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The G0/G1 Switch Gene 2 (*G0S2*): Regulating metabolism and beyond

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Abstract

The G0/G1 switch gene 2 (*G0S2*) was originally identified in blood mononuclear cells following induced cell cycle progression. Translation of *G0S2* results in a small basic protein of 103 amino acids in size. It was initially believed that *G0S2* mediates re-entry of cells from the G0 to G1 phase of the cell cycle. Recent studies have begun to reveal the functional aspects of *G0S2* and its protein product in various cellular settings. To date the best-known function of *G0S2* is its direct inhibitory capacity on the rate-limiting lipolytic enzyme adipose triglyceride lipase (ATGL). Other studies have illustrated key features of *G0S2* including sub-cellular localization, expression profiles and regulation, and possible functions in cellular proliferation and differentiation. In this review we present the current knowledge base regarding all facets of *G0S2* and pose a variety of questions and hypotheses pertaining to future research directions.

Keywords

G0/G1 switch gene 2; *G0S2*; lipolysis; adipocyte metabolism; cell proliferation; differentiation; quiescence/growth arrest; cell cycle; PPARs; cancer metabolism; apoptosis

1. Introduction

The G0/G1 switch gene 2 (*G0S2*) was discovered in the early 1990s by Russell and Forsdyke in cultured mononuclear cells during the drug-induced cell cycle transition from G0 to G1 phase [1] [2]. *G0S2* only exists in vertebrates, and has no homologs in lower organisms such as *Caenorhabditis elegans* and *Drosophila*. In both mouse and human, *G0S2* is located on chromosome 1 of the genome and encodes a small basic protein of 103 amino acids in size. The *G0S2* protein is highly conserved between species; there is 78% identity between mouse and human isoforms. No striking features are present in the protein structure that would hint at an immediate discernable function. According to protein secondary structure prediction, the *G0S2* protein contains two α -helices separated by a hydrophobic sequence with the potential to generate turns and assume a β -sheet conformation. In

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addition, there are several putative phosphorylation sites for protein kinase C (PKC) and casein kinase II within the sequence of *G0S2*, though no evidence has been obtained that *G0S2* is actually a phosphoprotein [1].

The expression of *G0S2* has been profiled in various human and mouse cell types. As with many highly regulated and conserved genes present throughout the genome, *G0S2* features a CpG-rich island that potentially allows for germ-line expression [1]. The promoter region of *G0S2* contains potential binding sites for the transcription factors AP1, AP2, AP3 and Nuclear factor of activated T-cells (NFAT), as well as a number of sequence motifs that can respond to transcriptional activation induced by specific agents including lectin, retinoic acid (RA), agonists for peroxisome proliferator-activated receptors (PPARs), glucose and insulin [1, 3–8]. Results from a limited number of studies have implied that *G0S2* is a multifaceted protein involved in proliferation, apoptosis, inflammation, metabolism, and carcinogenesis. In particular, recent studies have provided compelling evidence that *G0S2* is abundantly expressed in metabolically active tissues such as fat and liver, and acts as a molecular brake on triglyceride (TG) catabolism [8]. In this review, we have summarized the existing evidence on *G0S2* expression, and functional aspects to which *G0S2* has been thus far associated.

2. *G0S2* and proliferation of hematopoietic cells

A transient increase in *G0S2* mRNA, peaking between 1–2 h, was observed in human mononuclear hematopoietic cells in response to proliferative activation by lectin and a protein synthesis inhibitor [1]. The lectin-induced expression of *G0S2* was inhibitable by the immunosuppressant antibiotic cyclosporine A [9]. Cyclosporine A antagonizes the function of the calcium-dependent phosphatase calcineurin, which is required for activation of target genes of NFAT [10]. Consequently, it was postulated that *G0S2* expression is required to commit cells to enter the G1 phase of the cell cycle [1], and early inhibition of *G0S2* expression by cyclosporine A may be important in achieving immunosuppression [9]. However, recent evidence obtained by Yamada et al. from hematopoietic stem cells (HSCs) suggests that *G0S2* acts to inhibit cell proliferation and assists to maintain stem cell in a quiescent state [11]. While *G0S2* expression promoted quiescence in HSCs, silencing of endogenous *G0S2* expression in bone marrow cells increased blood chimerism upon transplantation as well as HSC division. Moreover, *G0S2* was found to directly interact with nucleolin, a multifunctional protein that regulates many aspects of DNA and RNA metabolism, protein synthesis and cell mass, and nucleocytoplasmic transport of newly synthesized pre-RNAs [11]. Thus, it was proposed that the cytosolic retention of nucleolin mediated by *G0S2* contributes to the decreased proliferation of HSCs [11]. Furthermore, a separate study by Kobayashi et al. showed that *G0S2* expression was remarkably augmented in peripheral mononuclear cells (PBMCs) isolated from patients with the systemic autoimmune disease vasculitis [12]. Transgenic expression of *G0S2* in mice under the control of a global β -actin promoter resulted in elevated serum levels of anti-nuclear antibody and anti-double strand DNA antibody, two autoimmunity-related markers. However, increased *G0S2* expression does not appear to be sufficient for autoimmunity induction, since these transgenic mice displayed no obvious vasculitis-related phenotypes [12]. Most recently, upregulated *G0S2* message expression in PBMCs was also reported in patients from an unfavorable group of acute graft-vs-host disease (aGVHD) after HSC transplantation [13].

