Gas6 and Tumor Associated Macrophages provide Targeting Therapy Opportunity

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Abstract Growth arrest-specific gene 6 (Gas6) is a gene that encodes the growth arrest-specific 6 (Gas6), a gamma-carboxyglutamic acid (Gla)-containing protein. A member of the vitamin K-dependent family of proteins, the Gas6 protein, which was originally found in growth-arrested fibroblasts, relies on the catalysis by vitamin K to activate. It is expressed in various tissues and has been found to play a role in the proliferation, survival, and migration of cells through the Gas6/TAM pathway. Tyro3, Axl, and MerTK (TAM) are Gas6's accompanying receptors that allow the protein to undergo the Gas6/TAM pathway. The Gas6/TAM pathway has been discovered to be an oncogenic signal in cancer pathogenesis following numerous experiments and studies. This review will discuss the roles of Gas6 and TAM receptors in cancers and how they are involved with tumour associated macrophages and metastasis. Finally, the review will introduce recent studies on Gas6/TAM targeting in cancer therapy, which will assist in the experimental design of future analyses and increase the potential use of Gas6 as a therapeutic target for cancer.

Keywords: Growth arrest-specific 6 (Gas6), Tyro3, Axl, and MerTK (TAM) Receptors, Tumor associated macrophages, Targeted Therapy

Introduction

In 1988, Gas6 was first discovered, and further research was conducted on the protein through mouse embryonic NIH3 T3 fibroblasts 5 years later in 1993 (Wu et al., 2018). The protein, which is composed of 678 amino acids, showed the highest affinities for Axl, Tyro3, and MerTK in decreasing order (Wu et al., 2018). Thus, it was discovered that the protein acts as a ligand and Axl, Tyro3, and MerTK (TAM) are its accompanying receptors. Gas6 binds to the TAM receptors on its hormone-binding globulin (SHBG) domain, and various pathways such as the phosphatidylinositol 3-kinase (PI3K), extracellular signal-regulated kinase (ERK), and nuclear factor kappa light-chain-enhancer of activated B cells (NF-κB) pathways are activated allowing for the regulation of cell proliferation, migration, apoptosis, and more (Law et al., 2018).

In the tumor microenvironment, Gas6, from cancer cells, interacts with tumour-associated macrophages to play a significant role in cellular processes. Tumour-associated macrophages, which typically have been found to infiltrate tumours, will start to upregulate the Gas6 gene in the tumour microenvironment (Tanaka & Siemann, 2021). The Gas6 protein will then interact with TAM (Tyro3, Axl, and MerTK) receptors on cancer cells, initiating intracellular messaging within cancer cells and immune cells. The pathway may eventually lead to cancer progression and an inhibition of immune response against the cancerous cells (Zhai et al., 2023).

This review discusses the activation of the Gas6/TAM pathways activated by the binding of proteins and further discusses the roles that they play in different cancers including multiple myeloma and their involvement with tumour associated macrophages and metastasis. Finally, studies on Gas6/TAM targeting cancer therapy, where success was observed by inhibiting the Gas6/TAM pathway will be reviewed. Hopefully, these breakthroughs assist in the experimental design of future analyses and increase the potential use of Gas6 as a therapeutic target for cancer.

GAS6 Structure

The Gas6 protein is a modular ligand so it can interchange components within the protein to promote efficient and versatile binding to its receptors. The protein is also categorized as a multi-domain ligand meaning it has numerous binding sites because it is composed of numerous domains which are each capable of binding to a specific receptor (Deng et al., 2022). Starting from the N-terminus to the C-terminus, the Gas6 protein contains a total of 678 amino acids which form 6 different domains: the γ-carboxyglutamic acid (Gla) domain, four epidermal growth factor (EGF)-like repeats, and the sex hormone-binding globulin (SHBG)-like domain which consists of 2 laminin G-like (LG) domains (Law et al., 2018; Sasaki et al., 2006).

