The role of interleukin 22 in multiple sclerosis and its association with c-Maf and AHR

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The aim of this paper was to summarise knowledge of IL-22 involvement in multiple sclerosis (MS) and the possible link between IL-22 and two transcription factors – AHR and c-Maf. The conclusion is that despite numerous studies, the exact role of IL-22 in the pathogenesis of MS is still unknown. The expression and function of c-Maf in MS have not been studied. It seems that the functions of c-Maf and AHR are at least partly connected with IL-22, as both directly or indirectly influence the regulation of IL-22 expression. This possible connection has never been studied in MS.

Key words: multiple sclerosis, IL-22, transcription factors, c-Maf, AHR, EAE

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INTRODUCTION

IL-22 is one of the pro-inflammatory cytokines which are most probably important in the pathogenesis of numerous autoimmune diseases, including multiple sclerosis. IL-22- and Th22-oriented therapies provide optimism for a significant improvement in the treatment of a number of autoimmune diseases. The current paper serves two main purposes. The first is to summarise the current state of research on IL-22 in MS. The second is to link the function of IL-22 and two transcription factors – c-Maf and AHR.

IL-22

Interleukin 22 belongs to the interleukin 10 family along with IL-10, IL-19, IL-20, IL-24, IL-26 and IL-28A, IL-28B, IL-29 (ref.1). Initially, it was believed to be a Th1-spectrum cytokine. Further investigations disproved this and identified Th17 and Th22 lymphocytes as its main source. Apart from these subpopulations, IL-22 is also produced by mast cells, CD11c+ dendritic cells, NK22 cells, γδ T, NKT and LTi lymphocytes. The role of IL-22 is two-fold – it has significant pro-inflammatory potential and it may also exhibit anti-inflammatory function. The receptor for IL-22 has a heterodimeric structure; it is composed of IL-10R2 and IL-22R1 (ref.2). The main binding point for IL-22 is the chain of its proper receptor – the IL-22R1 and the strength of the binding is increased by the IL-10 receptor chain, which stabilizes the interleukin-receptor complex. The STAT3 pathway is activated once the IL-22 binds to the receptor.

Co-stimulation with IL-1β and IL-23 was found to promote IL-22 in mast cell progenitors. While concomitant stimulation of Th17 by IL-17, IL-21 and IL-23 results in secretion of a mixture of cytokines, including IL-22 (ref.3). Although various lymphocyte subpopulations may differently regulate IL-22 secretion e.g. among the γδ T cells it can be also stimulated by TLRs. IL-23 seems crucial for this process among various cell subsets. The production of IL-22 may be decreased by the stimulation of c-Maf (ref.4) and probably also AHR (ref.5). The latter most probably depends on the ligand used. Diesel exhaust particle polycyclic aromatic hydrocarbons were found to significantly promote IL-22 production by peripheral blood mononuclear cells in asthmatic patients. Similarly, IL-22 production by innate lymphoid cells in a murine model of hepatitis was observed to be up-regulated by AHR and RORγT (ref.6). Moreover, expression of IL-22 is probably also increased in hypoxia in an HIF-1α-dependent mechanism. An in-depth summary of IL-22 secretion regulation can be found in Dudakov et al.7.

IL-22 is involved in a number of processes – both physiological and pathological. It is probably involved in the pathogenesis of atopic dermatitis and asthma. Its level is increased in an animal model of rheumatoid arthritis and IL-22 along with IL-4 may be important during pregnancy. It is also important for proper regeneration of the intestinal epithelium and maintenance of the intestinal barrier. IL-22 is also considered an important cancer-promoting cytokine.

