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Role of Growth Arrest Specific 6 Protein and TAM Receptors in Rheumatic Diseases: Review Article

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ABSTRACT

Background: Growth arrest specific 6 (GAS 6) is the ligand for the TAM family of receptors. The TAM acronym is for the three members of this family: Tyro3, Axl, and Mer. Deficiencies in GAS 6/TAM pathway are involved in chronic inflammation, impaired immunity and cancer development. Several studies have been made to declare the exact mechanisms of its work and how it can be used as a promising therapeutic target in autoimmune diseases.

Objective: This review article aimed to summarize what recent studies revealed about GAS6 and TAM receptors and its role in rheumatic diseases.

Methods: Growth Arrest Specific 6 Protein, TAM receptors, and the Rheumatic Diseases were all looked for in PubMed, Google scholar, and Science direct. References from relevant literature were also evaluated by the authors, but only the most recent or complete study from February 2004 to February 2021 was included. Due to the lack of sources for translation, documents in languages other than English have been ruled out. Papers that did not fall under the purview of major scientific investigations, such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations, were omitted.

Conclusion: GAS 6 and protein S are well known ligands of TAM receptors that are structurally and functionally similar. Plasma levels of GAS 6 and its soluble TAM receptors increase in blood of cases affected by systemic lupus erythematosus and lupus nephritis and can be used as markers for disease diagnosis and severity.

Keywords: GAS 6, TAM, Autoimmune diseases.

INTRODUCTION

GAS 6 is one of vitamin K–dependent proteins (VKD) [(1)]. GAS 6 is not synthesized in the liver like other VKD, but produced by heart, lungs, kidneys, endothelial, and muscle cells [(2)]. It is present in plasma in concentration around 20-50 ng/mL (0.25 nmol/L) [(3)]. The gene that codes GAS 6 was not discovered until 1988 through the screening of genes increased in growth arrest embryonic mice fibroblasts and its name came from its discover. They found six genes, which were named GAS 1 to GAS 6. In 1993, the gene was sequenced and they found similarity with plasma anticoagulant protein S sharing 44% of its structure [(4)]. Interestingly, both of them have different functions [(5)].

GAS 6 protein is composed of multiple domains with molecular weight of 75 kDa. It has an amino terminal γ carboxyglutamic acid (Gla domain) that enables VKD proteins to bind to anionic phospholipids at the cell surface. Gla domain is followed by a loop, which is held by a disulfide bridge and followed by 4 epidermal growth factor–like domains and in the end the carboxyterminal (C-terminal), consisting of 2 laminin G repeats, exists. They all form the sex hormone–binding globulin domain interacting with the TAM receptors [(6)].

Tyro3, Axl, and Mer form the 3 types of the TAM receptors group. Gas 6 and protein S act as ligands for the TAM receptors [(4)]. GAS 6 has higher affinity for Axl than Tyro than Mer receptors [(2)]. Cells of hematopoietic, epithelial, and mesenchymal sources express Axl while Tyro3 exists mainly in the central nervous system, kidneys, ovaries, and testes. Mer is mainly present in ovaries, testes, prostate, lungs, and kidneys and less commonly in the thymus, spleen, liver, small intestine colon, and placenta [(3)].

Proteolysis causes its shedding from the cell membrane to be present in the soluble form (sAxl) [(7)]. sAxl binds to all GAS 6 particles and that is why blood sAxl level (0.6nmol/L) are higher than GAS 6 level (0.25 nmol/L) [(7)]. The soluble receptors inhibit signaling by removing the ligand from cell bound receptors [(8)].

Function of GAS 6/TAM system:

GAS 6 is involved in several biological processes such as: proliferation, migration, differentiation, adhesion and leukocyte sequestration, platelet aggregation, hematopoiesis, apoptosis, and phagocytosis. Additionally, it is involved in injury, inflammation, and repair mechanisms [(9)].

- **Anti-apoptotic and mitogenesis:**

Bassyouni *et al.* [(6)] declared that several studies have investigated GAS 6 role in inhibition of apoptosis and mitogenesis in fibroblasts**,** EC**,** VSMC**,** oligodendrocytes**,** Schwann cells**,** lens epithelial cells**,** neurons and liver cells**.** GAS 6 was found to decrease cell death after serum starvation and TNFα-treatment in different cell types. TAM receptors and GAS 6 protein levels were noticed to increase in many cancer types such as leukemia, cancer of the thyroid gland, lung, uterus, endometrium, ovary, prostate, GIT tumors, breast cancer, Kaposi's sarcoma, malignant gliomas and renal cell carcinoma [(4)].