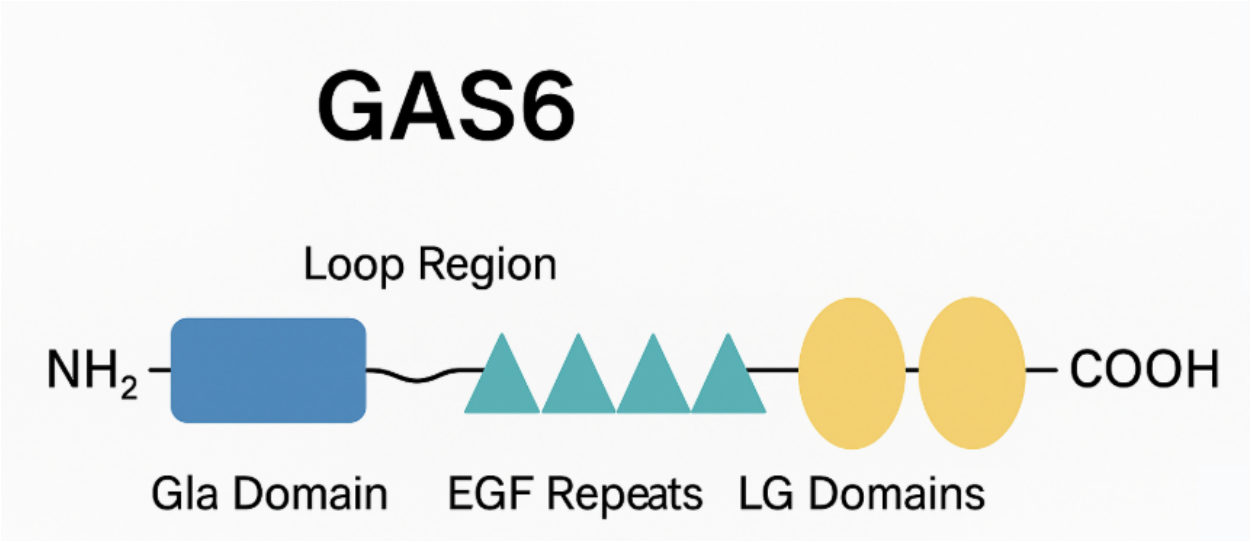

Figure 1: GAS6 domains and structure. This basic schematic shows the domains of Gas6 and their order. EGF stands for epidermal growth factor; LG stands for laminin G-like.

The different domains in the structure of the protein each play their own part in the overall function of the protein. To start off, the Gla domain near the N-terminal of the protein binds mainly to anionic phospholipids, such as phosphatidylserine on MerTK and Axl, to enable targeting and binding to its receptors (Geng et al., 2017). The binding of Gas6 to the TAM receptors is calcium-dependent, meaning it forms a Ca2+ phospholipid complex which acts as a docking platform for receptors, creating interaction possibilities (Mark et al., 1996). The Gla domain allows the Gas6 protein to identify itself to TAM receptors, activating signaling pathways which promote cell survival, proliferation, and more (Geng et al., 2017). Essentially, the domain is vital for biological processes which may promote tumour growth such as increasing survival of cells. Without this domain in the protein's structure, Gas6 would not have the ability to bind to many receptors and induce tumor growth in humans (Morizono et al., 2011).

The next part of Gas6's structure, the epidermal growth factor (EGF) repeats, are essential to Gas6's ability to specifically bind and activate the Axl receptor tyrosine kinase family (Gao et al., 2025). Before discussing EGF-like domains, it is important to note that they are different than epidermal growth factors, despite their similar names (Gao et al., 2025). Like the Gla domain, EGF-like domains facilitate and allow Gas6 to bind to the TAM receptors, successfully initiating the Gas6/TAM pathway (Laurance et al., 2012).

Finally, Gas6 has its SHBG-like domain which is made of 2 laminin G-like (LG) domains (Sasaki et al., 2006). The domain's structure is homologous to the N-terminal G domain of Sex Hormone-Binding Globulin (SHBG) which is a protein that regulates hormones in the blood (Salmi et al., 2019). This similarity in structure allows the domain to facilitate binding to receptors and stimulate cell

growth through the pathway (Salmi et al., 2019). Furthermore, a study by Mark et al. revealed that deletion variants of Gas6 that only contained the SHBG-like domain activated Rse, another receptor of Gas6, showing that the SHBG-like domain plays a much larger role in binding than anticipated (Mark et al., 1996).

Gas6 Function

The Gas6/TAM pathway has been a proven contributor to the survival of cancer cells. Studies have shown that in osteosarcoma cell lines MG63 and U2OS, the activation of Axl can protect tumour cells from apoptosis, causing the development of cancer (Han et al., 2013). Gas6 as well as TAM receptors are both highly expressed in cancer cells (Wu et al., 2018). Gas6 binds to the TAM receptors to activate MAPK/ERK, PI3K/Akt, and NF-kB signaling which promotes cancer cell survival and proliferation (Zhai et al., 2023). Targeting Gas6 and blocking MERTK reduces MM cell proliferation and increases the survival of the myeloma mice model (Kosta et al., 2022). These support the notion that Gas6/TAM plays a major role in the growth of various types of cancers.

