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LETTER TO THE EDITOR Open Access

Schnitzler's syndrome - a novel hypothesis of a shared pathophysiologic mechanism with Waldenström's disease

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Abstract

Schnitzler's syndrome is an auto-inflammatory disorder which is characterized by two mandatory features: an urticarial rash and a monoclonal gammopathy. Although the pathophysiology of this syndrome is not yet fully understood, a role for interleukin-1 seems apparent. While this presumed link between interleukin-1 and the monoclonal gammopathy is not yet elucidated, a mutual factor in pathophysiology however seems likely. Here we present a novel hypothesis of a shared pathophysiologic mechanism between Schitzler's syndrome and monoclonal gammopathy.

Keywords: Schnitzler's syndrome, Waldenströms macroglobulinemia, Autoinflammatory disease, Hypothesis, Interleukin-1, *MYD88*, *NLRP3*

Introduction

Schnitzler's syndrome - as first described in 1972 - is a rare disorder which is diagnosed in the presence of two mandatory clinical features: an urticarial rash and a monoclonal IgM gammopathy or, less common, an IgG gammopathy. These mandatory features are accompanied with at least two of the minor criteria which are listed in Table 1 [1].

The exact prevalence of Schnitzler's syndrome is not known, although it is thought to be an underdiagnosed syndrome [2]. Since 1972 approximately 200 cases can be found in literature. The male/female ratio has been calculated as 1.76 with a mean age of onset at 51.6 years (+/− 10 years) [2]. Approximately 15–20% of patients with Schnitzler's syndrome will eventually develop a lymphoproliferative disorder like Waldenström's macroglobulinemia. This percentage is comparable with the expectancy in patients with a monoclonal IgM gammopathy of unknown significance (MGUS) [2, 3]. There is no presumptive evidence available that Schnitzler's syndrome is a familial disorder (in contrast to known familial clustering of Waldenström's disease (WD) [4]. Only one personal communication is known in literature in whom a relative of a patient with Schnitzler's syndrome was known to have a monoclonal IgM gammopathy [5]. Treatment of Schnitzler's syndrome has been difficult and unsatisfactory in the past, partly because of the unknown pathophysiology of this disease. Since Anakinra - an IL-1 receptor antagonist – proved to be effective in a case of refractory Schnitzler's syndrome, a dominant role for interleukin-1 (IL-1) seems apparent [6]. To date this putative correlation between IL-1 and the presence of the paraprotein is not yet fully understood. Here, we present a novel hypothesis which might elucidate the correlation of Schnitzler's syndrome with MGUS and WD, through a possible mutual pathophysiologic origin.

Background

The origin of the autoinflammatory character of Schnitzler's syndrome remains poorly understood. IL-1 involvement seems likely because of the positive reaction to anti-IL1 treatment. In the future it might even be possible to treat Schnitzler patients with long-acting IL-1β antagonists in which 4–8 weekly administration could be equally successful compared with daily dosing as is used in case of Anakinra [7].

A dominant role for IL-1 and the efficacy of anti-IL-1 treatment is also seen in other autoinflammatory diseases

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Table 1 Clinical features of Schnitzler's syndrome

Major Criteria
• urticarial rash
• monoclonal IgM gammopathy (IgG less common)
Minor Criteria
• recurrent fever
• arthralgia or arthritis
• bone pain
• lymphadenopathy
• hepato- and/or splenomegaly
• elevated ESR and/or leucocytosis
• bone abnormalities

Diagnostic criteria for Schnitzler's Syndrome: the diagnosis is made when two major criteria are combined with at least two minor criteria

like e.g. Cryopyrin-Associated Periodic Syndrome (CAPS). In these patients, either a somatic or germline mutation in the *NLRP3* gene can be found resulting in a spontaneous increase of IL-1β activation by cleaving pro-IL-1β into its activated form. A mutation of the *NLRP3* gene in Schnitzler's syndrome might therefore be suspected. Such a mutation in this gene is however not always present in Schnitzler's patients. Only a few Schnitzler patients with severe clinical phenotypes have been described with a proven *NLRP3* gene mutation. In these cases the severity of the disease and the different mutations (somatic mosaicisms) seemed to correlate [8]. In the majority of patients, the exact background of the syndrome remains unexplained.

