Journal of Clinical & Experimental Neuroimmunology

Bellan, J Clin Exp Neuroimmunol 2015, 1:1

Editorial Open Access

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

Received date: Dec 01, 2015; **Accepted date:** Dec 04, 2015; **Published date:** Dec 07, 2015

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 autoimmunity 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-κB 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

1. Manfioletti G, Brancolini C, Avanzi G, Schneider C (1993) The protein encoded by a growth arrest-specific gene (gas6) is a new member of the vitamin K-dependent proteins related to protein S, a negative coregulator in the blood coagulation cascade, Mol Cell Biol 13: 4976-4985.
2. Lemke G (2013) Biology of the TAM receptors, Cold Spring Harb Perspect Biol 5: a009076.

3. Benzakour O, Gely A, Lara R, Coronas V (2007) Gas-6 and protein S: vitamin K-dependent factors and ligands for the TAM tyrosine kinase receptors family, Med Sci (Paris) 23: 826-833.
4. Castoldi E, Hackeng TM (2008) Regulation of coagulation by protein S, Curr Opin Hematol 15: 529-536.
5. Avanzi GC, Gallicchio M, Cavalloni G, Gammaitoni L, Leone F, et.al. (1997) GAS6, the ligand of Axl and Rse receptors, is expressed in hematopoietic tissue but lacks mitogenic activity, Exp Hematol 25: 1219-1226.
6. Nakano T, Higashino K, Kikuchi N, Kishino J, Nomura K, et al. (1995) Vascular smooth muscle cell-derived, Gla-containing growth-potentiating factor for Ca(2+)-mobilizing growth factors, J Biol Chem 270: 5702-5705.
7. Rothlin CV, Lemke G (2010) TAM receptor signaling and autoimmune disease. Curr Opin Immunol 22: 740-746.
8. Lemke G, Burstyn-Cohen T (2010) TAM receptors and the clearance of apoptotic cells, Ann N Y Acad Sci 1209: 23-29.
9. Scott RS, McMahon EJ, Pop SM, Reap EA, Caricchio R, et al. (2001) Phagocytosis and clearance of apoptotic cells is mediated by MER, Nature 411: 207-211.
10. Ballantine L, Midgley A, Harris D, Richards E, Burgess S, et al. (2015) Increased soluble phagocytic receptors sMer, sTyro3 and sAxl and reduced phagocytosis in juvenile-onset systemic lupus erythematosus. Pediatr Rheumatol Online J 13: 10.
11. Rothlin CV, Carrera-Silva EA, Bosurgi L, Ghosh S (2015) TAM receptor signaling in immune homeostasis. Annu Rev Immunol 33: 355-391.
12. Rothlin CV, Ghosh S, Zuniga EI, Oldstone MB, Lemke G (2007) TAM receptors are pleiotropic inhibitors of the innate immune response. Cell 131: 1124-1136.
13. Alciato F, Sainaghi PP, Sola D, Castello L, Avanzi GC (2010) TNF-alpha, IL-6, and IL-1 expression is inhibited by GAS6 in monocytes/macrophages. J Leukoc Biol 87: 869-875.
14. Prieto AL, Weber JL, Tracy S, Heeb MJ, Lai C (1999) Gas6,a ligand for the receptor protein-tyrosine kinase Tyro-3, is widely expressed in the central nervous system. Brain Res 816: 646-661.
15. Pierce AM, Keating AK (2014) TAM receptor tyrosine kinases: expression, disease and oncogenesis in the central nervous system. Brain Res 1542: 206-220.
16. Ji R, Meng L, Jiang X, Cvm NK, Ding J, et al. (2014) TAM receptors support neural stem cell survival, proliferation and neuronal differentiation. PLoS One 9: e115140.
17. Funakoshi H, Yonemasu T, Nakano T, Matumoto K, Nakamura T (2002) Identification of Gas6, a putative ligand for Sky and Axl receptor tyrosine kinases, as a novel neurotrophic factor for hippocampal neurons. J Neurosci Res 68: 150-160.
18. Prieto AL, O'Dell S, Varnum B, Lai C (2007) Localization and signaling of the receptor protein tyrosine kinase Tyro3 in cortical and hippocampal neurons. Neuroscience 150: 319-334.
19. Yagami T, Ueda K, Asakura K, Sakaeda T, Nakazato H et al. (2002) Gas6 rescues cortical neurons from amyloid beta protein-induced apoptosis. Neuropharmacology 43: 1289-1296.
20. Li R, Chen J, Hammonds G, Phillips H, Armanini M, et al. (1996) Identification of Gas6 as a growth factor for human Schwann cells. J Neurosci 16: 2012-2019.
21. Butts BD, Houde C, Mehmet H (2008) Maturation-dependent sensitivity of oligodendrocyte lineage cells to apoptosis: implications for normal development and disease. Cell Death Differ 15: 1178-1186.
22. Shankar SL, O'Guin K, Cammer M, McMorris FA, Stitt TN (2003) The growth arrest-specific gene product Gas6 promotes the survival of human oligodendrocytes via a phosphatidylinositol 3-kinase-dependent pathway. J Neurosci 23: 4208-4218.
23. Binder MD, Cate HS, Prieto AL, Kemper D, Butzkueven H (2008) Gas6 deficiency increases oligodendrocyte loss and microglial activation in response to cuprizone-induced demyelination. J Neurosci 28: 5195–5206.
24. Hoehn HJ, Kress Y, Sohn A, Brosnan CF, Bourdon S(2008) Axl-/- mice have delayed recovery and prolonged axonal damage following cuprizone toxicity. Brain Res 1240: 1-11
25. Binder MD, Xiao J, Kemper D, Ma GZ, Murray SS, et al. (2011) Gas6 increases myelination by oligodendrocytes and its deficiency delays recovery following cuprizone-induced demyelination. PLoS One 6: e17727.
26. Tsiperson V, Li X, Schwartz GJ, Raine CS, Shafit-Zagardo B (2010) GAS6 enhances repair following cuprizone-induced demyelination. PLoS One 5: e15748.
27. Gruber RC, Ray AK, Johndrow CT, Guzik H, Burek D, et al. (2014) Targeted GAS6 delivery to the CNS protects axons from damage during experimental autoimmune encephalomyelitis. J Neurosci 34: 16320-16335.
28. Weinger JG, Brosnan CF, Loudig O, Goldberg MF, Macian F (2011) Loss of the receptor tyrosine kinase Axl leads to enhanced inflammation in the CNS and delayed removal of myelin debris during experimental autoimmune encephalomyelitis. J Neuroinflammation 8: 49.
29. Sainaghi PP, Collimedaglia L, Alciato F, Molinari R, Sola D, et al. (2013) Growth arrest specific gene 6 protein concentration in cerebrospinal fluid correlates with relapse severity in multiple sclerosis. Mediators Inflamm 2013: 406483.
30. Weinger JG, Omari KM, Marsden K, Raine CS, Shafit-Zagardo B(2009) Up-regulation of soluble Axl and Mer receptor tyrosine kinases negatively correlates with Gas6 in established multiple sclerosis lesions. Am J Pathol 175: 283-293.
31. Ma GZ, Stankovich J, Kilpatrick TJ, Binder MD, Field J (2011) Polymorphisms in the receptor tyrosine kinase MERTK gene are associated with multiple sclerosis susceptibility. PLoS One 6: e16964.