The proteins in the Gas6/TAM pathway, including Gas6, Tyro3, Axl, and Mer, all play a part in the function of the pathway. The first receptor, Axl, coming from the Greek word “anexelekto” meaning uncontrolled, is a 140-kDa protein that is expressed everywhere in all different kinds of cells, which has been shown to induce tumors in nude mice (Scaltriti et al., 2016). Axl has been detected to be overexpressed in various cancers, denoting its role in cancer growth and proliferation (Yadav et al., 2025). Furthermore, Axl has also been determined to have a role in cell adhesion because of its extracellular domain which is independent of the tyrosine kinase domain (Yadav et al., 2025).

Another significant receptor is Tyro3 which was identified by numerous research groups in 1994 and is mostly expressed by the central nervous system (S. Miao et al., 2024). Mer, the final TAM receptor significant to Gas6, was identified in the same year as Tyro3 but is only expressed in the monocytic cell lineage (Lahey et al., 2022). When these 3 proteins were deleted in a study concerning triple knockout mice, the function of the TAM receptor stayed consistent, which suggested a redundancy in receptor function (Li et al., 2013). The mice lived but did not thrive, as they had numerous health issues where the immune system did not function properly. For example, the disability of phagocytosis of apoptotic cells resulted in the dysfunction of spermatogenesis as well as deregulated immunity (Li et al., 2013).

Recent studies have concluded that PI3K activation commonly occurs after GAS6/Axl binding (Law et al., 2018). In several cancer cell types and others including endothelial cells (ECs), vascular smooth muscle cells (VSMCs), fibroblasts, chondrocytes, oligodendrocytes, and neurons, antiapoptotic function of GAS6 requires PI3K/Akt activation (Kang et al., 2017). This makes the activation of the pathway crucial to cell survival and proliferation. Akt activation also leads to the inactivation of proapoptotic mediator Bad and the activation of nuclear factor kappa-light-chain-enhancer of activated B (NF kB) signaling which results in increased expression of anti-apoptosis gene Bcl2 (Mundi et al., 2016).

The binding of PI3K/Akt inhibitor to Axl is still a relatively unexplored area and will continue to undergo experiments relating to the topic. On Axl, a docking site for Src, a kinase that is involved in gas6-mediated survival, has been discovered (Rankin et al., 2014). Grb2, an adaptor protein, also has a reception site on Axl (Weinger et al., 2008). The protein may be involved with the Ras-mediated ERK1/2 activation (Bilal & Houtman, 2018). The Ras/ERK1/2 pathway mediates gas6 mitogenic activity, making it essential in controlling cell growth (L. Li et al., 2016). As well, it has been discovered that cell communication occurs through the SHP-2 phosphatase between the Gas6/Axl

pathway and the vascular endothelial growth factor type 2 (Qu, 2000). Other signalling molecules that may be involved in GAS6 signalling include the stress-activated protein kinase/c-Jun NH2-terminal kinase (JNK/SAPK), p38, and the Janus kinase-signal transducer and activator of transcription (JAK/STAT) pathways (Zhai et al., 2023). Overall, the TAM receptors together with Gas6 play a major role in cell proliferation and cancer growth.

Gas6 and Macrophages

Macrophages are a group of immune cells that can play varying roles in cancer depending on the specific macrophage. There are two different types of macrophages: pro-tumorigenic or M2-like macrophages can promote tumor growth whereas anti-tumorigenic or M1-like macrophages can suppress tumour growth (Yunna et al., 2020). Gas6 signaling with TAM receptors promotes the production of pro-tumorigenic and M2-like macrophages rather than anti-tumorigenic and M1-like macrophages (Purohit et al., 2025). This means that the immune system may be compromised, and the formation of new tissues and cells will all support the growth and proliferation of cancers. Tumour-associated macrophages in myeloma very often support macrophage phenotypes that increase cell proliferation and survival such as the M2-like and pro-tumorigenic phenotypes (Purohit et al., 2025). These macrophages secrete cytokines and other molecules that can prevent apoptosis in myeloma cells, allowing them to survive much longer and promoting tumour growth (Roszer, 2015). As well, these macrophages have been known to enhance osteoclast activity, which are used to break down old or damaged bone cells (Sun et al., 2021). However, after interacting with these macrophages, they will start to damage healthy bone cells, destroying the body (Sun et al., 2021).

Furthermore, Gas6 may inhibit anti-tumour abilities among natural killer (NK) cells by binding to the TAM receptors on the immune cells (Wu et al., 2018). This greatly weakens the body's abilities to kill tumour cells and defend against cancers (Wu et al., 2018). The interactions between Gas6 and the TAM receptors cause cells to further produce Gas6 to ultimately create a positive feedback loop where newly produced Gas6 does the same (Chiu et al., 2015; T. Li et al., 2016). This creates what is known as a "malignancy cycle" and improves the potency of cancers in the body (Mao et al., 2020).

