Linking neuroinflammation to motor neuron degeneration in ALS: The critical role of CXCL13/CXCR5

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Commentary

Linking neuroinflammation to motor neuron degeneration in ALS: The critical role of CXCL13/CXCR5

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Amyotrophic lateral sclerosis (ALS) is characterised by the combined degeneration of spino-bulbar motor neurons and of cortico-spinal neurons, leading to progressive paralysis and death within 3 to 5 years after onset of motor symptoms. Only few therapeutic options besides symptomatic and palliative care treatments exist in ALS, with riluzole still being the reference drug improving survival of a few months. Recently, several interventions such as combination of sodium phenylbutyrate and taurursodiol [1] or high caloric nutritional supplementation [2] showed disease modification activity in at least a subset of patients, although these findings require confirmation in larger studies.

Motor neuron degeneration is associated with important neuroinflammation in both mouse models of ALS, and in patients. ALS-related neuroinflammation classically features astrocyte and microglial activation, and other cellular actors of peripheral immunity have been involved. In mouse models, expression of mutant ALS gene in microglia or astrocytes appears critical for disease progression and neuroinflammation [3], and secreted factors from ALS glial cell types proved toxic to motor neurons [4]. Motor neurons themselves appear to produce neuroinflammatory mediators, either in response to axonal injury or to neuroinflammation [5]. Thus, ALS disease progression leads to the production of a soup of secreted immune mediators that impact, directly or indirectly, on motor neuron degeneration. However, which one(s) of these chemokines and cytokines are instrumental in the progression and could constitute valuable therapeutic target(s) remains poorly characterised.

In this article of *EBioMedicine*, Trolese and colleagues provide evidence for a role of the CXCL13 chemokine in disease progression of ALS [6]. This study stems from previous results by the same group that identified widely discordant disease progressions in two strains of transgenic mice of different genetic backgrounds expressing mutant SOD1-G93A. Using these two strains, the authors previously identified a prominent upregulation of the chemokine CXCL13 in motor neurons of fast progressing mutant SOD1 mice [7]. This was a potentially interesting observation as CXCL13 has been found to be upregulated upon axonal injury in spinal dorsal neurons and activate its receptor CXCR5 on astrocytes to modulate the cytokine production and astrocyte activation [8]. Furthermore, this CXCL13/CXCR5 pathway has also been highlighted in various neuroinflammatory diseases [9,10]. Trolese and collaborators first confirmed the selective overexpression of CXCL13 in motor neurons of fast progressing mice, and showed that its receptor CXCR5 was also upregulated in motor neurons. Importantly, release of CXCL13 in the cerebrospinal fluid (CSF) was progressively increased in ALS mice, suggesting that CXCL13 might act at distant sites throughout disease progression. Surprisingly however, intra-cerebroventricular neutralisation of CXCL13 in fast progressive ALS mice decreased their survival and increased functional impairment. Indeed, knock down of CXCL13 in motor neuron/glial co-cultures exacerbated motor neuron death, while conversely addition of CXCL13 prevented it. These effects might be mediated by astrocytes as CXCL13 inhibition was associated, both *in vitro* and *in vivo*, with decreased astrocytosis. CXCL13 and CXCR5 appeared to be also upregulated in motor neurons of ALS patients, but CXCL13 levels were lower in the CSF as compared to non-neurological controls.

The present study identifies a critical immune mediator as a possible target for disease modifying therapy in ALS. Altogether, the results of Trolese and collaborators suggest that increased CXCL13/CXCR5 signalling is beneficial in fast progressing mice. Thus, stimulating this pathway might prove useful for patients, although substantial further work is required to ascertain the therapeutic relevance of such strategy. Indeed, while Trolese and collaborators showed that decreasing CXCL13 signaling exacerbates the disease, experiments showing that CXCL13 agonism actually slows down disease progression in mutant SOD1 mice, and possibly also in non-SOD1 based models of ALS, are currently lacking. Another critical step before clinical translation would be to demonstrate that CXCL13 administration or agonism is devoid of adverse effects, especially because CXCL13 has been found to trigger pain hypersensitivity in mouse models [8].

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Besides identifying a potential therapeutic target, the current study might be a first step towards CXCL13 as a potential biomarker of ALS. In their study, Trolese and collaborators found that CXCL13 levels were decreased in CSF of ALS patients, in particular in spinal onset patients, while increased in patients with multiple sclerosis patients. The potential of CXCL13 as a biomarker in ALS, while possible, still needs to be consolidated in follow up clinical studies, with larger number of patients, and longitudinal follow up in order to study the effects of multiple confounding factors that could not be investigated in these pilot studies and comparison with current prognosis biomarkers such as circulating neurofilament levels.

In all, the study by Trolese and colleagues paves the way for further studies not only on CXCL13/CXCR5 pathway but also on other immune mediators that might be involved in disease progression, and provides hope that identification of ALS neuroinflammatory mechanisms might translate in clinically relevant interventions in the near future.

Contributors

Both authors contributed to the final version of the commentary.

Declaration of Competing Interests

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