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# Maternally Expressed Gene 3 in Metabolic Programming

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## Abstract

Maternally Expressed Gene 3 (MEG3) is a long noncoding RNA (lncRNA) that coordinates a diverse array of cellular processes by acting as a competitive endogenous (ce)RNA, epigenetic regulation, and interactions with key proteins such as p53. MEG3 expression is affected by epigenetic modifications driven by *in utero* nutrition and is involved the development of many metabolic dysfunctions. Here, we suggest that these bodies of research are connected and that epigenetic modification of MEG3 expression may assist in adaptation to different metabolic environments. To this end, we discuss how nutritional status either leads to an increase of MEG3 expression that protects against cancer and metabolic dysfunctions, or to its downregulation minimizing its pleiotropic costs of expression. Lastly, we identify research directions that would further shed light on the role of MEG3 within metabolism and its role with larger imprinted gene networks.

### Keywords

MEG3; epigenetic imprinting; metabolic programming; miRNA sponge

## 1. Introduction

Metabolic syndrome, the presentation of a collection of metabolic disorders including insulin resistance and obesity, is a global epidemic that burdens an estimated billion people worldwide [1,2]. Given that metabolic syndrome contributes to the pathogenesis of chronic diseases such as cardiovascular disease and diabetes, it is critical that we identify the factors that underlie its development [1,3]. Recent research has emphasized the impact of *in utero* exposure to different stressors (e.g., starvation, toxins, or hyperglycemia) leading to lifelong susceptibility to metabolic syndrome through epigenetic modifications [4–7]. However, the epigenetic mechanisms through which the intrauterine environment may predispose infants to metabolic syndrome remain unclear [5]. Nevertheless, epidemiological studies connecting

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the lifestyles of pregnant mothers to epigenetic alterations in their infants have identified promising candidate genes. The lncRNA Maternally Expressed Gene 3 (MEG3) is noteworthy because its expression is both modulated by the uterine environment and dysregulated in many diseases of metabolic dysfunction [8,9]. Despite this connection, whether epigenetic modification of MEG3 expression participates in metabolic programming remains unexplored. Here, we describe how changes in MEG3 expression may assist in adaptation to the distinct challenges of energy rich and poor environments. In addition, we suggest research directions that would further describe MEG3's role in metabolism.

## 2. Location, inheritance, and regulation of MEG3

The advent of next-generation sequencing data has revealed that lncRNAs act as ubiquitous coordinators of diverse biological processes. In this regard, the maternally imprinted lncRNA MEG3 is typical, participating in processes as distinct as cancer, diabetes, and tissue fibrosis [10–12]. MEG3 is located within the DLK1-DIO3 gene cluster, a locus rich in imprinted genes, at human chromosome 14q32.3 [13–15]. The "imprintedness" of this region is the result of the different epigenetic programs that occur on the maternal and paternal chromosomes [15]. On the paternal chromosome, the imprinting control center for the region, the MEG3 intergenetic differentially methylated region (IG-DMR), becomes hypermethylated during spermatogenesis [15]. Conversely, the maternal copy of the MEG3 IG-DMR becomes hypomethylated during oogenesis [15]. Post-fertilization, the methylation patterns at the maternal MEG3 IG-DMR locus are imprinted onto the maternally inherited MEG3 IG-DMR locus of the embryo [16]. As the imprinting control center of the locus, the MEG3 IG-DMR controls expression of MEG3 and the other imprinted genes within the locus through methylation of secondary DMRs. One of the secondary DMRs methylated by the MEG3 IG-DMR is the MEG3 DMR, located on MEG3's upstream promoter [17]. Although poorly understood, the mechanism by which methylation at the MEG3 DMR regulates MEG3 expression may involve interference in the binding of enhancers to the promoter region [18]. Because both the MEG3 IG-DMR and MEG3 DMR stay hypermethylated on the paternal copy, while remaining comparatively hypomethylated on the maternal copy, MEG3 is maternally expressed [15].