The serum IL-22 level is increased during relapse in relapsing-remitting MS patients compared to healthy controls, in patients with remission and those with primary progressive MS (ref.8). Similarly, an increase in CD4+IL-22+ percentage in peripheral blood was observed by N. Muls et al. during relapse when compared to remission. Similarly, the Th22 percentage in peripheral blood was found to be higher in MS patients than healthy controls. Nicol et al. described a novel subpopulation of T cytotoxic lymphocytes – Tc17 with intermediate...
Fig. 1. The role of IL-22 in the course of MS is still ambiguous and not fully understood. This scheme shows the experimentally-proven (continued line) and hypothetical (dashed line) effects of IL-22 in MS.

Fig. 2. The scheme shows the relation between IL-22, AHR and c-Maf. The demethylation of FoxP3 and methylation of IL-17 promoter requires prior proper AHR stimulation e.g. by FICZ. On the other hand, activated by Notch, AHR along with STAT3 and RORγT potently promote IL-22 secretion in Th17 cells. Similarly activation of AHR by FICZ increases IL-22 production. Bold green line indicate positive influence (induction or activation) while red line negative influence (supression).
expression of CD161 as another source of IL-22 in MS patients. Increase in serum IL-22 level and Th22 percentage were also confirmed in MS and neuromyelitis optica. The increase in IL-22 and IL-17 levels corresponds to fresh lesions in the central nervous system during MS (ref. 27). Perriard et al. showed that IL-22 is present in both white and gray matter in healthy controls and MS patients and that it is also involved in the stimulation of astrocyte survival. On the other hand, Zhen et al. noted that stimulation of oligodendrocytes with IL-22 leads to increased Fas expression, which may result in increased apoptosis. This is probably attenuated in healthy individuals by the Treg cells as an in vitro study of mouse Treg cells revealed their potential to lower the overexpression of Fas in oligodendrocytes. This effect was, however, not observed in the case of Treg cells from mice with EAE. This may be related to decreased level of FOXP3 expression in those cells, which is also probably related to IL-22 (ref. 28).

Tahrali et al. noticed an increased percentage of IL-22-producing NK cells in MS patients. In further in vitro tests, they observed that stimulation with IL-4 had nearly no effect on the IL-22 secretion by those cells – despite the fact that in healthy subjects IL-4 stimulation causes NK22 cell differentiation into an NK2 subpopulation and cessation of IL-22 secretion. The level of IL-22 in the central nervous system during the course of EAE rises with a peak at the time-point of maximal disability and a significant decrease during remission. Similar results were obtained by Kreymborg et al., who studied IL-22 expression in the central nervous system infiltrating lymphocytes in various phases of EAE (ref. 29). IL-22 turned out to be unnecessary for EAE to develop – IL-22-deficient mice developed the disease similarly to wild type mice. In an in vitro investigation stimulation of lymphocytes from MS patients with melatonin led to a significant decrease during remission. This appears to be related to a phenomenon observed by Scandinavian scientists. They noted the increased risk of MS in those who worked night-shifts at a young age. That effect was ascribed to a phenomenon observed by Scandinavian scientists. They noted the increased risk of MS in those who worked night-shifts at a young age. That effect was ascribed to

Physical and mental fatigue is a major symptom of MS. According to Rohit Bakshi, it is even the most prevalent one, and for 40% of patients also the one which most limits their daily activity. The occurrence and intensity of fatigue are linked, among other factors, to the influence of various cytokines, most commonly TNF-α and IFN-γ (ref. 30). An initial study by a Brazilian team revealed a possible link of fatigue with IL-22 (ref. 31). An in vitro study revealed higher potential for IL-22 production by lymphocytes from MS patients with significant fatigue compared to those without fatigue. The same team in another study noted that a 12-week training not only lowered the fatigue, but also the potential for IL-22 production. Further studies are needed for an in-depth understanding of this phenomenon.

The deregulation of IL-22 levels may be related both to the change in IL-22 expression and in its serum binding protein – the IL-22BP (IL-22RA2). IL-22 as the only cytokine of the IL-10-family has its own soluble binding protein and, moreover, it has higher affinity for IL-22 than the membrane receptor. This indicates the importance of IL-22 level regulation and the potential risk related to the disturbance in IL-22 level.

