Gas6/TAM System: A Promising Target in Neuroimmunology

Mattia Bellan
Department of Translational Medicine, Università del Piemonte Orientale (UPO), Novara, Italy

Corresponding author: Mattia Bellan, Università del Piemonte Orientale, UPO, via Solaroli 17, 28100 Novara, Italy, Tel: +390321/3733966, E-mail: bellanmattia@yahoo.it

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Introduction

Growth Arrest Specific 6 (Gas6) is a vitamin K-dependent protein [1], the biological activity of which is mediated by TAM receptors, a family of Tyrosine Kinases which includes three different members: Tyro3, Axl and Mer [2]. TAM receptors are also activated by Protein S [3], which shares structural similarities with Gas6, but is mainly expressed in the liver and exerts an anticoagulant effect in vivo [4]; conversely, Gas6 is more widely expressed (lung, heart, kidney, intestine, endothelial cells, bone marrow, vascular smooth muscle cells, monocytes and liver) [5,6] and has much more pleiotropic effects. Gas6/TAM seems to be particularly relevant in the regulation of immune system, raising interest in its potential involvement in autoimmune diseases [7]. First of all, Gas6 mediates the recognition of apoptotic bodies (AB) by TAM receptors, acting as a bridge between phosphatidylserine on external cell membrane of AB and TAM receptors expressed by phagocytic cells [8,9]. A defective TAM-mediated phagocytosis has been claimed as potentially relevant in the development of autoimmune conditions, such as Systemic Lupus Erythematous (SLE) [10]. Furthermore, it has been shown that Gas6/TAM system plays a major role in switching off inflammation [11], by inducing the expression of the suppressor of cytokine signalling proteins SOCS 1 and 30 [12]; Gas6 is also able to suppress IL-1, IL-6 and TNFα expression by TLR-activated monocytes/ macrophages via activation of PI3K/Akt pathway and inhibition of NF-kB nuclear translocation [13].

Neuroimmune diseases are between the best proved conditions associated to Gas6/TAM disregulation. The first hypothesis of involvement of this system in neuroimmunology belongs to the finding that Gas6 and its receptors are extensively expressed in the central nervous system (CNS) [14]. Tyro3 seems to be the main mediator of Gas6 effects in brain, being widely expressed in CNS; Axl is expressed in hippocampus and cerebellum, while Mer levels of expression are low to undetectable in normal brain [15]. Gas6/TAM signalling shows relevant neurotropic functions [16]; in fact the brain of embryonic and adult rats expresses Gas6 and TAM receptors proportionally to synaptogenesis of cerebral tissues [17,18], positively affecting the proliferation of hippocampal and cortical neurons [19] and Schwann cells [20].

Furthermore, Gas6/TAM system has an important protective role against demyelination. Oligodendrocytes are the myelin-producing cells and their apoptosis represents a key moment in the development of demyelinating diseases [21]; Gas6 has been proved to promote survival of oligodendrocytes in experimental models of demyelination [22]. In fact, Gas6−/− mice showed a more severe demyelination after cuprizone challenge than wild type mice: this was associated with a reduced oligodendrocytes number [23]. Axl seems to be relevant in mediating Gas6 activity on CNS, since Axl−/− mice fed cuprizone show more oligodendrocytes apoptosis and less efficient phagocytosis of AB than wild type mice [24], resulting in a prolonged axonal damage. Interestingly, rhGas6 is able to increase the degree of myelination in vitro [25]. Similarly, the direct administration of rhGas6 in CNS of mice after cuprizone challenge and withdrawal resulted in increased oligodendrocytes maturation, AB clearance, remyelination and axonal survival [26].

Similar results have also been obtained in experimental autoimmune encephalomyelitis (EAE); Gas6 k−o mice exhibit higher disease activity and axonal damage and enhanced expression of several proinflammatory mRNA molecules. On the other hand, intracerebral administration of Gas6 significantly improves the clinical scores and reduces axonal damage and demyelination [27]. Again, the role of Axl seems to be crucial, since Axl−/− mice show a defective clearance of myelin debris [28].

Taken together, these experimental findings suggest a role for Gas6/TAM system in demyelination; this is probably the expression of the regulatory activity on brain inflammation and neural survival and damage. Furthermore Gas6/TAM system might play a role in the recovery after an MS relapse. Beside experimental models, anyway, the role of these molecules is supported by some in vivo evidences. In 2013, Sainaghi et al. [29] showed higher CSF Gas6 concentration in patients suffering from shorter, less severe relapses of Multiple Sclerosis (MS); the authors postulated that Gas6 plays a protective role and a failure in CSF Gas6 concentration increase may affect the self-limitation of CNS inflammation and neural damage. This is particularly interesting if we consider that CSF Gas6 concentrations are unrelated to the plasmatic levels, being therefore the expression of a local Gas6 production. An impairment of Gas6/TAM system in MS has also been postulated by Weinger et al. [30] who showed that Gas6 is positively correlated to the protein expression of the soluble variants of TAM receptors in the normal brain, being conversely negatively correlated to them in established MS lesions, suggesting an embalancement of the system in disease condition. Finally, as a further clue, polymorphisms in the Mer gene were associated with MS susceptibility [31].

In conclusion, Gas6/TAM system is a very interesting target in the comprehension of the pathogenetical mechanisms underlying neuroimmune diseases development, particularly MS. Further studies could clarify the potential role of these proteins as markers of disease activity and potential target of treatment.

References