The interaction between GAS 6 protein and Axl in cancer cells is involved in different mechanisms of tumor progression and metastasis, including tumor cell proliferation, migration, invasion, survival,

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angiogenesis, therapeutic resistance, and immune response [10].

- **Phagocytosis:**

As mentioned in **Bassyouni *et al.*** [6], the Gla domain of GAS 6 protein binds negatively charged phospholipids on the surface of the cell undergoing apoptosis to be engulfed, while the LG domains bind to the phagocytic cell, which has TAM receptor on its surface. Phosphatidylserine (PS) lies inside the cell membrane. PS exposure in the cell membrane occurs following cell injury, activation, and apoptosis. Unless dead cells are removed properly, secondary necrosis will occur and lead to inflammation.

- **GAS 6/TAM inflammation:**

Binding of GAS 6 protein to TAM receptors inhibits interleukins 1 and 6 and tumor necrosis factor alpha release from Toll-like receptors activated monocytes and macrophages and decrease inflammatory reactions in the activated dendritic cells by inhibiting cytokine production [11].

- **GAS 6/Axl in innate immunity:**

TAM receptors play a role in protection of innate immune cells (macrophages, dendritic and NK cells) from apoptosis and are involved in phagocytosis of apoptotic bodies. There are different immune strategies to inhibit inflammatory reactions, the interaction between GAS 6 and TAM receptors is an important mechanism. Chronic activation of monocytes and macrophages by inhibiting inflammatory reactions, mediated by Toll-like receptors and cytokine receptors, is prevented by TAM receptors [12].

- **GAS 6 and TAM in the vasculature:**

GAS 6 has a vital role in both inflammatory reactions and thrombosis which makes it an important regulator of the cardiovascular system. It is involved in repair of many cardiovascular diseases [4]. GAS 6/Axl system helps the survival and proliferation of vascular smooth muscle cells and endothelial cells that cause formation of new blood vessels. Briefly, GAS 6 acts in different mechanisms that have direct effects on cardiovascular diseases [13].

- **GAS 6 in CNS:**

The interaction between growth arrest specific 6 and its receptors is important for brain development during fetal life. It is involved in removing cellular and myelin debris from inflammatory demyelination that is vital to begin recovery of myelin fibers. It also helps vitality of neurons and glial cells in the CNS, important to the myelination process [14].

- **GAS 6 and mesangial cell proliferation:**

GAS 6/Axl pathway increases proliferation rate of mesangial cells that cause the development of inflammatory renal disease [15]. Levels of GAS 6 released from the kidney are higher in chronic rejection of transplanted kidneys, lupus nephritis, glomerulonephritis and IgA Nephropathy [16]. **Zhen *et al.*** [17] suggested that kidney affection occurs by 2 mechanisms. The first is that the coagulation cascade is activated in severe human and experimental glomerulonephritis and inhibiting GAS 6 (which acts as a coagulation factor and as a regulator of thrombosis) can cause bleeding and anemia by inhibiting platelet aggregation. The second is through its anti-inflammatory effect.

- **TAM Receptors Implications in rheumatic diseases:**

Autoimmunity and abnormalities in TAM signaling pathway are suggested by many authors to be strongly connected. TAM receptors level in circulating immune cells and plasma concentrations of GAS 6 are reduced in systemic lupus 5098aptor5098atosus, Behcet's disease, rheumatoid arthritis, inflammatory bowel disease, and psoriasis patients. On the contrary, concentrations of circulating soluble TAM receptors are elevated in patients with systemic lupus 5098aptor5098atosus, Sjogren's syndrome, rheumatoid arthritis and Behcet's disease which support the theory about the important role of TAM receptors in the development of autoimmunity [12].

- **Rheumatoid arthritis (RA):**

It has been found that arthritis is more significant in mice deficient in Axl and Mer receptors, which confirm that defects in GAS 6/TAM pathway are involved in development of autoimmune diseases such as RA and that Axl and Mer receptors prevent development of autoimmune diseases. Mer is increased in non-inflammatory joint diseases like osteoarthritis and RA in remission and also believed to react with interleukin 10 to inhibit release of proinflammatory cytokines and accumulation of dead cells [18].