No significant difference in serum IL-22BP level was noted in MS patients, but an increase in its mRNA was observed in monocytes and dendritic cells. It seems that during relapse IL-22 escapes the control of IL-22BP. Moreover, some SNPs of the gene for the IL-22 soluble receptor (IL22RA2) are probably linked to the increased risk of both EAE and MS (ref. 32). At the same time, another study revealed that IL22ra2-deficient mice showed a milder course of EAE, which suggests a protective role of IL-22 as well as potential negative effects of an increased IL-22BP serum level.

c-Maf

c-Maf is a transcription factor with numerous functions e.g. it is necessary for the TGF-β mediated suppression of IL-22 production in Th17 (ref. 33) or along with Sox5 for the expression of RORγT in Th17 cells.

The c-Maf synthesis is mediated by IL-6, which, in turn, leads to an increased IL-21 production by the activation of IL-21 promoter and CNS-2 (ref. 34). IL-21 stimulates IL-22 expression in Th lymphocytes. As previously mentioned, TGF-β causes inhibition of the described mechanism. Transgenic mice lacking c-Maf have a significantly lower IL-21 expression than wild-type mice.

C-Maf may act agonistically with AHR. The IL-27-induced AHR joins c-Maf, which leads to the activation of IL-10 and IL-21 promoters in Treg1 lymphocytes. Moreover, IL-27 by c-Maf stimulation also increases IL-21 synthesis. By autocrine signaling, the latter stimulates and promotes the survival of IL-10-secreting Treg1 (ref. 35). Increased level of IL-27 and IL-33 in the central nervous system seems to alleviate the symptoms of EAE (ref. 36).

Table 1. Selected AHR ligands divided into agonists, antagonists and selective modulators.

<table>
<thead>
<tr>
<th>Type</th>
<th>Molecules</th>
<th>References</th>
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<tr>
<td>Agonists</td>
<td>TCDD, β-NF (β-Naphthoflavone), FICZ (6-Formylindolol[3,2-b]carbazole), ITE (Methyl 2-(1H-indole-3-carbonyl)-1,3-thiazole-4-carboxylate)</td>
<td>56,71,73–75</td>
</tr>
<tr>
<td>Antagonists</td>
<td>GNF-351</td>
<td>76</td>
</tr>
<tr>
<td>Selective modulators</td>
<td>SGA-360</td>
<td>77</td>
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PTIP – under no PTIP influence the production of IL-22 rises while that of IL-17 decreases. Generally, c-Maf seems to block the expression of IL-22 in Th17, while AHR along with RORγT promote it. On the other hand, as previously mentioned, c-Maf along with Sox5 promotes expression of RORγT in Th17, thus indirectly promoting IL-22 production.

Besides, c-Maf promotes IL-4 secretion by joining its promotor. Nevertheless, c-Maf cannot freely regulate any of those cytokines; the exact type of phosphorylation of c-Maf determines which one is affected. In the case of IL-4 regulation, the degree of stimulation positively correlates with the phosphorylation level of tyrosine in c-Maf, namely Tyr(21), Tyr(92), Tyr(131) (ref. 33). Currently, there is no data on the expression of c-Maf in MS patients.

