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C-type lectin domain family 12, member A: A common denominator in Behçet's syndrome and acute gouty arthritis

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ABSTRACT

C-type lectin domain family 12, member A (CLEC12A) is a C-type lectin-like pattern recognition receptor capable of recognizing monosodium urate crystals. Monosodium urate crystals, the causative agents of gout are also among the danger-associated molecular patterns reflecting cellular injury/cell death. In response to monosodium urate crystals, CLEC12A effectively inhibits granulocyte and monocyte/macrophage functions and hence acts as a negative regulator of inflammation. Behçet's syndrome and gout are autoinflammatory disorders sharing certain pathological (neutrophilic inflammation), clinical (exaggerated response to monosodium urate crystals) and therapeutic (colchicine) features. We propose the hypothesis that decreased expression of CLEC12A is a common denominator in the hyperinflammatory responses observed in Behçet's syndrome and gout. Major lines of evidence supporting this hypothesis are: (1) Downregulation/deficiency of CLEC12A is associated with hyperinflammatory responses. (2) *CLEC12A* polymorphisms with functional and clinical implications have been documented in other inflammatory diseases. (3) Colchicine, a fundamental therapeutic agent used both in Behçet's syndrome and gout is shown to oppose the downregulation of CLEC12A. (4) Behçet's syndrome and gout are characterized by a hyperinflammatory response to monosodium urate crystals and other than gout, Behçet's syndrome is the only inflammatory condition exhibiting this exaggerated response. (5) Genomewide linkage and association studies of Behçet's syndrome collectively point to 12p12–13, the chromosomal region harboring *CLEC12A*. (6) Patients with severe forms of Behçet's syndrome underexpress CLEC12A with respect to patients with mild forms of the disease. If supported by well-designed, rigorous experiments, the forementioned hypothesis pertinent to CLEC12A will carry important implications for therapy, designing experimental models, and uncovering immunopathogenic mechanisms in Behçet's syndrome and gout.

Background

C-type lectin domain family 12, member A (CLEC12A) and monosodium urate crystals

Lectins are a diverse group of proteins exhibiting high specificity and binding properties for carbohydrate moieties. C-type lectins (CLECs) as their name implies, are calcium dependent lectins which require calcium while binding to their specific carbohydrate moieties [1]. Concisely, CLECs are believed to be the most prevalent lectins in immunity. While mediating immune responses, CLECs mainly act as adhesion molecules or signaling receptors [2].

C-type lectin domain family 12, member A (CLEC12A, also known as MICL and CLL1) is a glycoprotein encoded by the gene *CLEC12A* located at 12p13.2 [3]. Initially, CLEC12A was identified as an inhibitory C-type lectin-like receptor whose expression was primarily restricted to granulocytes and monocytes and hence given the name myeloid inhibitory C-type lectin-like receptor (MICL) [4]. Detailed characterization of CLEC12A demonstrated that it is a transmembrane protein containing a cytoplasmic immunoreceptor tyrosine-based inhibitory motif (ITIM) [4]. As expected, chimeric analyses showed that CLEC12A can inhibit cellular activation through its cytoplasmic ITIM and is a negative regulator of granulocyte and monocyte function [4]. Further studies documented that CLEC12A is also expressed on dendritic cells and is down-regulated following cellular activation [5].

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Subsequent research enabled identification and characterization of the murine homolog of CLEC12A. Known by the names Clec12a, Micl, and KLRL1, this protein was found to be expressed on granulocytes, monocytes/macrophages, dendritic cells, natural killer (NK) cells, B cells, and CD8+ T cells [6–8]. Being structurally and functionally similar to CLEC12A, this protein is also able to recruit inhibitory phosphatases upon activation, and hence act as an inhibitory receptor [8].

Recently, both CLEC12A and Clec12a were shown to recognize monosodium urate crystals (MSU), which are accepted as cardinal danger signals of dead cells [9,10].

- CLEC12A is an inhibitory C-type lectin-like receptor and negatively regulates granulocyte and monocyte functions [4,8].
- CLEC12A is expressed in a wide variety of immune system cells, innate immune system cells being the most important [4,5,7,8].
- CLEC12A is able to recognize monosodium urate crystals [9].