During gestation and embryonic development, maternal nutrition as well as environmental and emotional stressors modulate methylation at the maternal MEG3 IG-DMR and MEG3 DMR. Methylation at the MEG3 IG-DMR and MEG3 DMR is highly sensitive to the uterine environment, so much so that MEG3 expression is highly differential even between identical twins [19]. In response to starvation, consumption of a Mediterranean diet, environmental toxins, or stressors such as maternal depression, these DMRs are hypermethylated [8,20–24]. Conversely, gestational diabetes mellitus, maternal obesity, or a high-fat diet cause them to become hypomethylated [8,25–27]. These methylation changes regulate MEG3 expression from lower to higher levels, respectively. They can also be transmitted intergenerationally, affecting second generation as well as first generation offspring [16]. Interestingly, prenatal exercise improves the metabolic health of pups and is associated with changes in the transcriptome; however, while epigenetic modifications of MEG3 are associated with both muscle development and exercise, there are no MEG3 DMR

methylation changes associated with prenatal exercise [28–31]. To conclude, MEG3 is maternally expressed owing to the methylation of the paternal MEG3 IG-DMR. Malnutrition and stress induce epigenetic alterations that reduce MEG3 expression, while overnutrition increases MEG3 expression via promoter hypomethylation (Figure 1).

## 3. MEG3-driven metabolic adaptation

The fetal origins hypothesis suggests that epigenetic changes *in utero* affect susceptibility to future disease [36]. However, whether epigenetic modification of MEG3 expression is adaptive or maladaptive has not been evaluated. Published data suggests that elevated MEG3 induced by *in utero* hyperglycemia may actually be beneficial, protecting against the development of metabolic diseases such as diabetes [37]. For example, heightened MEG3 expression impedes the development of diabetes by maintaining β-cell mass in the pancreas. Within β-cells, MEG3 is one of the most enriched genes and is essential for insulin production and cell maintenance [38,39]. MEG3 knockdown reduces insulin synthesis and promotes β-cell apoptosis, leading to impaired glucose tolerance and diminished insulin secretion [37]. Mechanistically, this diminishment is the result of reduced MafA expression, a key stimulator of insulin production and a required gene in β-cell maintenance [40–43]. MEG3 knockdown also increases expression of IGF2, which sensitizes β-cells to oxidative damage, inflammation, and is associated with weight gain at middle age [44,45]. Further linking MEG3 expression to diabetes, healthy individuals have higher MEG3 levels in their β-cells, blood serum, and retinal epithelium compared to diabetic individuals [46,47]. While the low levels of MEG3 expression presented by diabetic individuals could be considered solely a symptom of their condition, genome wide association studies, studies of imprinting disorders, and molecular examination of diabetic β-islets suggests MEG3 dysfunction plays a causal role. Susceptibility to both type 1 and 2 diabetes are associated with MEG3 polymorphisms, providing a link between altered MEG3 function and risk of diabetes [48–50]. Further, dysregulated MEG3 expression in the imprinting disorders Temple Syndrome, Silver-Russell Syndrome, and Prader William's Syndrome explains similarities between the conditions, a clinical overlap that includes obesity, insulin resistance, and other metabolic dysfunctions [51]. Lastly, in diabetic pancreatic islets, MEG3 is not regulated by glucose levels [46]. This suggests that the reduced MEG3 levels in diabetic patients preceded the chronic hyperglycemia caused by their condition [46]. To summarize, MEG3 maintains β-islet function to protect against diabetes.

In addition to preserving β-islet function, MEG3 shields epithelial tissue from hyperglycemia induced inflammation, apoptosis, and oxidative stress. Given that epithelial dysfunctions such as retinopathy and atherosclerosis are closely associated with insulin resistance and obesity, this may represent an additional mechanism through which increased MEG3 expression is adaptive in calorie-rich environments [52,53]. As an example, in diabetic retinopathy MEG3 alleviates the endothelial dysfunction caused by chronic hyperglycemia [54]. MEG3 serum levels in diabetic individuals with diabetic retinopathy are reduced compared to diabetic persons without diabetic retinopathy and healthy controls [47]. MEG3 protects against diabetic retinopathy—and endothelial dysfunction generally—through numerous, distinct pathways. These include: i) MEG3-dependent inhibition of the NF-κB pathway, hence reducing inflammation and apoptosis caused by hyperglycemia [55];

ii) downregulation of VEGF and TGF-β1, two critical genes involved in diabetic retinopathy [47]; iii) dampening of inflammation-induced p53 activation, a condition associated with obesity and diabetes, which, in turn, protects endothelial tissue from DNA damage and apoptosis [56]; iv) MEG3-dependent reduction in radical oxygen species production and lipoprotein oxidation in endothelial cells [57]; and v) protection of endothelial progenitor cells through upregulated HDAC7 expression and decreased miR-140–5p expression [58]. In short, MEG3 helps maintain epithelial function under hyperglycemic stress, preventing the development of diabetic retinopathy and endothelial dysfunction in metabolic syndrome.

