear factor kappa B) pathway and the MAPK (mitogen-activated protein kinases) pathway including ERK1/2 (extracellular signal-regulated kinase), JNK (C-Jun N-terminal kinase), and P38 necessary to induce pro-inflammatory cytokines (TNF-α, IL-1, and IL-12) [12]. Following viral nucleic acid binding to the endosomal TLR3/7/8/9, the activated IRF (interferon regulatory factor) induces the production of type I interferon [15]. Type I IFN production stimulated by TLR3 and TLR4 involves IRF3 and IRF7, while TLR7, TLR8, and TLR9 involve IRF5 and IRF7. Last but not least, TLR expression is tightly regulated by several means including pro-inflammatory cytokines such as IFN-γ.

Table 1 Microbial and endogenous host ligands reported to activate immune cell Toll-like receptors (TLR)

TLR	Immune cells	Microbial ligand (PAMPs)	Endogenous ligand (DAMPs)	Signal adapter	Cytokine production
TLR1 (+TLR2)	Cell surface Mo, MΦ, DC1, B cell	Triacylated lipoproteins (Pam3CSK4), LPS, PGN	HSP, HMGB1, proteoglycans	MyD88, Mal	Pro-INF
TLR2	Cell surface Mo, MΦ, MC, B cell	Zymosan, LPS, PGN	HSP, HMGB1, proteoglycans	MyD88, Mal	Pro-INF
TLR3	Endosomes B cell, T cell, NK, DC1	dsRNA viruses (poly (I:C))	mRNA, tRNA	TRIF	Pro-INF, type1 IFN
TLR4	Cell surface/endosomes Mo, MΦ, DC, MC, IE	LPS	HSP, HMGB1, proteoglycans, fibronectin	MyD88, TRAM, TRIF, Mal	Pro-INF, type1 IFN
TLR5	Cell surface Mo, MΦ, DC, IE	Flagellin		MyD88	Pro-INF
TLR6 (+TLR2)	Cell surface Mo, MΦ, MC, B cell	Diacylated lipoproteins(FSL-1), zymosan			
TLR7	Endosomes Mo, MΦ, DC2. B	ssRNA viruses	ssRNA/IgG complexes	MyD88	Pro-INF, type1 IFN
TLR8	Endosomes Mo, MΦ, DC, MC	ssRNA viruses, imidazoquinolines (R848), guanosine analogs (loxoribine)	ssRNA/IgG complexes	MyD88	Pro-INF, type1 IFN
TLR9	Endosomes Mo, MΦ, DC2, B,T	Unmethylated CpG (CpG ODNs)	Chromatin, IgG complexes	MyD88	Pro-INF, type1 IFN
TLR10	Endosomes Mo, MΦ, DC	Profilin-like proteins		MyD88	Pro-INF

Mo monocytes, *MΦ* macrophages, *DC1* dendritic cells type 2, *DC1* dendritic cells type 2, *MC* mast cells, *IE* intestinal epithelium, *Pro-INF* pro-inflammatory cytokines, *HSP* heat shock proteins, *HMGB1* high mobility group protein 1, *LPS* lipopolysaccharides, *PAMPs* pathogen-associated microbial patterns, *DAMPs* danger-associated molecular patterns, *PGN* peptidoglycans

TLR and Rheumatoid Arthritis

Lessons from Clinical Studies

In healthy individuals, the synovium is important for providing nutrients to the cartilage and lubricants to allow cartilage mobility. With RA initiation, important changes in the synovium are observed including expansion of the synovial intimal lining composed of FLS and MLS (macrophage-like synoviocytes). Such expansion is associated with FLS with overexpression of TLR2/3/4/7 and production of a high amount of IL-6 and MMP3 (metalloproteinase 3). Regarding MLS, they produce a large panel of pro-inflammatory cytokines in response to TLR overexpression and hyper response. In addition to being overexpressed at the FLS and MLS cell surface, an abnormal presence of bacterial DNA and bacterial peptidoglycans has been reported in joints of patients with RA [16, 17] as well as demonstration that active TLR-4 ligands are increased in the serum and synovial fluid of RA patients [18].