Although there is no direct obvious link between Waldenström's macroglobulinemia and IL-1 with its associated auto-inflammatory diseases, it still seems likely that MGUS or WD and Schnitzler's syndrome have a mutual factor in pathophysiology as the latter can not be diagnosed in the absence of a MGUS or WD. Waldenström's macroglobulinemia is an incurable, IgM-secreting lymphoplasmacytic lymphoma. By performing whole-genome sequencing Tréon et al. [9] described the presence of a specific mutation, p.(Leu265Pro) in the *MYD88* gene in patients with IgM MGUS and Waldenström's disease. MYD88 is a key downstream adaptor molecule in most Toll-like receptors and IL-1 receptors which can cause an induction of NF-κβ either by ectopic expression [10] or by a gain-of-function mutation in *MYD88,* like p.(Leu265Pro) as described above (see Fig. 1). This NF-κβ signaling is of importance for the growth and survival of Waldenström's macroglobulinemia cells [9].

Although an alleged Schnitzler's syndrome without a monoclonal gammopathy has been mentioned before [11], the presence of a monoclonal gammopathy is stated mandatory to accomplish the diagnosis of Schnitzler's

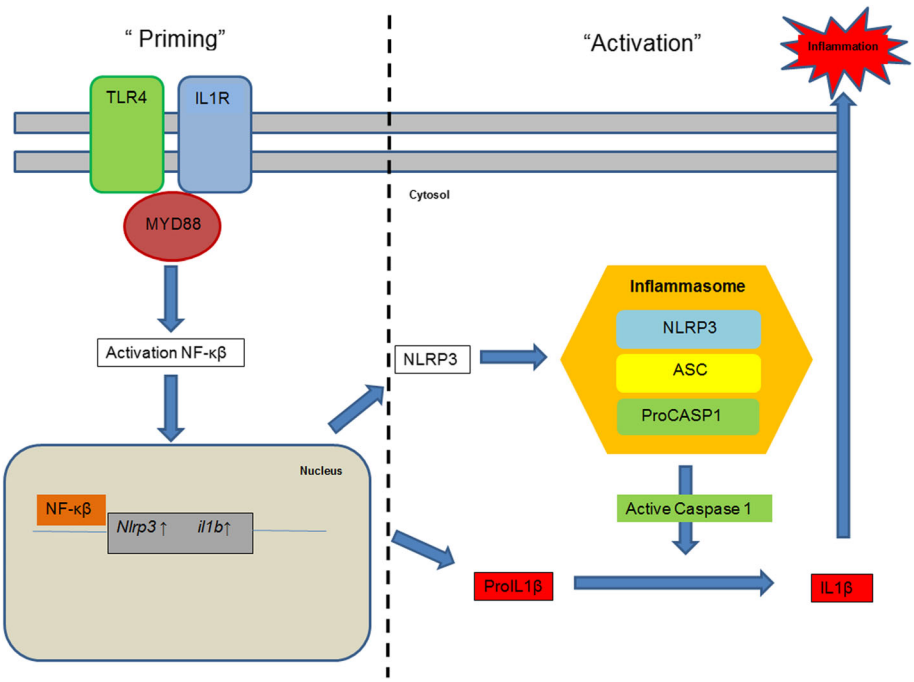

Fig. 1 The NLRP3 inflammasome pathway. Here the role of MYD88 as a downstream adaptor molecule in the toll-like receptors and IL-1 receptors is shown in the NLRP3 inflammasome pathway. It has already been proven that MYD88 can cause an induction of NF-κβ which is of importance for the survival of Waldenström's macroglobulinemia cells. MYD88 serves however hypothetically as a mutual factor in the pathophysiology of MGUS or WD and Schnitzler's syndrome due to its relation with NF-κβ, NLRP3 and the inflammasome. Furthermore, the increased activity of the inflammasome as seen in Schnitzler's syndrome might theoretically – via IL1-receptors and MYD88 - increase the dysregulation in the NF-κβ pathway influencing the MGUS or WD

syndrome [1]. In contrast with known Schnitzler's patients, the MGUS might not be detectable at first consultation. To date the focus on Schnitzler's syndrome has been on the presence of a *NLRP3* mutation solely, whereas the contribution of MYD88 and NF-κβ signaling has not been intensively investigated yet. Bauernfeind et al. [12] showed that MYD88-mediated signaling can activate the promotor of *NLRP3* and, in case of unique *NLRP3* promotor sequence-variants, can indeed lead to enhanced NLRP3 promotor activity [13]. This dysregulated NLRP3 expression could possibly evoke autoinflammatory symptoms. Increased transcription of both *NLRP3* and *IL-1β* genes due to MYD88 dependent (early phase) NF-κβ activity has been described by Chilton et al. [14]. Furthermore, it was established that MYD88 deficiency and NF-κβ inhibition influence the induction of NLRP3 protein in response to bacterial products (lipopolysaccharides) in a negative manner. This indicates that NLRP3 expression is controlled by signals resulting from NF-κβ activation.