3. *G0S2* in cancer development

Several studies have linked the epigenetic regulation of *G0S2* expression to carcinogenesis. The *G0S2* gene was reported to be hypermethylated in several human cancer cell lines as

well as in squamous head, neck and lung cancers [14–16]. A causal relationship between DNA methylation and suppression of *G0S2* expression was established by the treatment of LC-1/sq squamous lung cancer cells with DNA demethylating agent 5-Aza-2'-deoxycytidine [15]. Moreover, *G0S2* was found to localize different subcellular membrane structures including endoplasmic reticulum (ER) and mitochondria [4, 17]. A study by Welch et al. showed that *G0S2* interacts with Bcl-2 at the mitochondria and thereby modulates its anti-apoptotic activity in human cancer cells [17]. Although *G0S2* does not possess the traditional Bcl-2 homology domain, its ability to interact with Bcl-2 effectively disrupts the formation of the anti-apoptotic heterodimeric complex of Bcl-2/Bax [17].

Combined with its growth arrest-associated expression in preadipocyte cells and epigenetic silencing in cancer, the identification of the proapoptotic activity of *G0S2* raises the possibility that *G0S2* is a tumor suppressor gene. The fact that knockdown of *G0S2* promoted oncogene-induced transformation supports this idea [17]. However, there were no observable effects on growth arrest or apoptosis when *G0S2* was overexpressed in LC-1/sq cancer cells [15]. If anything, slight increases in cell proliferation were observed in response to increased *G0S2* levels, which was believed to be more likely a result of carcinogenesis rather than a primary cause [15]. Therefore, further investigation is needed to understand the functional involvement of *G0S2* in carcinogenesis.

In addition, the *G0S2* was also found to be a target of all-trans retinoic acid (RA) in human acute promyelocytic leukemia (APL) cells [5]. RA treatment is a model of effective therapy based on inducing terminal differentiation of APL cells. Both mRNA and protein of *G0S2* were rapidly induced in cultured human APL cells and in APL transgenic mice treated with RA. Moreover, the *G0S2* promoter contains RA response element (RARE) half-sites, and mutations within RARE blocked all RA induced transcriptional activation [5]. While the evidence supporting *G0S2*'s ability to act as a RA target gene is convincing, the functional role of *G0S2* in the RA response of APL remains undefined.

4. *G0S2* as a regulator of lipid metabolism

4.1. Adipose lipolysis

In a search for novel genes involved in mesenchymal lineage differentiation, Bachner and colleagues identified *G0S2* as an adipose-specific factor whose expression can be upregulated by bone morphogenetic protein 2 (Bmp-2) in mouse embryos [18]. The *G0S2* expression is highly restricted to BAT and WAT at embryonic day 18.5 as revealed by in situ hybridization analysis. Later studies confirmed that *G0S2* mRNA is also most highly expressed in adipose tissue of adult animals [4, 19, 20] and humans [21]. In cultured human Simpson–Golabi–Behmel syndrome (SGBS) and mouse 3T3-L1 preadipocyte cell lines, both *G0S2* mRNA and protein steadily increase as the cells enter the growth arrest stage preceding the terminal differentiation [4, 8, 21]. However, despite its postulated role as a cell cycle regulator, whether *G0S2* plays any active role in the cell cycle withdrawal during adipogenic differentiation remains unclear.