Innate immune system, inflammation and its regulation

For sake of simplicity, human immune system is divided into two principal components, namely the innate and the acquired immune systems. Innate immune system has anatomical barriers with physical, chemical, and biological components of defense and additionally, has cellular (e.g., dendritic cells, granulocytes, monocytes/macrophages, mast cells, NK cells, γδ T cells) and humoral (e.g., complement system, interferons, cytokines, chemokines) components [11,12].

Immune responses start with the recognition of a non-self molecule (the "self–non-self theory", infectious agents) or a damage/danger signal (the "danger theory", endogenous/self molecules) [13]. In the case of innate immunity, this recognition is achieved through pattern-recognition receptors (PRRs) (i.e., Toll-like receptors, RIG-I-like receptors, NOD-like receptors, and C-type lectin receptors) [14]. PRRs are able to recognize and interact with both pathogen-associated molecular patterns (PAMPs, components of infectious agents) and damage/danger-associated molecular patterns (DAMPs, endogenous/self molecules occurring on the occasion of cell death). While the number of identified DAMPs are increasing, one of the oldest DAMPs which is uric acid is gaining popularity [9,10]. Following PRR-ligand (i.e., PRR-PAMP, PRR-DAMP) interaction, the intracellular signaling pathways activated by PRRs lead to increased expression of inflammatory mediators which generate the inflammatory response aiming to resolve infection or tissue injury [14,15].

As a general rule, the inflammatory response is a well-coordinated, appropriate, and "calculated" reaction with beneficial effects [16]. However, an incoordinated, inappropriate or aberrant inflammatory response, as in the case of autoinflammatory diseases, may be disastrous by causing profound and severe tissue injury [17]. So it becomes evident that, during inflammation, the activation of innate immune system cells needs to be controlled. Correspondingly, it has been revealed that inflammatory responses are tightly regulated by inhibitory receptors (an example of which is CLEC12A), specific inhibitory cells, and protein or lipid mediators. It is a well-known fact that in some circumstances, activating and inhibitory receptors of innate immune system cells recognize similar/identical ligands and the net result is determined by the relative strengths of the opposing signals (Fig. 1) [18].

- Inflammation is the immune system's response to infections and/or tissue damage.
- During the development of the inflammatory response, innate immune system cells recognize infectious agents and/or endogenous danger signals through a group of receptors, collectively named as pattern-recognition receptors (PRRs) [14].

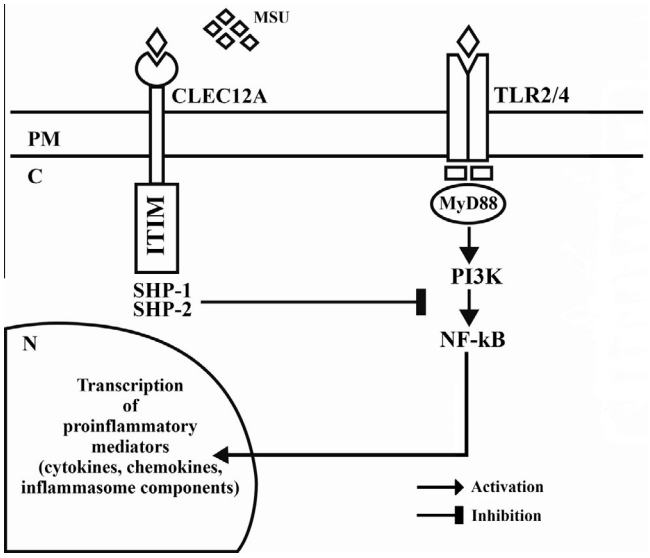

Fig. 1. Possible interaction between activatory (TLR2/4) and inhibitory (CLEC12A) pattern recognition receptors for monosodium urate crystals. In this simplified and schematized diagram, signaling pathways and interactions of activatory (TLR2/4) and inhibitory (CLEC12A) PRRs for MSU is shown. In the case of MSU engagement to both TLR2/4 and CLEC12A, the strong signal will predominate and will be the determining factor between the fate of cellular activation and the fate of cellular inhibition. C, cytoplasm; CLEC12A, C-type lectin domain family 12, member A; ITIM, immunoreceptor tyrosine-based inhibitory motif; MSU, monosodium urate crystals; MyD88, myeloid differentiation primary response 88; N, nucleus; NF-kB, nuclear factor kappa B; PI3K, phosphatidylinositol 3-kinase; PM, plasma membrane; SHP-1/2, SH2 domain-containing SHP-1 and SHP-2 tyrosine phosphatases; TLR2/4, Toll-like receptors 2 and 4.