Analysis of T and B cells present in the synovial sublining with APC (DC, macrophages, mastocytes) reveals CD4+ memory T cells that can be diffusively organized or associated with mature B cells and antibody-producing plasmablasts to form ectopic germinal centers. Peripheral memory T cells have been proposed as an interesting biomarker associated with the biological response to disease-modifying antirheumatic drugs (DMARDs) [19, 20]. Present in the synovial fluid space, neutrophils express TLR and contribute to joint damage by the release of pro-inflammatory cytokines and MMPs.

Lessons from Mouse Models

In RA animal models, activation of the TLR pathway is used to induce the disease in susceptible strains (Table 2). The disease can be reproduced in IL-1 receptor antagonist (Ra)-deficient mice that spontaneously develop autoimmune arthritis due to excessive IL-1R/TLR signaling [21]. Autoimmune arthritis in this model is dependent on the microbial flora since germ-free mice do not develop arthritis. Coupling IL-1Ra and TLR2 knockdown revealed a more severe arthritis with Treg reduction, while the IL-1Ra and TLR4 knockdown had a markedly lower capacity to produce IL-17 [22, 23]. Analysis of the microbiota in the IL-1Ra-deficient mice revealed an aberrant intestinal flora and, when the fecal microbiota was transferred into wild-type mice, they reproduce IL-17 production by the lamina propria and T helper (TH)17 expansion [23].

Mice expressing both the T cell receptor (TCR) transgene KRN and the MHC class II molecule A(g7) (K/BxN mice) develop a severe arthritis, and sera from these mice cause a similar arthritis in a wide range of mouse strains, due to Abs recognizing glucose-6-phosphate isomerase. This mechanism is dependent on the IL-1R/TLR pathway since neither IL-1R nor MYD88 knockdown mice develop synovitis after the transfer of the arthritogenic sera [24]. The functional