The *G0S2* promoter encompasses a potential PPAR-responsive element (PPRE), and *G0S2* was shown to be a direct target of PPAR γ [4]. When co-expressed in human HepG2 hepatoma cells, PPAR γ stimulated the reporter activity driven by the *G0S2* promoter via the PPRE sequence. In accordance, treatment with a PPAR γ agonist rosiglitazone significantly increased *G0S2* protein expression in cultured mouse adipocytes [8]. PPAR γ is a highly expressed member of the PPAR family of nuclear receptor transcription factors in adipose tissue and functions as a master regulator of adipogenesis [22–26]. Activation of PPAR γ and stimulation of its target genes are prerequisite for the acquisition of metabolic features specific to adipocytes, such as insulin-dependent fatty acid (FA) and glucose uptake,

triacylglycerol (TG) synthesis and storage, adrenergically stimulated lipolysis, and synthesis and secretion of adipokines. The fact that G0S2 expression is upregulated by PPAR γ during adipogenesis indicates that G0S2 may be involved in one or more of these adipose-specific functions promoted by PPAR γ .

In addition to PPAR γ agonism, the adipose expression of G0S2 is subject to regulation by various hormonal and nutritional conditions. In particular, G0S2 protein in adipocytes is upregulated by insulin and downregulated by β -adrenergic signals, suggesting a role for G0S2 in either promoting energy storage or inhibiting energy catabolism [8]. Consistent with this notion, G0S2 expression was found to be very low in adipose tissue during fasting but increased after feeding [7, 19]. Moreover, protein levels of G0S2 decrease in perigonadal fat depots and increase in mesenteric fat depots in high fat fed animals when compared with mice fed with chow diet [27]. In humans, a separate study found reduced mRNA and protein content of *G0S2* in subcutaneous fat tissue from poorly controlled type 2 diabetic subjects [28]. Collectively, these studies suggest a potential role of *G0S2* in the control of energy homeostasis at both physiologic and pathologic levels.

A major advance in understanding the function of *G0S2* was the discovery that the TG hydrolase activity of adipose triglyceride lipase (ATGL) can be selectively inhibited by G0S2 [8]. Lipolysis in adipocytes is mediated by cytosolic lipases that catalyze the hydrolysis of TG stores in lipid droplets (LDs) in response to fasting and/or caloric restriction. The most important, and rate-limiting lipase of TG hydrolysis is ATGL [29–34]. ATGL is a widely expressed enzyme that is responsible for catalyzing the first step in a sequence of three reactions in adipose TG hydrolysis. Inhibition of ATGL results in blocked lipolysis and ultimate accumulation of triglyceride if no compensatory mechanism is activated. Structurally, the N-terminal half of ATGL contains a predicted α/β -hydrolase fold and an overlapping patatin-like domain [35, 36]. The patatin domain is named after the potato tuber protein patatin [37], a weak acyl lipid hydrolase. The catalytic site of ATGL is located within the patatin-like domain and is characterized by an unconventional catalytic dyad similar to that of human cytosolic phospholipase A2 (cPLA2) [35]. A hydrophobic stretch of 45 amino acids in the C-terminal region has been recognized to mediate targeting ATGL to the surface of TG-containing LDs [38, 39]. It is now known that the *in vivo* enzyme action of ATGL is decided not only by its lipase activity, but also by its LD localization and the interaction with a co-activator protein called CGI-58 (comparative gene identification-58; also known as α/β hydrolase fold containing protein 5, ABHD5) [39–44]. In humans, mutations of CGI-58 and ATGL were identified as a cause of various forms of neutral lipid storage disease characterized by TG deposition in multiple nonadipose tissues [45]. Clinical phenotypes that arise from mutations of CGI-58 differ slightly than those caused by ATGL mutations. Typically, CGI-58 mutations lead to a variety of conditions characterized by ichthyosis [46–50]. On the other hand, phenotypes that result from ATGL mutations are most often associated with skeletal and cardiomyopathies [51–55]. Both CGI-58 and ATGL mutations produce hepatomegaly and in certain instances liver steatosis [46–51, 53–55].