- C-type lectin receptors (of which CLEC12A is a member) are among the well-known PRRs [14].
- Endogenous/self molecules capable of binding to and activating the PRRs are known as damage/danger-associated molecular patterns (DAMPs).
- Uric acid (monosodium urate crystal) is an important DAMP [9,10].
- The inflammatory response is regulated by inhibitory receptors (an example of which is CLEC12A), inhibitory cells, and inhibitory soluble mediators. The fate of the inflammatory response is determined by the balance between the activating and inhibiting factors [18].
- In autoinflammatory diseases (e.g., Behçet's syndrome, acute gouty arthritis), an aberrant, inappropriate or dysregulated intense inflammatory response is observed.

Behçet's syndrome and the exaggerated immune response to monosodium urate crystals

Behçet's syndrome (BS) is a chronic multisystemic inflammatory disorder of an unknown etiology [19]. Although mucocutaneous and ocular lesions are the most common findings, vascular, gastrointestinal, musculoskeletal and central nervous system involvement can also occur [20]. Though still incompletely understood, an exaggerated and mainly innate immune system derived inflammatory action is accepted as the pivotal pathogenic mechanism in BS [21,22].

Many of the BS patients demonstrate a type of skin hyperreactivity called the pathergy reaction (PR). Although the frequency of PR positivity varies considerably among different populations, PR is included in the criteria for diagnosis of BS [23,24]. Also, patients with BS demonstrate an exaggerated inflammatory reaction to intradermal injection of MSU (urate skin test) in a quite similar way to PR [25,26]. Interestingly, as is the case for PR, the frequency

of positivity of the skin response to MSU is varying among different populations [25].

- Behçet's syndrome (BS) is a chronic multisystemic inflammatory disorder of an unknown etiology. Currently, BS is also listed as one of the autoinflammatory diseases [21].
- Patients with BS demonstrate a characteristic skin hyperreactivity, both in the form of a pathergy reaction (following a clean skin prick) and to intradermal injection of monosodium urate crystals (urate skin test) [25,26].

Hyperuricemia, monosodium urate crystals and acute gouty arthritis

Uric acid (UA) is the end product of purine metabolism in humans and is a poorly water-soluble molecule. Hyperuricemia is variably defined as a plasma UA level >6.8–7.0 mg/dL (the approximate concentrations at which UA is supersaturated in plasma). In patients with hyperuricemia, chief complications are gout and UA urinary stones.

Gout is a disease caused by deposition of MSU in tissues, primarily in periarticular tissues and/or synovial fluid. The disease typically starts and progresses with bouts of very intense arthritis (acute gouty arthritis). As previously stated, MSU act as a DAMP recognized by PRRs both at cell membrane and cytoplasm [9,10,27]. With regard to MSU induced inflammation, inhibition and activation signals have been documented [9,28,29]. While CLEC12A mediated signal is the inhibitory one, the activation signals acting in concert result in the synthesis, processing, and release of interleukin (IL) 1β and IL-18, well-known cytokines for their potent inflammatory actions (Fig. 2) [9,30].

There is an important unresolved question on the development of gout. Although acute gouty arthritis occurs in patients with hyperuricemia and the risk of developing acute gouty arthritis parallels plasma UA levels; for any given plasma UA level, only a portion of hyperuricemic patients go on to develop this complication [31]. The underlying rationale for this fact remains to be elucidated.

- Gout is a metabolic disease characterized by hyperuricemia and deposition of monosodium urate crystals (MSU) in tissues, mainly in and around joints.
- Gout is also classified as an autoinflammatory disease by the bouts of very intense arthritis (acute gouty arthritis) it causes [29].
- Uric acid (UA) in the form of MSU, is an important damage/danger-associated molecular pattern with well-defined pattern-recognition receptors that recognize it (e.g., Toll-like receptor 2, Toll-like receptor 4, CLEC12A) [9,10,27–30].
- Because of reasons yet unknown, for any given plasma UA level, only a portion of hyperuricemic patients go on to develop acute gouty arthritis [31].