Further, MEG3 protects against non-alcoholic fatty liver disease, a common manifestation of metabolic syndrome [1,59]. In metabolic syndrome, visceral fat and hyperglycemia induce liver damage via chronic inflammation and ROS production [60–62]. This causes hepatic stellate cells to produce excessive extracellular matrix, leading to liver fibrosis [62,63]. However, MEG3-mediated upregulation of p53, smoothened protein encoded by the SMO gene, and miR-212 can dampen this maladaptive activation of hepatic stellate cells by means of apoptosis [64]. Additionally, MEG3 is progressively downregulated during liver fibrosis progression and is diminished in fibrotic livers compared to healthy controls. Together, this suggests that MEG3 has a role in curbing liver fibrosis, as seen in non-alcoholic fatty liver disease [65,66].

However, the narrative that upregulated MEG3 expression is purely protective against metabolic syndrome is muddled by the fact that MEG3 itself contributes to insulin resistance by stimulating hepatic gluconeogenesis. In the liver, MEG3 is regulated dynamically by glucose and is increased in mice fed a high-fat diet, palmitate, oleate, or linoleate, and in ob/ob mice [9,37]. This increase in MEG3 expression is caused by changes in histone acetylation driven by high-fat-mediated inhibition of HDAC1 and HDAC3 [9]. MEG3 production is also stimulated by glucagon, a key promoter of gluconeogenesis, which induces hepatic MEG3 expression by increasing the levels of CREB, which bind to a CREB response element on its promoter [67]. Subsequently, MEG3 induces gluconeogenesis by upregulating FOXO1, CRTC2, G6PC and PEPCK, all drivers of hepatic gluconeogenesis [9,67]. MEG3 further drives gluconeogenesis by competitively binding to micro (mi)RNAs that otherwise limit gluconeogenesis, such as miR-214 and miR-302a-3p [67,68]. MEG3 upregulation is sufficient to exacerbate hyperglycemic dysfunctions in the liver while its hindered expression attenuates metabolic distortions (e.g., downregulation of glycogen content and upregulation of triglyceride content) in mice fed a high-fat diet [9,67]. Lastly, transient MEG3 overexpression causes cholestatic liver injury by facilitating SHP mRNA decay, resulting in the disruption of bile acid and liver enzyme homeostasis [69]. To conclude, MEG3 may contribute to metabolic syndrome by impairing hepatic insulin sensitivity and altering metabolism in the liver. Why MEG3 promotes gluconeogenesis while protecting against its harmful effects across different organs is an unresolved question.

## 4. Role of MEG3 in cancer prevention

In addition to its role in metabolism, MEG3 functions as a potent tumor-suppressor, an advantageous quality in cancer-prone, energy-rich environments. To illustrate how energetic excess contributes to cancer development, excess fat is thought to cause as many as 20% of

all cancer cases while moderate caloric restriction in adult monkeys reduces cancer risk by 50% [70,71]. MEG3 limits cancer progression through several independent mechanisms, including the upregulation of the canonical tumor suppressor p53, the repression of angiogenesis, and autophagy suppression. On account of this, MEG3 knockdown or downregulation is observed in 25% of neuroblastomas, 81% of hepatocellular cancers, 82% of gliomas, and is associated with poor prognosis [14,72–81].

MEG3 halts cancer progression, in part, by upregulating the canonical tumor suppressor p53. MEG3 induces p53 accumulation by suppressing MDM2, a protein which tags p53 for degradation [82]. In addition, MEG3 directly interacts with p53 to facilitate the activation of downstream targets implicated in the reduction in autophagy, promotion of apoptosis, and cell cycle arrest [76,82–85].

MEG3 also restricts cancer growth by disrupting the PI3K/AKT signaling cascade. Excessive activation of the PI3K pathway is common across cancers and contributes to tumorigenesis by encouraging cell survival and division [86]. In gliomas, MEG3 stops the translocation of AKT to the plasma membrane by downregulating miR-93 [87], thus dampening the activation of downstream target genes. MEG3 further inactivates the PI3K/AKT pathway by upregulating PTEN, which buffers PI3K signaling [88].