The Gas6/MerTK pathway is especially important for macrophages' roles in cancer. Gas6 will bind to the phosphatidylserine (PS) located on apoptotic cells and subsequently bind to MerTK receptors on macrophages, enabling the pathway (Nishi et al., 2019). Efferocytosis, which is when phagocytes engulf or clear apoptotic cells, requires MerTK for M2 macrophages to undergo the process (Lin et al., 2022). Also, the pathway activates anti-inflammatory pathways while inhibiting pro-inflammatory pathways, providing opportunities for cancers to grow and spread (Vago et al., 2021). The Gas6/MerTK pathway may further impair inflammatory responses by inducing the expression of Suppressor of Cytokine Signaling 1 (SOCS1) to promote tumour growth (Wang et al., 2017). Finally, the pathway may also increase Interleukin-10 (IL10) secretion, which is a cytokine that also has anti-inflammatory properties. Overall, the Gas6/MerTK pathway is crucial for macrophages, especially in maintaining anti-inflammatory conditions.

Gas6 Potential in Cancer Immunotherapy

Gas6 blockade presents potential for targeted therapy as it was shown to restore NK cell activation.This improved the NK cell ability to attack cancers, especially in tumour-draining lymph nodes and metastatic lesions (Graham et al., 2024). Furthermore, the restoration of NK was shown to reduce metastasis, thereby proving itself as a potential for therapeutics (Chan & Ewald, 2022).

Due to Gas6's role in the proliferation of various cancers, it has been continuously pursued as a therapeutic target for cancer patients. In a study conducted that involved sequencing plasma DNA to analyze the response against cancer immune therapies, Gas6 was discovered to provide resistance against breast cancer therapies suggesting that Gas6 is hindering immune responses against cancer (Murtaza et al., 2013). As well, as previously mentioned, Gas6, along with the TAM receptors, activates the Gas6/TAM pathway which is proven to strengthen cancers. By targeting this pathway directly and ensuring that transduction is inhibited, then the overall impact of Gas6 on tumours may be reduced. A study by Kim et al. showed that there was a negative correlation between Gas6 and immune activation-related genes meaning that Gas6 likely suppresses the immune system's response to cancers (Kim et al., 2023). They concluded that targeting this pathway, due to its resistant impacts, may be a novel therapeutic strategy for the future (Kim et al., 2023). Furthermore, Tanaka et al. reviewed numerous Gas6 and Axl inhibitors and found that promising results and efficacy were shown (Tanaka & Siemann, 2021).

However, there are also concerns about the limitations of targeting Gas6 because of its limited expression among different cancers (Y. R. Miao et al., 2024). Further studies have shown that Gas6 is not essential in all tumours which limits the applicability of this therapy in those tumour types. (Y. R. Miao et al., 2024). All in all, Gas6 has been proven as prospective target for therapies and should continue to be pursued in hopes of finding a treatment that has widespread use among cancers.

In natural killer (NK) cells, the Gas6/Axl pathway is crucial in promoting their development and maturation through the expression of certain receptors (Park et al., 2009). On the other hand, in the tumour microenvironment, cytotoxic activity is reduced as Gas6 inhibits NK cell function; therefore, blocking Gas6 may improve NK cell function and its anti-tumour properties (Chirino et al., 2020). The Gas6/AXL pathway upregulates the expression of important NK cell-specific receptors (both inhibitory and activating) and associated genes necessary for target recognition and killing (Zhai et al., 2023).

Conclusion

In certain experiments, GAS6 has shown increased expression in multiple type of cancer cells. The Gas6/TAM pathway has been discovered to be an oncogenic signal in cancer pathogenesis following numerous experiments and studies. When Gas6 and TAM receptors were downregulated, cancers were found to have be less resistant to immune cells. Therapeutic targeting of GAS6 by warfarin or other therapies improved the survival of mice and reduced the cancer growth. Therefore, this therapy has promise for future cancer treatments.

In conclusion, our studies suggest that in pancreatic cancer, Gas6 is secreted by both TAMs and CAFs and blockade of Gas6 signalling has a dual anti-metastatic effect by acting on both the tumor cells and the NK cells. Thus, inactivation of Gas6 signalling can promote anti-tumor immunity, via NK cell activation, in pancreatic tumors. Since this Gas6-dependent immune regulation of NK cells is also conserved in humans, anti-Gas6-Axl therapies are likely to promote anti-tumor immunity, via NK cell activation, in pancreatic cancer patients. This study provides further mechanistic insights into the mode of action of anti-Gas6 therapies and suggests the use of NK cells as an additional biomarker for response to anti-Gas6 therapies in pancreatic cancer patients.

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