Hypotheses

In light of the existent and the above summarized literature concerning CLEC12A, BS, and acute gouty arthritis, the following hypotheses are proposed:

1. In patients with BS, the exaggerated skin response to MSU is related to underexpression of CLEC12A.
2. By compromising the inhibitory control of innate immune system cells, decreased expression of CLEC12A in BS results in the development of a more intense inflammatory response. Through this mechanism, underexpression of CLEC12A may be underlying a more generalized pro-inflammatory immune abnormality in patients with BS.
3. In patients with hyperuricemia, decreased expression of CLEC12A is associated with the development of acute gouty arthritis.

Discussion

Autoinflammatory diseases constitute a heterogenous and growing group of clinical disorders characterized by "episodes of seemingly unprovoked inflammation without high-titer autoantibodies or antigen-specific T lymphocytes" [32]. The innate immune system with its cellular components (e.g., granulocytes, monocyte/macrophages, dendritic cells, NK cells), PRRs, and soluble mediators (e.g., interleukins, chemokines) dominates the pathogenesis of autoinflammatory diseases. Currently, both BS and gout are included in the classification schemes of autoinflammatory diseases [32,33].

Gout is a prevalent disease with a still increasing prevalence [34]. BS has a characteristic geographical distribution with high prevalences along the ancient trading route named as the Silk Road. Both diseases are known to impair the quality of life of the sufferers. Additionally, while gout appears to be an independent risk factor for cardiovascular mortality and morbidity, BS has a significant morbidity profile and is reported to be a cause of increased mortality in the young male patients [35].

Recently, Qing et al. proposed that, polymorphisms involving the innate immunity genes may confer susceptibility to gout [36]. Apprehensibly, same may be true for BS, which has a strong genetic background. Polymorphisms of CLEC12A gene may modulate its overall inhibitory action in innate immune responses.

Identifying a shared gene important for both BS and gout may provide new insights into the immunopathogenic mechanisms of these diseases, and thereby may point to new molecular targets with therapeutic implications.

The pros and cons of the hypotheses

1. **Effects of the downregulation of CLEC12A.**

It is shown that in neutrophils, the downregulation of CLEC12A enhances MSU-induced neutrophil activation [37]. Also, by conducting in vivo experiments Neumann et al. demonstrated that, following challenges with MSU or necrotic cells, Clec12a-deficient mice exhibit hyperinflammatory responses [9]. In another in vivo experiment, injection of mice with a rat anti-Clec12a monoclonal antibody resulted in an enhanced antibody production mainly through dendritic cell effects [38]. Polymorphisms of *CLEC12A* gene may adversely alter the expression, ligand binding characteristics, and ITIM functions of the protein and thereby modulate its inhibitory action in innate immune responses. Such a polymorphism with clinical implications has already been documented in an inflammatory arthritis [39].

Another mechanism instrumental in downregulating CLEC12A was previously touched on in BS. An in vivo priming of neutrophils without full activation had been suggested [40]. The same scenario assuming a state of "in vivo" neutrophil preactivation had been implicated in BS [41]. As CLEC12A is downregulated following cellular activation, the primed state of neutrophils in patients with BS may provide another explanation for the downregulation of CLEC12A [5,8,37].

2. **Behçet's syndrome, acute gouty arthritis, neutrophils, CLEC12A, and colchicine**

The hallmarks of BS are the mucocutaneous lesions and these lesions characteristically demonstrate significant neutrophil infiltrates [42]. Another cutaneous finding typically observed in BS is the PR. PR also occurs in neutrophilic dermatoses which