Another mechanism through which MEG3 arrests cancer development is by acting as a competitive endogenous RNA (ceRNA) to “sponge” tumorigenic miRNAs. In gastric cancer, MEG3 promotes apoptosis by upregulating Bcl2 through sponging miR-181 [10] while the loss in proliferation of glioma results from the sponging of miR-19a by MEG3 [89]. By competitively binding to miR-21–5p, MEG3 suppresses proliferation and promotes apoptosis of cervical cancer cells [90] while sensitizing non-small cell lung cancer to cisplatin [76,91]. In pancreatic cancer, MEG3 directly targets miR-183 to downregulate p38/ERK/AKT and Wnt/β-catenin signaling, resulting in reduced growth and metastasis [92]. Overall, MEG3 offers anti-cancer protection through interaction with an expansive array of miRNAs, with more interactions surely still undiscovered.

Lastly, MEG3 limits cancer growth by suppressing angiogenesis, a process that is required for the robust metabolic needs associated with tumor development and metastasis [93–95]. In mouse MEG3-null embryos, there is an upregulation of key angiogenic genes in the VEGF pathway, such as VEGFA and VEGRF1, leading to increased microvessel formation [96]. Further, in human umbilical cord, MEG3 knockdown accelerates VEGF-mediated angiogenesis through VEGFR2 upregulation [97]. MEG3 interference stimulates epithelial cell division, sprouting, and tube formation through activation of Notch signaling, which ultimately leads to blood flow improvement [98] and enhanced tumor growth [99]. This may explain why MEG3 levels are reduced in cancer exosomes, which are small secreted vesicles that facilitate intercellular signaling [100,101].

To conclude, MEG3 limits cancer progression by restricting angiogenesis, sponging tumorigenic miRNAs, and interfering in canonical cancer pathways. As calorie-rich environments are tumorigenic, the epigenetic upregulation of MEG3 by caloric excess may be adaptive.

## 5. Pleiotropic costs of MEG3 expression

However, increased MEG3 expression also reveals pleiotropic costs, tradeoffs which may hurt more than help in the absence of a nutrient-rich environment. One of these costs is accelerated cellular senescence, a state of permanent growth arrest and altered gene expression associated with tissue dysfunction, cancer, and aging [102]. Through interactions with p53, p21, PI3K/AKT and mTOR, MEG3 potently fights cancer, but can also induce senescence [74,82,103,104]. Expression of recombinant MEG3 gene is sufficient to trigger replicative senescence in cervical cancer lines [103]. Overexpression of MEG3 has been reported in senescent HUVECs, aged liver and muscle, mesenchymal stromal cells, and cardiovascular atrial tissue, thus connecting MEG3 to aging [33,34,105,106]. In aged HUVECS, MEG3 silencing rescues aging-associated changes in sprouting angiogenic activity [107]. In fact, 69% of upregulated mRNAs present in late-passage human adipose-derived stem cells vs. early-passage cells map to the DLK1-DIO3 locus, making the DLK1-DIO3 locus a putative hotspot in aging tissue [35] (Figure 2).

In addition to induce cell senescence, MEG3 exacerbates damage from injury by promoting cell death and inhibiting cell growth and angiogenesis. MEG3 has been linked to p53-mediated neuronal cell death following ischemic stroke [108]. Further, inhibition of PI3K/AKT by MEG3 exacerbates neuronal cell injury following subarachnoid hemorrhage [109] and, conversely, MEG3 silencing improves blood flow to tissues following ischemic injury [107]. MEG3 knockdown not only protects PC12 cells against hypoxic injury [110], but it also shields cardiomyocyte-derived H9c2 cells from hypoxic damage by sponging miRNAs that activate the PI3K/AKT/FOXO3a pathway [111]. Similarly, MEG3 silencing accelerates tibia fraction healing by upregulating the Wnt/β-catenin pathway [112]. In summary, increased MEG3 expression reduces the ability for the body to recover from a variety of injuries (Figure 2).