The inhibitory capacity of G0S2 on ATGL was originally characterized by Yang *et al.* [8], and subsequently confirmed by Coraciu *et al.* [43] and Schweiger *et al.* [21]. Immunofluorescence staining of G0S2 protein expressed in HeLa cells revealed the localization of G0S2 at the surface of LDs [8]. Studies employing co-expression approaches showed that G0S2 is able to prevent turnover of LDs mediated by ATGL. More importantly, it was determined that G0S2 directly interacts with ATGL and is capable of inhibiting the TG hydrolase activity of ATGL even under the CGI-58 co-activated conditions [8, 21, 39]. Mutagenesis analysis revealed that the hydrophobic domain of G0S2 and the patatin-like domain of ATGL are the primary regions of interaction, and an effective interaction is

required for eventual inhibition of ATGL by G0S2 [8, 43]. Functionally, overexpression of *G0S2* decreased both basal and hormone-stimulated lipolysis in cultured adipocytes and adipose tissue explants. Knockdown of endogenous G0S2, on the other hand, enhanced lipolysis in mature adipocytes [8, 21]. Collectively, these studies clearly prove that G0S2 is a unique inhibitor of ATGL and ATGL-catalyzed lipolysis.

Under physiologic conditions, adipose lipolysis is stimulated by β -adrenergic signals. In white adipocytes ATGL translocates to LDs following addition of a β -agonist isoproterenol to simulate lipolysis [8, 45]. Unexpectedly, it was demonstrated that endogenous G0S2 is simultaneously recruited to LDs through direct interaction with ATGL; knockdown of ATGL eliminated G0S2 localization to LDs [8]. A separate experiment demonstrated that C-terminally truncated ATGL mutants, which fail to localize to LDs, translocate to the LDs upon coexpression with G0S2 [21]. Therefore, ATGL and G0S2 are able to influence each other's localization to LDs. The question arises as to why a lipolytic inhibitor such as G0S2 is needed at the LD surface when TGs are hydrolyzed. Although an unequivocal answer has to be derived from further investigation, we propose a model in which two cytosolic pools of ATGL, G0S2-bound and unbound, concomitantly undergo translocation onto LDs in adipocytes [8]. While translocation of unbound ATGL leads to acute activation of TG hydrolysis, prolonged adrenergic stimulation subsequently downregulates G0S2, thereby releasing G0S2-bound ATGL for sustained lipolysis. Furthermore, tumor necrosis factor alpha (TNF- α) is known to potently stimulate basal lipolysis in adipocytes, which may contribute to hyperlipidemia and peripheral insulin resistance in obesity [56–58]. As surveyed in adipocytes, TNF- α drastically decreased expression of G0S2 at both messenger and protein levels [59]. Overexpression of G0S2, on the other hand, significantly decreased TNF- α -stimulated lipolysis mediated by ATGL with CGI-58 [59]. Therefore, it is speculated that early reduction in G0S2 content may be permissive for TNF- α -induced lipolysis.

4.2 *G0S2* in liver, muscle and skin

In addition to its relatively high expression in adipose tissue, the expression of G0S2 is moderate in liver and lower in skeletal muscle and heart [4, 8]. While it is subject to regulation by PPAR γ and increases under fed conditions in adipose tissue, *G0S2* expression in liver is upregulated during chronic fasting and when PPAR α is activated [4]. PPAR α is well defined as the key regulator of FA catabolism in the liver [60]. *G0S2* was differentially expressed between livers of PPAR α -null mice and wild type mice indicates that hepatic *G0S2* is a possible target gene of PPAR α [4]. However, a direct activation of *G0S2* expression by PPAR α appears unlikely as overexpression of PPAR α and treatment with PPAR α agonist Wy14643 failed to stimulate the promoter activity of *G0S2* in HepG2 cells [4].

G0S2 also contains a carbohydrate response element (ChoRE) within its promoter, allowing for direct responsiveness to glucose [61]. While investigating glucose-regulated gene expression in rat primary hepatocytes, Ma *et al.* discovered that the *G0S2* promoter activity was induced by 2.5 fold when culture conditions were switched from low (5.5 mM) to high (27.5 mM) glucose. Deletion of the putative ChoRE sequence within the promoter blocked any response to glucose. Subsequent studies decisively identified *G0S2* as a direct target of the ChREBP/Mlx dimer, a hybrid transcription factor that regulates the expression of glucose-responsive genes [61].