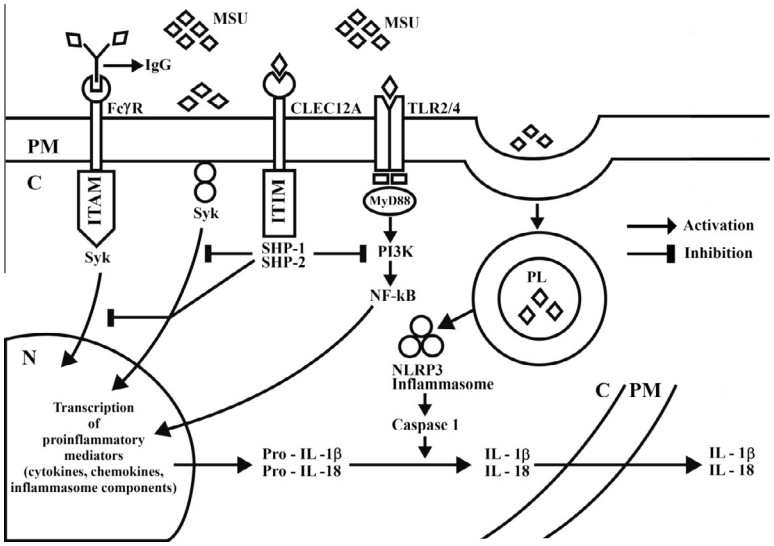

Fig. 2. The interplay between the activatory and inhibitory recognition mechanisms of monosodium urate crystals. A simplified and schematized diagram demonstrating the receptor based and direct activatory and CLEC12A mediated inhibitory recognition mechanisms of MSU and the potential interactions between them. C, cytoplasm; CLEC12A, C-type lectin domain family 12, member A; FcγR, Fc receptor for immunoglobulin G; IgG, immunoglobulin G; IL-1β, interleukin-1beta; IL-18, interleukin-18; ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; MSU, monosodium urate crystals; MyD88, myeloid differentiation primary response 88; N, nucleus; NF-kB, nuclear factor kappa B; NLRP3, NACHT, LRR and PYD domains-containing protein 3; PI3K, phosphatidylinositol 3-kinase; PL, phagolysosome; PM, plasma membrane; Pro-IL-1β, pro-interleukin-1beta; Pro-IL-18, pro-interleukin-18; SHP-1/2, SH2 domain-containing SHP-1 and SHP-2 tyrosine phosphatases; Syk, spleen tyrosine kinase; TLR2/4, Toll-like receptors 2 and 4.

harbor dense neutrophilic infiltrates and are now known to be autoinflammatory disease entities [43]. Acute gouty arthritis is the prototype of the crystal arthritis and is characterized by a heavy neutrophil infiltration of the involved joint [44]. Similarly, BS synovitis typically demonstrates a striking neutrophilic inflammation [45]. As such, both BS and gout are classified as autoinflammatory diseases characterized by recurrent attacks of inflammation primarily mediated by neutrophils.

CLEC12A is an inhibitory receptor expressed by neutrophils and many other innate immune system cells [4,5,7,8]. Through its cytoplasmic ITIM domain, CLEC12A is shown to inhibit neutrophil, macrophage, dendritic, and NK cell functions [4,7,37,38]. As stated above, any influence causing a downregulation of CLEC12A results in a proinflammatory state and vice versa. Colchicine is a well-known anti-inflammatory drug specifically used in three autoinflammatory diseases, namely, acute gouty arthritis, familial Mediterranean fever (FMF), and BS. Classically, the anti-inflammatory effect of colchicine is attributed to its disruption of microtubules in neutrophils, thereby impairing neutrophil chemotaxis and phagocytosis. It is also documented that colchicine has an effect on gene expression [46]. Importantly, in an MSU induced inflammation model, colchicine was shown to counteract the downregulation of CLEC12A [37]. These findings pertinent to neutrophils, CLEC12A and colchicine are in support of the hypothesis that BS and acute gouty arthritis may be sharing CLEC12A in their immunopathogenesis.

3. Monosodium urate crystal induced inflammation in Behçet's syndrome and acute gouty arthritis

As mentioned earlier, BS patients demonstrate a characteristic cutaneous response to intradermally injected MSU (urate skin test) [25,26]. Although the frequency of positivity of this skin response is varying between different populations, to the best of our knowledge, BS is the only inflammatory disease in which an exaggerated inflammatory response to intradermal injection of MSU is observed [25,47]. In order to elucidate the mechanism of this response, Gogus et al. studied the oxidative burst reaction of neutrophils to MSU in vitro [48]. They found that, when compared to healthy controls, the oxidative burst of neutrophils and monocytes was significantly increased in patients with BS [48].