- **Systemic Lupus Erythematosus** (SLE)**:**

Removal of dead cells and inhibition of immune response are two important functions of TAM receptors that are impaired in Systemic Lupus Erythematosus and lead to a condition similar to systemic lupus in mice, and in humans active lupus disease. Lupus disease diagnosis and activity can be measured by levels of TAM receptors and GAS 6. Additionally, promising papers favor the use of TAM receptors as a therapy for lupus and lupus nephritis [19].

Removal of apoptotic cells is deficient in SLE patients. This function is the responsibility of monocytes and macrophages, which recognize apoptotic cells through multiple surface receptors including (TAM) receptors that has an important function in maintaining innate immunity and efficient removal of dead cells, this

is vital for the stability and normal function of immune system [20].

- **Lupus Nephritis (LN):**

Bellan *et al.* [11] performed a study of plasma level of GAS 6 and TAM receptors in lupus nephritis and reported that they were positively correlated with plasma creatinine concentration and 24-hour protein in urine, which may be a reflection to a disturbed cleavage of the membrane receptor. Metalloproteases cause cleavage of the extracellular domains of TAM receptors to produce soluble forms of the re5099aptor (sTAM) that may be the cause of kidney inflammation and glomerular damage that cause the proteinuria. Increase in sMer is also associated with impaired removal of apoptotic cells, leading to production of autoreactive B cells and production of pathogenetic autoantibodies and immune complexes that cause damage to the kidney.

- **Sjögren Syndrome (SS):**

Qin *et al.* [21] reported that primary SS patients show decrease of TAM receptors mRNAs levels in peripheral blood mononuclear cells, and increase in sMer levels, which is correlated with anti-RO and anti-LA autoantibodies levels and disease activity indicated by the SS disease activity index score. Additionally, **Chen *et al.*** [22] reported that plasma level of GAS 6 is less in primary SS cases than control group in blood and labial salivary glands**.**

- **Systemic Sclerosis (SSc):**

Bellan M., *et al.* [14] studied the role of GAS 6 and TAM receptors in evaluating the cardio-pulmonary complications of systemic sclerosis disease and suggested that GAS 6 and its receptors sAxl and sMer can establish if patients affected by SSc have been complicated with either pulmonary hypertension (PAH) or interstitial lung disease (ILD) as sMer is suggested to be an accepted marker for PAH while GAS 6 together with sAxl for ILD**.**

CONCLUSION

Many researchers studied the role of Growth arrest-specific 6 protein (GAS 6) and MER receptors in autoimmunity, viral infection and cancer development. GAS 6 and protein S are well known ligands of tam receptors that are structurally and functionally similar. Plasma levels of GAS 6 and its soluble tam receptors increase in blood of cases affected by systemic lupus erythematosus and lupus nephritis and can be used as markers for disease diagnosis and severity grading. Additionally, GAS 6 and TAM receptors can be used as disease markers and a potential target for therapy in rheumatoid arthritis and Sjogren's syndrome.