Elevated MEG3 expression may also contribute to the development of neurological disorders. MEG3 is involved in brain development, with its isoforms dynamically expressed across developing regions and its expression levels decreasing as neurons differentiate after birth [113,114]. Within neurons, MEG3 promotes apoptosis, directs cell fate, and limits long-term potentiation by inhibiting PI3K/AKT signaling [96,115–119]. Additionally, MEG3 may affect neural function by regulating angiogenesis within the brain [96]. Epidemiological studies have connected hypomethylation of the MEG3 IG-DMR with childhood maladaptive behavior and lesser social relatability [120,121]. Elevated MEG3 is also implicated in addiction, being upregulated in the nucleus accumbens of heroin users and in mice given methamphetamine [122,123]. However, this correlation may be the result of drug-induced elevation in cAMP levels and subsequent cAMP-response element-mediated MEG3 transcription, instead of MEG3 having a causal role [68,124]. In addition, MEG3 expression is increased in both human and animal models of Huntington’s disease, with its knockdown resulting in a decrease in aggregates caused by mutant huntingtin. Further, aberrant expression of miRNAs, copy number variants, and coding variants from the DLK1-DIO3 locus are correlated with schizophrenia, anxiety, and psychosis [125–129]. Overall, while the mechanisms through which MEG3 affects brain function are still mostly

uncharacterized, it appears that elevated expression may result in a variety of dysfunctions (Figure 2).

Additionally, elevated MEG3 expression contributes to cardiac fibrosis. In response to pressure overload, cardiac fibroblasts secrete matrix metalloproteinases that remodel cardiac tissue, leading to heart stiffness, diastolic dysfunction, and heart fibrosis [130]. In cardiac fibroblasts, MEG3 contributes to matrix metalloproteinase-2 (MMP2) signaling by assisting p53 and the fibrotic cytokine TGF-β. Through interaction with MMP2, MEG3 participates in fibrosis progression; conversely, silencing of MEG3 reduces fibrosis and prevents diastolic dysfunction in mouse cardiac tissue following transverse aortic constriction surgery [12,130]. In addition to fibrosis, MEG3 also contributes to heart hypertrophy, a condition where cardiomyocytes are enlarged and heart fibroblasts are overactive, causing an increase in heart rigidity and susceptibility to adverse cardiovascular events [12]. In models of cardiac hypertrophy, MEG3 induces maladaptive cardiomyocyte growth by competitive binding to miR-361–3p, which normally inhibits the pro-hypertrophic factor HDAC9. Silencing MEG3 is sufficient to restore miR-361–3p/HDAC9 axis function, partially reversing the excessive growth of cardiomyocytes that causes cardiac hypertrophy [131]. To conclude, increased MEG3 expression comes at the cost of heart fibrosis and dysfunction (Figure 2).

## 6. Conclusions and Perspectives

Even as investigation into MEG3 has helped describe its role within metabolism, there remain unanswered questions. One of these is whether MEG3 affects metabolism via the thyroid. The thyroid regulates metabolism by releasing hormones that control basal metabolic rate, appetite, and the breakdown of fat [132–134]. Perhaps not coincidentally, MEG3 is expressed at its highest level in the thyroid compared to all other organs [125]. Further, imprinting disorders of the DLK1-DIO3 locus all share pathologies typical of thyroid dysfunction, including obesity, appetite dysregulation, growth retardation, and disrupted timing of puberty [133,135–138]. All of this would suggest that MEG3 affects metabolism by regulating thyroid hormones. However, investigation thus far into MEG3's role in the thyroid function has been limited to its contribution to cancer. Thus, experiments probing the relationship between MEG3 and thyroid hormones may reveal an exciting new avenue through which MEG3 may affect metabolism. Further, it is worth investigating how MEG3 coordinates with other imprinted genes within the DLK1-DIO3 region and with other imprinted loci. Because the DLK1-DIO3 locus is regulated as a cohesive unit via the MEG3 IG-DMR, the effects of MEG3 are inherently tethered to that of the other genes within the locus such as DLK1, which also affects insulin resistance and glucose metabolism [139,140]. Further, MEG3 controls expression of other imprinted genes that affect metabolism and growth, such as IGF2, SNURF, and IPW [135,141]. With this in mind, we hypothesize that MEG3 may coordinate with a broader imprinted gene network that affects metabolic imprinting collectively. Studying the function and regulation of other genes within the DLK1-DIO3 locus and within other imprinted regions under different metabolic challenges would help evaluate this hypothesis. Lastly, while the literature suggests that the modulation of MEG3 expression may help mammals adapt to hyperglycemic challenge, experimental validation is necessary. *In vivo* studies investigating how MEG3 knockdown or

overexpression affects the development of disease in animals given a high-fat diet or under caloric restriction would be the most direct approach. While this is complicated by the fact that MEG3 is unique to mammals and that maternal MEG3-knockout causes perinatal death in mice, inducible knockout or transgenic models may provide a solution [142].