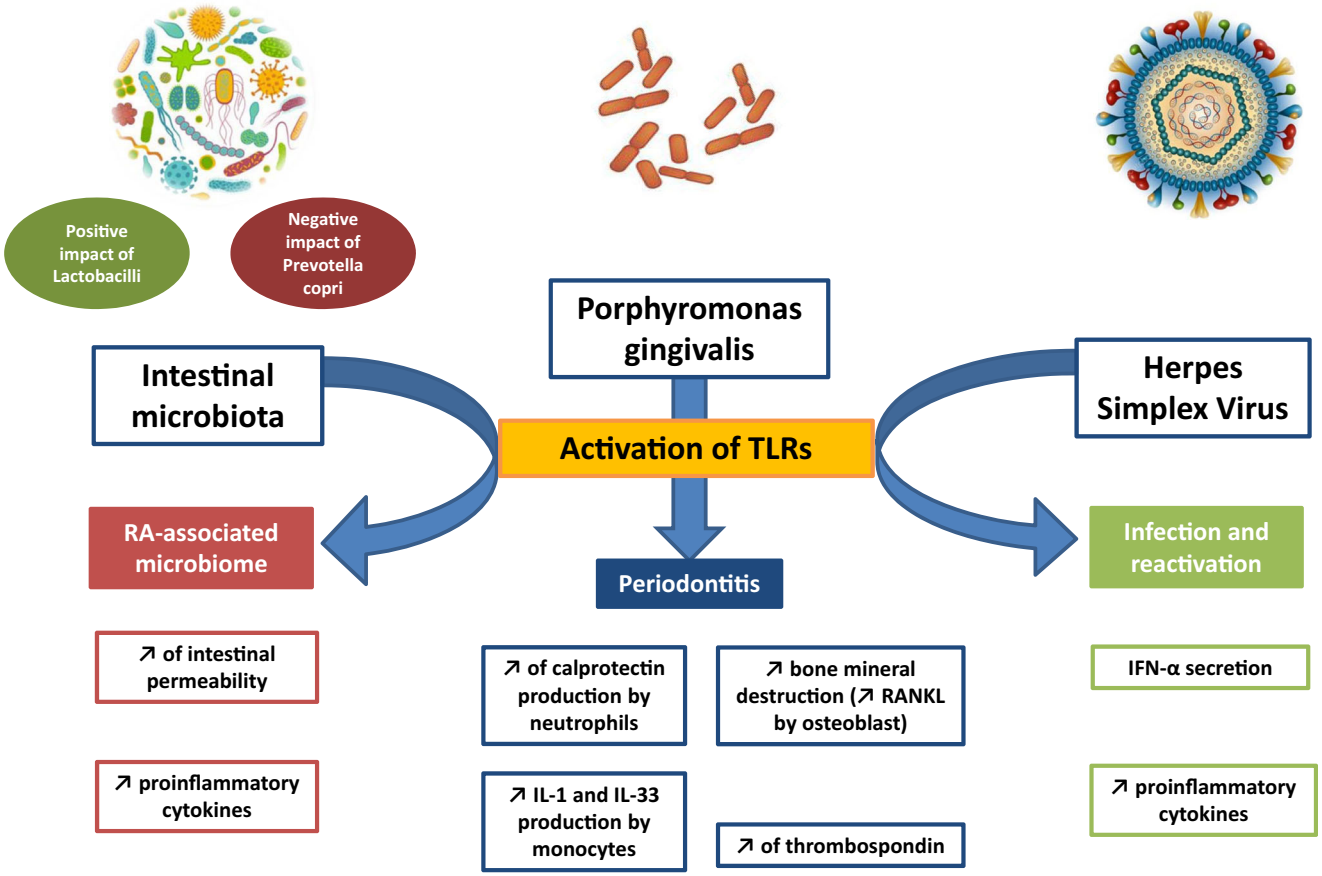

Fig. 3 Effects of microorganisms on IL1/TLR pathway and RA development. Several infectious agents have been related to the development of RA. The most famous is *Porphyromonas gingivalis*, responsible for periodontitis infection. The bacterium is well-known for producing an enzyme, the PPAD (prokaryotic peptidylarginine deiminase), able to convert the arginine of various peptides to citrulline. The citrullinated proteins are then recognized by the immune system and especially when presented by the HLA-DR4. This germ also activates the TLR2 on a chronic basis, leading to the expression of many inflammation markers and stimulating osteoclasts for bone destruction in the RA. Some particular intestinal microbiota profiles have also been described in RA patients, characterized by the presence of *Prevotella copri* among others, and leading to auto-immune diseases like inflammatory bowel disease and colitis, but also RA, through the activation of IL-1R/TLR pathway. Some protective bacteria have also been identified, such as lactobacilli, reducing inflammation and restoring healthy intestinal microbiota. RA patients are concerned as well by a higher frequency of HSV infections or reactivations, causing a TLR2 and a TLR9 activation which results in the production of inflammatory molecules

significance of TLR2 and TLR4 was tested after serum transfer revealing the protective role of TLR2 on joint inflammation and bone erosion by controlling the FcγR (Fc gamma receptor) response in macrophages [25], while TLR4 mediated pro-inflammatory cytokine production by joint macrophages and mast cells [26]. The mechanisms by which the gut microbiota affects arthritis development were further explored revealing the importance of follicular helper T cell differentiation, instead of a TH17-dependent mechanism [27].

Lessons from Genetic and Epigenetic Studies

More than 100 genetic variants have been characterized for RA, and among them, several involve the TLR pathway (Table 3). Regarding TLR2, a dinucleotide polymorphism present in intron 2 is suspected to confer susceptibility to RA in a Korean population [28], while it is the TLR3 rs3775291 A allele that is significantly associated with RA in sero-negative Danish patients [29]. Several groups have further evaluated TLR4 polymorphisms supporting roles for a TLR4 Asp299Gly mutation (rs4986790) in RA pathogenesis, in preventing chronic periodontal disease mediated by *Porphyromonas gingivalis*, and in providing a more effective response following anti-TNF biotherapy [30–32]. TLR4 rs1927911 is associated with disease activity [33]. For TLR8 rs5741883, a moderate association with RF positivity has been reported by a Danish group [34]. TLR9 rs187084 presents regional variations with a susceptibility to RA, and an anti-TNF therapy response is reported in RA patients from Turkey and Poland [30, 35]. With regard to downstream TLRs, TRAF1 rs7021206 is associated with RA susceptibility in those patients positive for RF and ACPA, and TRAF5 rs7514863 represents another RA susceptibility risk factor [36, 37].