Hypothesis

Hypothetically, Schnitzler's syndrome could not be solely a disease primarily caused by a mutation in 'the inflammasome'-gene (*NLRP3*) but might be a result of the increased NF-κβ activation. This increased NF-κβ activation is also seen in MGUS or Waldenström's macroglobulinemia. As mentioned before, the presence of a monoclonal IgM is a mandatory criterion for diagnosing Schnitzler's syndrome. However not every patient with a monoclonal IgM will develop the characteristics of this autoinflammatory disease.

MYD88 can activate the promotor of *NLRP3* and NF-κβ activation seems to control the NLRP3 expression. So theoretically, in case of a MYD88 mutation or increased NF-κβ activation as seen in patients with MGUS or WD - the presence of a certain single nucleotide polymorphism or mosaic mutation in *NLRP3*, may slightly dysregulate NLRP3 which can no longer be compensated. In this hypothesis this will then indeed lead to an increased transcription of pro-IL-1β to activated IL-1β in the inflammasome. Maybe this will eventually result in the clinical presentation of Schnitzler's syndrome with the presence of monoclonal IgM.

With the abovementioned hypothesis in mind, the increased NF-κβ activation could apparently be controlled to a certain extent lowering the monoclonal gammopathy levels to an undetectable level in some patients. This temporary balance will at some point turn into detectable abnormalities. The influence of NF-κβ activation on the inflammasome may result in elevated levels of IL-1 which could then possibly lead – via IL1-receptors and thus MYD88 – to increasing dysregulation in the NF-κβ pathway (see Fig. 1). By doing so, this will enhance the growth and survival of Waldenström's macroglobulinemia cells. This however is mere speculation at this time.

Discussion

The possible link between the presumed role of IL-1 in Schnitzler's syndrome and the monoclonal gammopathy is to be further examined. It would be of interest to investigate whether and how the treatment with IL-1 antagonists is able to positively influence the presence or progression of the macroglobulinopathy and the associated complications. To date only one patient with Schnitzler's syndrome, treated with Anakinra showed a reduction of M-protein concentration [15]. In other cases the M-protein levels remained stable during treatment, which lead to the assumption that treatment antagonizing IL-1 has the ability to withhold further growth of plasma cell clones. It is speculated that combining Anakinra with dexamethasone might clear the malignant clone and reduce M-protein levels. This has been illustrated in some patients with indolent malignant myeloma who were at risk for progression to an active myloma [16, 17].

Furthermore, the *NLRP3* gene function is to be assessed in patients with Schnitzler's syndrome in order to screen for any possible abnormalities or polymorphisms. To our knowledge no *MYD88* analysis has been performed on patients with a known Schnitzler's syndrome. This analysis, in combination with *NLRP3* analysis in these patients, would be of interest for a better understanding of the pathogenesis of both entities. Besides the abovementioned work-up, a thorough inquiry in patients with WD, concerning the family history for Schnitzler-like manifestations could reveal familial clustering of both diseases. Genetic linkage could be used to investigate the presence of a shared molecular pathogenesis of both entities, however sufficient number of meiosis are essential for this kind of analysis. Haplotype sharing may therefore be a better alternative, but also here, sufficient number of families are necessary for mapping the mutation-containing haplotype. Future research may hopefully lead to a better understanding of the – to this point – enigmatic pathophysiology of Schnitzler's syndrome.

Abbreviations

CAPS: Cryopyrin-associated periodic syndrome; IL-1: Interleukin-1; MGUS: Monoclonal gammopathy of unknown significance; WD: Waldenström's disease

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Authors' contributions

All authors have made substantial contributions to the conception and elaboration of this hypothesis, been involved in the drafting and revising of this manuscript, have given final approvement of the version to be published and agreed to be accountable for all aspects of the work. FvL, PS, JP, MvG, and MV have made substantive intellectual contributions concerning dermatological, immunological and genetic aspects respectively of this hypothesis.

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