Compared to that in adipose tissue and liver, expression of *G0S2* in muscle is less well studied. Like in adipocytes, insulin also has a profound stimulatory effect on *G0S2* expression in skeletal muscle. Supporting evidence is derived from real time PCR analysis of *G0S2* mRNA content in skeletal muscle biopsies collected from healthy human subjects

after a euglycemic hyperinsulinemic clamp [6]. Another study showed that PPAR β/δ activation induces *G0S2* expression in cardiac fibroblasts [3]. Although PPAR β/δ activation is known to attenuate cardiac fibrosis by inhibition of myofibroblast trans-differentiation [62], no evidence was provided to suggest a direct involvement of *G0S2* in this downstream effect of PPAR β/δ .

Increased *G0S2* expression was recently reported in skin cells isolated from patients with epidermolysis bullosa (EB) [63], a group of hereditary skin disorders characterized by blistering in response to minor injury, heat, or friction. Interestingly, there is a restriction in the release of FAs and glycerol from EB cells, though whether this is due to lipolytic inhibition mediated by *G0S2* remains to be determined.

5. Perspectives & Discussion

Thus far, *G0S2* has been best characterized in its anti-lipolytic role as an inhibitor of ATGL. While the majority of functional studies on *G0S2* have been conducted in adipocytes, *G0S2* is well expressed in liver and may be equally important in regulating hepatic lipid homeostasis. For example, in response to fasting, *G0S2* expression decreases in adipose tissue but increases in liver [4, 7, 19]. This expression switch may serve to promote repartitioning of free fatty acids (FFAs), released via adipose lipolysis, to the liver. In fasting liver, very low density lipoprotein (VLDL) production and mitochondrial β -oxidation often cannot keep up with the FFA influx. Through inhibiting lipolysis and thus facilitating FA storage as TGs in LDs, *G0S2* may play an important role in a defense mechanism against the potential cytotoxic effects of excess FFAs, which may include overproduction of cell-damaging reactive oxygen species (ROS) and impairment of insulin sensitivity. Evidence obtained earlier from liver-specific ATGL depletion suggests that lipolysis is required for preferential generation of FAs that can be used for synthesis of ligands or precursors of ligands for PPAR α [64–66]. Therefore, though it experiences a marked increase during fasting, the endogenous *G0S2* level may need to be delicately controlled so that sufficient ATGL action would still be allowed to mediate PPAR α activation and FA oxidation.

In parallel with fasting conditions, models of mouse and human obesity also show decreased levels of *G0S2* in WAT [7, 8]. It is possible that increased TNF- α production and impaired insulin sensitivity both contribute to the downregulation of *G0S2* expression in adipocytes. We speculate that reduced levels of *G0S2* lead to the increased basal lipolytic capacity that in turn results in the elevation of plasma FFA levels. In human obesity, increased plasma FFA levels may exacerbate peripheral lipotoxicity and thus, decreased *G0S2* expression in adipocytes may be relevant for the development of insulin resistance and type 2 diabetes. The recent report demonstrating reduced adipose expression of *G0S2* in type 2 diabetic humans supports this scenario [28]. Furthermore, it would also be interesting to evaluate the status of *G0S2* in liver under obese conditions. Fasting, a condition that induces hepatic steatosis [67, 68], yields increased expression of *G0S2* in liver. Interestingly, a similar increase in *G0S2* protein levels occurs in the liver of mice with diet-induced obesity (X. Yang *et al.*, unpublished data). An increased hepatic expression coupled with a decreased adipose expression of *G0S2* may establish ideal conditions for enhanced TG storage and impaired FA oxidation in liver, contributing to the development of nonalcoholic fatty liver disease.

Clearly there are other mechanisms outside of post-mitotic cells in which *G0S2* is functioning, including its ability to alter apoptosis and potentially proliferation and differentiation. These aspects of *G0S2* may prove essentially important for the regulation of cancer development. We suspect that *G0S2* most likely has a dual mechanistic function, one being ATGL-dependent and the other ATGL-independent (Fig.1). ATGL is broadly

expressed and is a major regulator of metabolism in a variety of cell types. For the effective development and growth of cells, both energy and substrates for membrane biogenesis are required. Hydrolysis of TGs by ATGL may be required to provide FFAs that can further be processed for membrane synthesis or energy production through oxidation. In fact, when quiescent yeast reenters the cell cycle, cyclin-dependent kinase 1 (CDK1) phosphorylates and activates the functional ATGL ortholog Tgl4 lipase, liquidating fat and providing FAs for cell-cycle entry [69]. In mammalian cells ATGL and G0S2 may be at the same crossroads of lipid metabolism and cell growth. It is certainly plausible that downregulation of G0S2 would contribute to increases in ATGL-mediated lipolysis, which in turn makes available the new FFAs to meet the proliferative needs. Suppression of G0S2 expression would be an ideal path for a growing cancer cell to ensure successful flow of needed substrates for membrane synthesis and energy production. Moreover, this mechanism needs not be limited to carcinogenesis, and may contribute to growth control of wild type cells as well.