Table 2 TLR-associated genetic risk factors in rheumatoid arthritis (RA)

Polymorphisms	Gene location	Clinical associations	Reference
TLR2 (dinucleotide repeat)	Intron	RA susceptibility	[28]
TLR3 (rs3775291)	Coding region (Leu412Phe)	Seronegative RA	[29]
TLR4 (rs4986790, rs4986791)	Coding region Asp 299 Gly of TLR 399 Ile	RA activity, periodontal disease, and anti-TNF response	[30–32]
TLR4 (rs1927911)	Intron	RA susceptibility	[33]
TLR8 (rs5741883)	Intron	RF positivity	[34]
TLR9 (rs187084, rs5743836)	Intron and TF binding site	RA susceptibility and anti-TNF response	[30, 35]
IRAK1 (rs3027898)	Coding region (Ser532Leu)	RA susceptibility	[81]
TRAF1 (rs7021206)	Intron and TF binding site	Association with RF and ACPA	[36]
TRAF5 (rs7514863)	Intron	RA susceptibility in UK	[37]

Among the epigenetic factors associated with RA, increasing evidence supports a role for miRNAs in the regulation of the TLR pathway [38]. MiRNAs are defined as short non-coding RNAs capable of gene expression modulation via direct binding to the 3′-UTR (untranslated region) of target mRNAs [39]. One way in which miRNAs can affect the IL-1R/TLR pathway is by controlling TLRs and IL-1R, and this includes miR19a and miR140-5p/miR6089 which regulate TLR2 and TLR4, respectively [40–42]. A second way is to act as an endogenous ligand for TLR as demonstrated with Let-7b which possesses a GU-rich domain able to stimulate TLR7 in myeloid cells leading to pro-inflammatory M1 macrophage differentiation [43]. A third way is to target TLR/IL-1R adapter molecules, and the best example is miR146a, demonstrated to be overexpressed in RA, which controls IRAK1 and TRAF6 except when the C allele is present since it is considered to be protective for RA development [44]. Another example is miR10a which is downregulated in RA FLS with IRAK4 and TAK1 as targets and which is upregulated in those patients responding to methotrexate [45, 46].

Infections, TLR, and Rheumatoid Arthritis

Among potential infectious sources of PAMPs, oral microbiota and commensal intestinal microbiota are suspected. In this regard, epidemiologic data have been reported pointing to a positive association between RA and upper respiratory tract infection on one hand [47], while, on the other hand, it is a negative association that was observed relative to gastrointestinal and urogenital tract infections [48].

Microbiota

Recent studies suggest that alteration of intestinal microbiota, known as gut dysbiosis, contributes to the occurrence or development of RA through an impaired balance between pro- and anti-inflammatory immune responses [49]. In particular, *Prevotella copri*, a Gram-negative anaerobic bacterial member of the Bacteriodetes phylum, defined the microbiome of RA patients and is implicated in other autoimmune diseases including inflammatory bowel disease and colitis [50]. The consequential effects of these shifts include alterations in the metabolic composition of the gut, hyperactivation of the IL-1R/TLR pathway, upregulation of pro-inflammatory cytokines, increased intestinal permeability, and increased inflammation [51]. Differential microbiome compositions exist between males and females [52]. Moreover, intervention at the level of the microbiota appears to attenuate symptoms as reported with lactobacilli, playing a positive role in restoring intestinal health, and decreasing inflammation [53].

Table 3 miRNA controlling the TLR pathway dysregulated in rheumatoid arthritis (RA)

miRNA	Target	Clinical association	Reference
↗miR-146a (rs2910164)	TRAF6, IRAK1	RA susceptibility	[81]
↘miR10a	↗IRAK4, TAK-1	MTX therapy response, FLS proliferation and migration	[45, 46]
Let-7b	TLR7 (ligand)	Joint inflammation (monocytes ➔ M1)	[43]
↘miR19a/b	↗TLR2	↗IL-6 and MMP3 (FLS)	[40]
↘miR140-5p	↗TLR4	↗IL-6, IL-8, proliferation (FLS)	[41]
↘miR6089	↗TLR4	↗IL-6, IL-29, TNF-α	[42]