MSU are among the most potent proinflammatory stimuli for neutrophils. It is known that in acute gouty arthritis, yet incompletely understood molecular mechanisms modulate recognition of dormant periarticular/intraarticular MSU. Some of these mechanisms have been clarified and reviewed elsewhere [28,29,37,49,50]. While the activating signals for MSU are numerous, one important inhibitory receptor, namely CLEC12A is characterized [9,37]

4. Genomewide linkage and association studies in Behçet's syndrome and the locus of *CLEC12A*

A genomewide linkage screen to identify the BS susceptibility genes revealed evidence for linkage to 15 non-HLA chromosomal regions including 12p12–13 [51]. Importantly, this region was shown to increase its importance following the addition of further markers [51]. A genomewide analysis but this time an association study, identified 6 possible genomic regions including 12p12.1 as genomic segments harboring BS susceptibility loci [52]. As can be seen, the region 12p12–13 was pointed out in both genomewide studies and the locus of *CLEC12A* which is 12p13.2 lies in close proximity to this region [3].

Recently, another genomewide association study identified an association at *KLRC4*, which is also an innate immunity gene [53]. Interestingly, *KLRC4* is located within the NK complex which contains several C-type lectin genes and *KLRC4*'s location (12p13.2–p12.3) exactly matches that of *CLEC12A*'s (12p13.2) [3,54].

5. Differential expression of CLEC12A among patients with Behçet's syndrome

Xavier et al. performed a comparative genomewide expression analysis between 15 BS patients and 14 healthy controls [55]. By borrowing their microarray data from Gene Expression Omnibus (GEO) database (GEO accession number GSE17114) [56], researchers at Ankara University Biotechnology Institute conducted a different analysis comparing two subsets of BS patients. According to the original data presented in the report

of Xavier et al., their 15 BS patients were grouped as either "patients without vascular involvement, mucocutaneous Behçet" (group M, $n = 11$) or "patients with vascular involvement, vasculo-Behçet" (group V, $n = 4$) for the analysis. When these two groups were compared with respect to their genomewide expression profiles, *CLEC12A* expression was found to be 2.29-fold decreased in vasculo-Behçet patients (geometric mean of intensities in group M: 187.96, geometric mean of intensities in group V: 82.04, fold change: 2.29, parametric p-value: 0.0012194) (Fig. 3) [57]. As vasculo-Behçet is accepted as the severe form of BS, this finding seems to support the hypothesis which states "underexpression of CLEC12A may be underlying a more generalized pro-inflammatory immune abnormality in patients with BS".

6. **Both Behçet's syndrome and gout are complex disorders**

BS and gout are complex disorders caused by the interaction between multiple genetic and environmental variables [58,59]. In the case of complex disorders, the interaction between a polygenic genetic background and multiple environmental factors seems to determine the occurence of these diseases. The polygenic background of an individual is constituted by the continuously interacting susceptibility and protection genes which are present in the genome. As such, for BS and gout, it is clearly impossible to put all the blame on CLEC12A and the facts presented in this article may point to CLEC12A only as a susceptibility/protection gene shared in the immunopathogenesis of both BS and gout.

Another important issue with regard to BS is its varying prevalence and differing disease expression around the globe. As previously stated, BS has high prevalences along the Silk Road and it is important to note that the more severe presentations of BS are cumulated in the same region [60]. A similar situation is also observed with respect to PR and urate skin test. As any specific and common environmental factor has not been identified yet, shared genetic factors (e.g., *HLA-B51* allele positivity, *CLEC12A* polymorphisms) may explain the gathering of BS, its severe forms, and PR and urate skin test positivity [61].

7. **Frequency of gout among patients with Behçet's syndrome**

At this point, an important question would be whether the prevalence of gout is increased among BS patients or not. To the best of our knowledge, there is no study reviewing the subject yet and we believe that the question is worth investigating. With regard to such a study, two important points should be kept in mind. First, as hyperuricemia is a prerequisite for developing gout, initially, UA metabolism should be investigated in patients with BS.