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REFERENCES

1. **Py Z, Xl C, Yh L *et al.* (2014):** Growth arrest-specific gene 6 protein promotes the proliferation and migration of endothelial progenitor cells through the PI3K/AKT signaling pathway. International J. Of Molecular Medicine, 34: 299-306.
2. **Pilli V, Datta A, Dorsey A *et al.* (2020).** Modulation of protein S and growth arrest specific 6 protein signaling inhibits pancreatic cancer cell survival and proliferation. Oncology Reports, 44: 1322-1332.
3. **Van der Meer J, van der Poll T, van't Veer C (2014):** TAM receptors, Gas6, and protein S: roles in inflammation and hemostasis. The American Society of Hematology Blood, 123 (16): 2460-2469.
4. **Laurance S, Lemarié C, Blostein M (2012):** Growth Arrest-Specific Gene 6 (gas6) and Vascular Hemostasis. American Society for Nutrition. Adv Nutr., 3: 196–203.
5. **Studer R, Opperdoes F, Nicolaes G *et al.* (2014):** Understanding the functional difference between growth arrest-specific protein 6 and protein S: an evolutionary approach. Open Biol., 4 (10): 1-11.
6. **Bassyouni R, Gaber S, Gomaa A *et al.* (2018):** Gas6 /TAM system: physiological insights and diseases. Fayoum University Medical Journal, 1 (1): 5-23.
7. **Hsiao F, Lin Y, Hsieh P *et al.* (2013**): Circulating Growth Arrest-Specific 6 Protein Is Associated With Adiposity, Systemic Inflammation, and Insulin Resistance among Overweight and Obese Adolescents. J Clin Endocrinol Metab., 98 (2): 267–274.
8. **He L, Zhang J, Jiang L *et al.* (2010):** Differential Expression of Axl in Hepatocellular Carcinoma and Correlation with Tumor Lymphatic Metastasis. Molecular Carcinogenesis, 49 (10): 882-891.
9. **Martín C, Pérez-Ginés V, Rebeca M *et al.* (2021):** Electrochemical immunosensing of Growth arrest-specific 6 in human plasma and tumor cell secretomes. Electrochemical Science Advances, 2: 1-12.
10. **Tanaka M, Dietmar W (2020):** Gas6/Axl Signaling Pathway in the Tumor Immune Microenvironment. Cancers, 12 (7): 1850. doi: 10.3390/cancers12071850
11. **Bellan M, Quaglia M, Nerviani A *et al.* (2021):** Increased plasma levels of Gas6 and its soluble tyrosine kinase receptors Mer and Axl are associated with immunological activity and severity of lupus nephritis. Clinical and Experimental Rheumatology, 39: 132- 138.
12. **Paolino M, Penninger J (2016):** The Role of TAM Family Receptors in Immune Cell

Function: Implications for Cancer Therapy. Cancers, 8: 97-104.

13. **Tutusaus A, Marí M, Pérez O *et al.* (2020):** Role of Vitamin K-Dependent Factors Protein S and GAS6 and TAM Receptors in SARS-CoV-2 Infection and COVID-19-Associated Immunothrombosis. Cells, 9: 2186. doi: 10.3390/cells9102186
14. **Wium M, Paccez J, Zerbini L (2018):** The Dual Role of TAM Receptors in Autoimmune Diseases and Cancer: An Overview. Cells, 7: 166-169.
15. **Gong S, Xu Z, Liu Y *et al.* (2019):** Plasma sMer, sAxl and GAS6 levels correlate with disease activity and severity in lupus nephritis. Eur J Clin Invest., 49: e13064. doi: 10.1111/eci.13064
16. **Fiebeler A, Park J, Muller D *et al.* (2004):** Growth arrest specific protein 6/Axl signaling in human inflammatory renal diseases. Am J Kidney Dis., 43: 286-295.
17. **Zhen Y, Lee I, Finkelman F *et al.* (2018):** Targeted inhibition of Axl receptor tyrosine kinase ameliorates anti-GBM-induced lupus-like nephritis. J Autoimmun., 93: 37-44
18. **Pagani S, Bellan M, Mauro D *et al.* (2020):** New Insights into the Role of Tyro3, Axl, and Mer Receptors in Rheumatoid Arthritis. Disease Markers, 20: 1614627. doi: 10.1155/2020/1614627
19. **Cohen P, Shao W (2019):** Gas6/TAM Receptors in Systemic Lupus Erythematosus. Disease Markers, 19: 7838195. doi: 10.1155/2019/7838195
20. **Lorenz G, Desai J, Anders H (2014):** Lupus nephritis: update on mechanisms of systemic autoimmunity and kidney immunopathology. Curr Opin Nephrol Hypertens., 23: 211-217
21. **Qin B, Wang J, Ma N *et al.* (2015):** The association of Tyro3/Axl/- Mer signaling with inflammatory response, disease activity in patients with primary Sjögren's syndrome. Joint Bone Spine, 82 (4): 258–263.
22. **Chen C, Chen H, Chang C *et al.*, (2015)**: Growth arrest-specific 6 protein in patients with Sjögren syndrome: determination of the plasma level and expression in the labial salivary gland. PLoS One, 10 (10): e0139955.
23. **Bellan M, Dimagli A, Piccinino C *et al.* (2020):** Role of Gas6 and TAM Receptors in the Identification of Cardiopulmonary Involvement in Systemic Sclerosis and Scleroderma Spectrum Disorders. Disease Markers, 20: 2696173. https://doi.org/10. 1155/2020/2696173