AHR

AHR is a transcription factor involved in the differentiation of Th17 and Treg cells, it is also one of the transcription factors involved in regulation of IL-22 production. TCDD, a strong AHR agonist, is one of the most commonly used molecules in studies involving the AHR function. In a mouse model of Crohn disease, the application of TCDD led to strong symptom attenuation due to induction of Treg and suppression of Th17 lymphocytes. The effect is related to epigenetic changes – increased methylation of IL-17 promoter and concomitant demethylation of FOXP3 promoter. That action was also proved in another study on mouse model of Crohn disease by Benson and Shepard as well as in autoimmune uveitis by Zhang et al. Quintana et al. in an EAE study discovered that TCDD-mediated activation of AHR leads to the attenuation of symptoms, which is probably related to the observed Th17/Treg balance shift towards Treg, while the use of FICZ, another AHR agonist, had the opposite effect. Similarly, Hanieh and Alzahrani observed EAE symptom attenuation after TCDD-mediated AHR activation and ascribed it to the increased miR-132 expression in Th lymphocytes. On the other hand, the effect of both FICZ and TCDD may depend also on other factors like the route of administration and immune cells affected. It is worth noting that miR-132 performs opposite functions in B lymphocytes – it increases the production of pro-inflammatory cytokines and therefore may escalate EAE or MS symptoms. It was also noticed that AHR is involved in DHEA-mediated amelioration of EAE symptoms. On the other hand, AHR-deficient mice develop milder course of EAE (ref. 34).

AHR is an important regulator of IL-22 transcription. In fact, it seems to be essential for IL-22 production by γδ T (ref. 44), Th22 and Th17 (ref. 45) cells. Activation by FICZ leads to a significant upregulation of production. Moreover, environmental pollutants like polycyclic aromatic hydrocarbons may upregulate the activity of AHR by inhibition of cytochrome P450I, which is responsible for FICZ cleavage. Another important site for AHR-related immunoregulation is the intestines, where the commensal bacteria produce significant amounts of AHR ligands and therefore regulate the immune system. This is especially important as the intestinal microbiota may be involved in the pathogenesis of multiple sclerosis.

The literal effect depends on the type of AHR ligand. These are divided into three groups – agonists, antagonists and selective modulators (Table 1). Such a division is related to the activation or inhibition of two possible pathways – X/DRE and non-X/DRE. An agonist activates both, an antagonist inhibits both, and a selective modulator activates one while blocking the other. The X/DRE pathway is related to the relocation of AHR to the nucleoplasm and its direct influence on the expression of DNA. The activation of non-X/DRE leads to direct protein-protein interaction, and only indirectly regulates the expression of DNA. AHR antagonists cause the Treg/Th17 balance shift towards Treg, while agonists trigger opposite effects. Nevertheless, there are some known exceptions; the before-mentioned TCDD, despite being an agonist, causes a Th17/Treg balance shift towards Treg. In a study by Gagliani et al., concomitant stimulation with TGF-β1 and FICZ causes the differentiation of Th17 into Treg1 (ref. 70). AHR may not be necessary for the effect, but it was also noted that AHR antagonists cause significant decrease in the speed of the process. The use of ITE, another AHR agonist, also causes an increase in Treg percentage. It appears that the exact effect of AHR agonist depends on the dose and time of the AHR activation. A low dose and short period of activation may lead to the expansion of Th17 lymphocytes, while larger dose and longer period cause an increase in Treg cells.

CONCLUSION

Despite numerous studies, the exact role of IL-22 in the pathogenesis of MS is still unknown. The expression and function of c-Maf in MS have not been studied. It seems that the functions of c-Maf and AHR are at least partially connected with IL-22, as both directly or indirectly influence the regulation of IL-22 expression. This possible connection has never been studied in MS, either.

Search strategy and selection criteria

The aim of the paper was to summarise the knowledge of IL-22 involvement in multiple sclerosis and the possible link between IL-22 and two transcription factors – AHR and c-Maf. Therefore, Pubmed and Scopus were searched for all relevant studies. Following keywords were used: “MS”, “multiple sclerosis”, “EAE”, “experimental autoimmune encephalomyelitis”, “IL-22”, “interleukin 22”, “AHR”, “c-Maf” and the mixtures thereof. The initial search was performed in 2017 and was then updated in 2018 and in January 2019. Only peer reviewed papers written in English were included.

ABBREVIATIONS

AHR, Aryl hydrocarbon receptor; c-Maf, Transcription factor Maf; CD, Cluster of differentiation (designation);
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and pathogenic subset of CD4+ T cells involved in multiple sclerosis.


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