Overall, research suggests that MEG3 is involved in mammalian adaptation to the metabolic environment through interactions with p53, PI3K/AKT, and miRNA networks. In an energy abundant environment, elevated MEG3 levels generally protect against many of the most common afflictions associated with hyperglycemia. However, MEG3 expression also carries many pleiotropic costs such as cellular senescence, impaired injury recovery, heart fibrosis, and neurological impairments. These pleiotropic costs may suggest why MEG3 expression is regulated by nutrient availability. In nutrient-rich environments, MEG3-driven prevention of metabolic syndrome and cancer outweighs its costs. However, in nutrient-poor environments, high levels of MEG3 expression may do more harm than good. The cost of a maladapted epigenome is best illustrated by the differing fates of the children exposed to prenatal starvation during The Dutch Hunger Winter compared to The Siege of Leningrad. During The Dutch Hunger Winter, those prepared *in utero* for scarcity then raised on a normal diet developed cancer and cardiovascular disease at an elevated rate [7]. By comparison, children born during The Siege of Leningrad were starved *in utero* and endured prolonged starvation, thus conferring protection against these risks [7]. Given that the developing world is undergoing a comparable transition from food scarcity to excess [143], how developmental nutrition may predispose individuals to chronic disease remains a pressing yet unanswered question.

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## Highlights

- MEG3 regulates gene expression through interaction with DNA, RNA and/or proteins.
- MEG3 regulates gene expression by sponging miRNAs.
- Dysregulation of MEG3 found in several pathophysiological conditions and in aging.