Table 4 Toll-like receptor overexpression and/or hyper-response in rheumatoid arthritis (RA)

Cells, area	TLRs	Function	References
Synovial lining	↗TLR2/3/4/7		[18]
Macrophage-like synoviocytes (MLS)	↗TLR2/9	TNFα, IL-6, IL1β	[67]
Fibroblast-like synoviocytes (FLS)	↗TLR2/3/4/9	IL6,VEGF, MMP3	[82]
DC1 from monocytes	TLR2/4 hyper response	TNF-α, IL6	[18]
PBMC	TLR4 hyper response	IL6, GCSF	[83]
Neutrophils	TLR4 hyper-response	Calprotectin	

MMP metalloprotease, *VEGF* vascular endothelial growth factor, *TNF* tumor necrosis factor

Porphyromonas gingivalis

Several arguments support *P. gingivalis* as an important etiological factor in RA. First, *P. gingivalis* is associated with periodontitis, an inflammatory disorder of the mouth, and it is a well-known environmental risk factor associated with RA [54]. Second, *P. gingivalis* has the particularity to express a prokaryotic peptidylarginine deiminase (PPAD) able to convert arginine to citrulline, thereby becoming a target for ACPA [55]. Such capacity appears to be unique and not shared with other common oral prokaryotic organisms. Further evidential support that LPS (lipopolysaccharide) from *P. gingivalis* activates TLR2 leading to the upregulation of the extracellular matrix protein TSP1 (thrombospondin-1) and IL-33 in monocytes. IL-33 is an IL-1 family cytokine that is important in regulating T helper type 2 anti-inflammatory cytokines and mast cell development to the production of calprotectin by neutrophils and to the bone mineral release and matrix degradation by increasing osteoclast differentiation in response to RANKL (receptor activator of NF-KB ligand) overexpression [56–59]. Furthermore, the TLR2 response to *P. gingivalis* is reduced in the presence of cigarette smoke extract, another important RA risk factor. This supports the assumption that periodontitis is increased in tobacco smokers and also that smokers have fewer signs of inflammation [60, 61]. Third, elevated levels of *P. gingivalis* DNA have been isolated in the synovial fluids of inflamed joints from patients with RA and, in particular, in those harboring the RA susceptibility, HLA-DR shared epitope DR4 [62]. Fourth, treating RA patients with anti-TNF mAb reduces *P. gingivalis* oral colonization and periodontal disease but a persistent periodontal disease hampers the treatment response [63, 64]. In the SKG RA mouse model, *P. gingivalis* extra-articular injection in the peritoneum enhances the severity of the disease, and this is dependent on the TH17/IL-7 signaling pathway [65].

Herpes Simplex and TLR

For a long time, HSV (herpes simplex virus) is suspected of being involved in RA although the debate is still open as to whether or not the increasing reports of HSV reactivation during RA results, in fact, from an alteration in the immune system which then increases the susceptibility to infection or if the infectious events predispose one to RA [66]. Furthermore, innate resistance to HSV relies on the activation of TLR2 and TLR9, two TLRs overexpressed in monocytes from active RA and which display higher production of pro-inflammatory cytokines in response to TLR agonists [67] (Table 4). This then supports a role for HSV and other HHV (human herpes virus) family members in the exacerbation of RA symptoms [47]. Indeed, HSV genomic DNA can engage TLR9 and result in the secretion of IFN-α by pDCs [68], while the HSV envelope glycoprotein gB and dUTPase are both recognized by TLR2, which leads to the activation of NF-κB and secretion of pro-inflammatory cytokines [69, 70].

Conclusions

The discovery of TLRs has opened up new perspectives in autoimmune diseases and, in particular, in RA. As a consequence, blocking TLR signals represents an attractive therapeutic approach as demonstrated with an anti-TLR2 mAb able to decrease spontaneous pro-inflammatory cytokine release from RA synovial tissue explant cultures [71], or with hydroxychloroquine—a DMARD that suppresses the TLR9-mediated human B cell capacity to differentiate to plasmablasts [72]. Hence, controlling TLR activation in RA, as well as identifying RA patients who will respond to these therapies, and a better knowledge of the innate immune mechanisms as reviewed in this special issue [49, 73–80] open new therapeutic perspectives.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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