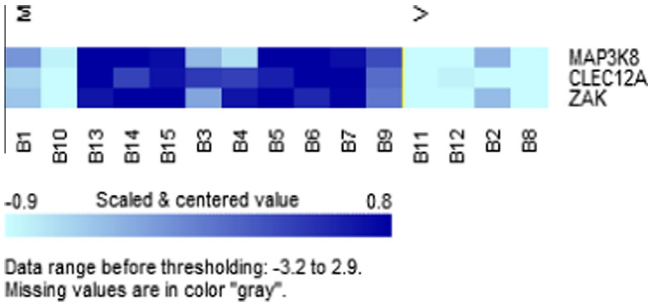

Fig. 3. Heatmap representation for the expression profiles of *CLEC12A* and two other arbitrarily selected genes (*MAP3K8* and *ZAK*) in patients with Behçet's syndrome. The heatmap displays the expression profiles of *CLEC12A* together with *MAP3K8* and *ZAK* in 15 patients with BS (B1–B15). *CLEC12A*, C-type lectin domain family 12, member A; M, mucocutaneous Behçet; *MAP3K8*, mitogen-activated protein kinase kinase kinase 8; V, vasculo-Behçet; *ZAK*, sterile alpha motif and leucine zipper containing kinase AZK.

Secondly, it must not be forgotten that, virtually all BS patients are receiving treatment with anti-gout medications (e.g., colchicine, glucocorticoids, nonsteroidal anti-inflammatory drugs) which may actually prevent the occurrence of gout in this patient population.

Future perspectives

What to do next?

The following research should be designed and conducted for the validation of our proposed hypotheses:

1. Screening, documentation and association studies of the existent polymorphisms of *CLEC12A* among populations with high and low BS prevalences.
2. Screening, documentation and association studies of the existent polymorphisms of *CLEC12A* among patients with asymptomatic hyperuricemia and patients with gout.
3. Comparative functional studies with the polymorphic variants of CLEC12A shown to be associated with BS and/or gout. These functional studies could be designed in vivo (transgenic and/or knockout mouse) or in vitro (cell culture) and at transcriptome, proteome, cell, tissue or organism levels.
4. Prevalence of hyperuricemia and potential variations in UA metabolism in patients with BS.

Implications

If our proposed hypotheses are validated through carefully designed rigorous experiments, we believe that, they may harbor important implications for therapeutic approaches, experimental model design, and elucidation of immunopathogenesis in autoinflammatory disorders including BS and gout. To mention a few;

1. Kim et al. by using decapeptides representing ITIM-like sequences demonstrated that, it is possible to inhibit the expression of inflammatory mediators with such short peptide sequences [62]. By using a similar approach, it may be possible to simulate the inhibitory function of the ITIM domain of CLEC12A. This intervention may prove to be beneficial in terms of anti-inflammatory therapy in patients with BS and gout.
2. Animal models are of great value in both elucidating the pathogenesis of diseases and for the therapeutic trials of new molecules. Up until now, there has not been a successful animal model of BS, displaying many of the clinical characteristics of the syndrome. We believe that, an *HLA-B51* transgenic and *CLEC12A* knockout animal model will prove to be very useful as an animal model of BS.
3. Control of inflammation via inhibitory receptors is an important theme in the maintenance of immune system homeostasis. Identification and characterization of the inhibitory receptors and the signaling pathways they are involved may provide important insights into the pathogenesis of autoinflammatory diseases. Being one of the recently characterized inhibitory CLEC receptors, CLEC12A has the potential to help us uncover the immune abnormalities observed in BS, gout, and presumably other inflammatory diseases.

Conclusion

CLEC12A is a C-type lectin-like pattern recognition receptor recognizing monosodium urate crystals as a danger-associated molecular pattern. Both in vivo and in vitro, CLEC12A is shown to effectively inhibit granulocyte and monocyte/macrophage functions and hence is an inhibitory receptor. Substantial amount of

evidence points to a shared immunopathogenic role of CLEC12A in Behçet's syndrome and gout. We believe that CLEC12A harbors important implications for therapy, designing experimental models, and uncovering immunopathogenic mechanisms in Behçet's syndrome and gout.

Declaration of conflict of interest

The authors declare no potential conflicts of interests with respect to the authorship and/or publication of this article.

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