G0S2's expression profile during adipocyte differentiation indicates a viable function in cell growth arrest. As also has been observed in HSCs, increased expression of G0S2 appears to be a key component in regulating or maintaining quiescence of stem cells [11]. Increasing evidence points to the dual roles of cell cycle regulators in the control of both cell proliferation and the adapted metabolic responses [70–73]. For example, in response to proliferative stimuli, the cdk-pRB-E2F complex can function to facilitate a switch from oxidative to glycolytic metabolism and subsequent channeling of the glycolytic products toward *de novo* FA synthesis [72, 73]. Despite a probable role of G0S2 in cell proliferation, however, it is unclear whether G0S2 possesses a regulatory function in cell cycle that is separate from its role as a lipolytic inhibitor.

Alternatively, G0S2 has been shown to localize to mitochondria and promote apoptosis by interacting with the anti-apoptotic protein Bcl-2 [17]. This interaction, and other possible roles at the mitochondria, would also likely function in an ATGL-independent manner (Fig. 1). Downregulation of G0S2 expression could be a prime avenue for growing cells, especially cancer cells, in preventing death or/and growth arrest. Inhibition of apoptosis would be essential for continued proliferation and eventual homeostasis. While there is evidence as reported supporting *G0S2*'s pro-apoptotic function, it is important to note that this mechanism may be cell type-specific. For example, TNF- α treatment of cancer cells potently induces apoptosis and NF- κ B-mediated *G0S2* expression [17]. However, the presence of high levels of G0S2 do not seem to induce apoptosis in adipocytes, which are known to be quite resilient to apoptotic death [74]. TNF- α treatment of adipocytes significantly reduces G0S2 levels, resulting in increased lipolysis [59]. Further investigation is required to uncover the mechanisms underlying the current discrepancies in regard to the effect of TNF- α on G0S2 expression in different cell types.

In summary, the current evidence illustrates important and critical roles of G0S2 in a multitude of cell types. As usual, new insights raise many new questions. For example, what are the biochemical mechanisms by which G0S2 regulates ATGL, nucleolin and Bcl-2? What is the *in vivo* relevance of G0S2 in modulating energy metabolism, cell growth and apoptosis? Is the metabolic regulation mediated by G0S2 a crucial determinant of a cell's decision to proliferate, differentiate or die? Elucidating the function of *G0S2* and its regulation may be of great importance to our understanding of not only lipolysis, but also other physiologic and pathologic processes that ultimately depend on lipolytic outputs.

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Abbreviations

G0S2	G0/G1 Switch Gene 2
PKC	protein kinase C
RA	retinoic acid
PBMCs	peripheral mononuclear cells
ATGL	adipose triglyceride lipase
HSCs	hematopoietic stem cells
TG	triacylglycerol
FA	fatty acid
FFA	free fatty acid
FABP	Fatty acid binding protein
BAT	brown adipose tissue
WAT	white adipose tissue
PPRE	PPAR-responsive element
LDs	lipid droplets
cPLA2	human cytosolic phospholipase A2
CGI-58	comparative gene identification-58
ChoRE	carbohydrate response element
TNF-α	tumor necrosis factor- α
VLDL	very low density lipoprotein
ROS	reactive oxygen species
APL	promyelocytic leukemia
RARE	retinoic acid response elements

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Highlights

- In this review we describe the G0/G1 switch gene 2 (G0S2) and its functions.
- We illustrate the key features of G0S2's localization, expression, and regulation.
- We present the currently known functions of G0S2 in lipid metabolism and beyond.
- We pose further questions and hypotheses for future research directions of G0S2.

Figure 1. ATGL-dependent and independent functions of G0S2

G0S2 potentially regulates cell growth/survival in ATGL-dependent and independent fashions. By inhibiting ATGL-catalyzed lipolysis, G0S2 limits the availability of FFAs for membrane biogenesis and energy production, resulting in decreased proliferation. Separately, G0S2 can interact with Bcl-2, thereby disrupting the formation of the anti-apoptotic complex of Bcl-2 and Bax. This ATGL-independent function negatively impacts cell survival.