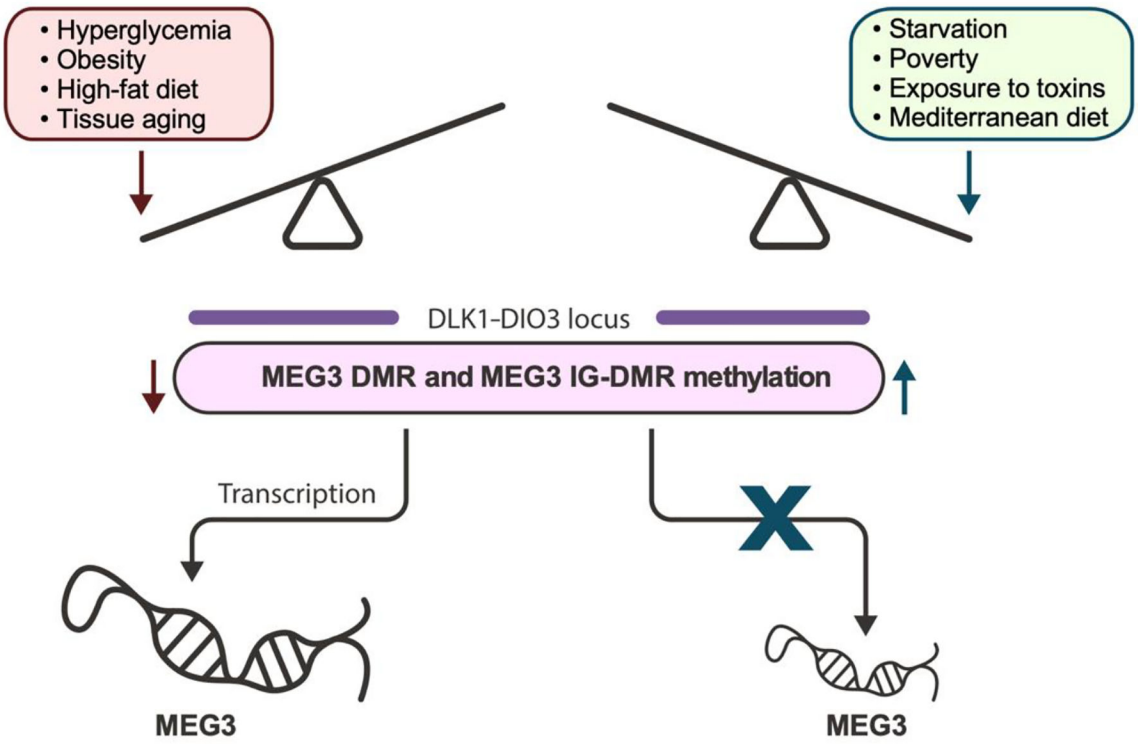


**Figure 1:**

Epigenetic regulation of MEG3 expression. Overnutrition and obesity increase MEG3 expression by hypomethylating the MEG3 IG-DMR and MEG3 DMR whereas starvation and other stressors contribute to the decrease in MEG3 expression via hypermethylation. MEG3 IGDMR methylation in most tissues decreases with age, with the notable exception of skeletal muscle [32–35]. Consumption of a Mediterranean diet has been associated with lower MEG3 expression.

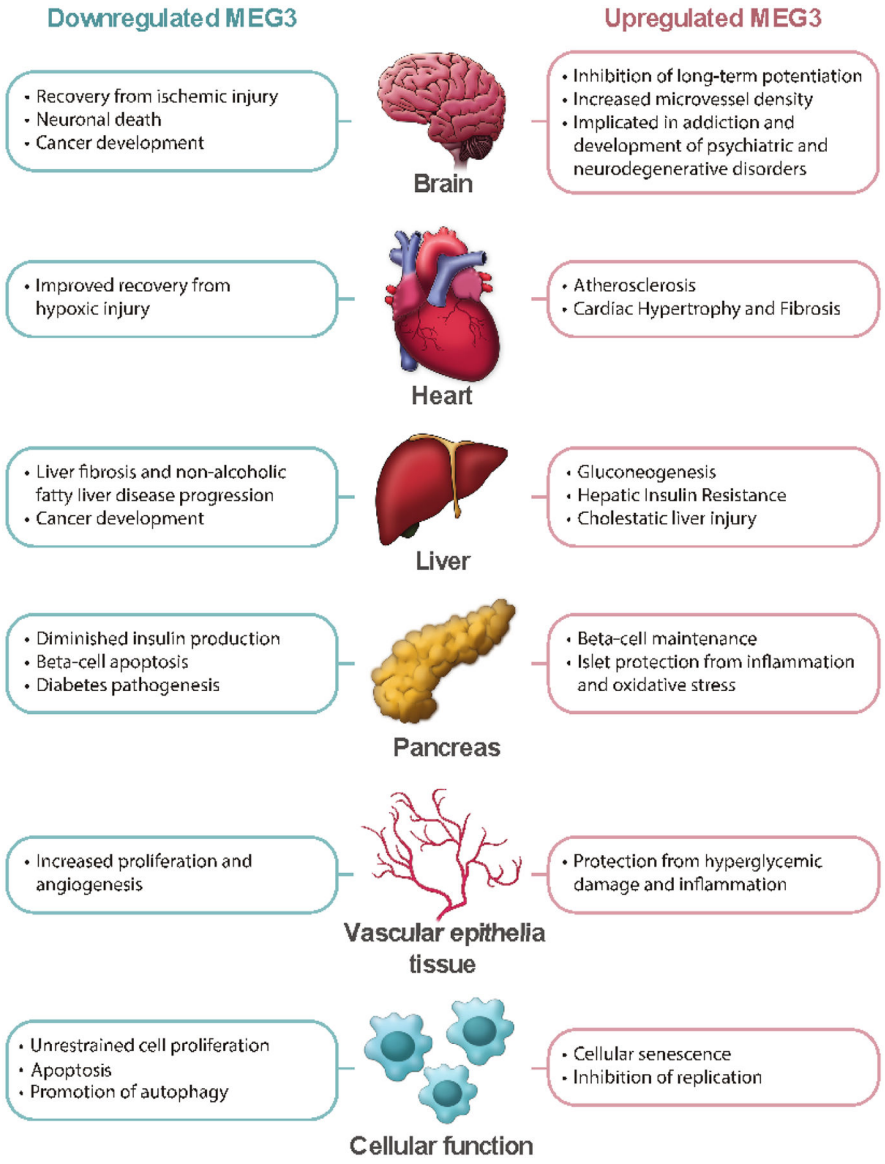


**Figure 2:**

Schematic representation of the pleiotropic effects of MEG3 expression in various organs and tissues.