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- GDF15 is one of the most up-regulated proteins during aging and a key molecule in the mechanisms of human stress response.
- The role of GDF15 in aging and age-associated diseases is more complex than previously thought and not yet totally clear.
- Given the biological complexity of GDF15 and the its involvement in several processes, GDF15 may be considered the central core of a bow tie architecture, characterized by a fan in (different age-related stress stimuli that activate GDF15 transcription factors), and a fan out (different downstream effects at central and peripheral level).
- Based on available evidence, we hypothesise that GDF15 may be a part of an anti-inflammaging response and play a role in a dormancy program to mediate tissue tolerance during inflammation and to protect from apoptosis.
- As GDF15 is associated with both positive and detrimental effects, its activity is proposed to be an example of antagonistic pleiotropy (beneficial in young age and detrimental in old age).

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Abstract:

Growth differentiation factor 15 (GDF15) is recently emerging not only as a stress-related mitokine, but also as a key player in the aging process, being the most up-regulated protein with age and associated with a variety of age-related diseases (ARDs). Many data indicate that GDF15 has protective roles in several tissues during different stress and aging, thus playing a beneficial role in apparent contrast with the observed association with many ARDs. A possible detrimental role for this protein is then hypothesised to emerge with age. Therefore, GDF15 can be considered as a pleiotropic factor with beneficial activities that can turn detrimental in old age possibly when it is chronically elevated. In this review, we summarize the current knowledge on the biology of GDF15 during aging. We also propose GDF15 as a part of a dormancy program, where it may play as a mediator of defence processes aimed to protect from inflammatory damage and other stresses, according to the life history theory.

Key words: GDF15; age-related diseases; inflammaging; stress; metabolism; dormancy program.

Introduction

Growth differentiation factor 15 (GDF15), originally described as macrophage inhibitory cytokine-1, is a distant member of the transforming growth factor-β superfamily (Bootcov et al., 1997) and is considered a stress responsive cytokine induced by mitochondrial dysfunction, cellular stress, inflammation or mitochondrial unfolded protein response (UPRmt) pathway, with positive effects on health and lifespan of model organisms. For this reason, it perfectly suits the definition of "mitokine" as provided by Dillin and co-workers (Durieux et al., 2011).

In contrast with this tenet, GDF15 expression is very low in healthy individuals and young subjects (Fujita et al., 2016; Tsai et al., 2018; Conte et al., 2019; 2020a). The levels of GDF15 dramatically increase in chronic or acute illness conditions, in presence of age-related diseases, such as cardiovascular diseases, insulin resistance and type 2 diabetes, neurodegeneration, renal chronic disease and cancer, as well as with aging independently from the health state, thus GDF15 has been proposed as a novel biomarker of biological aging in humans (Lee et al., 2021; Liu et al., 2021). Accordingly, several studies in humans have in fact reported that GDF15 is the most up-regulated protein during aging (Fujita et al., 2016; Tsai et al., 2018; Tanaka et al., 2018; Lehallier et al., 2019; Conte et al., 2019; 2020a; 2020b; 2021; Liu et al., 2021). The value of GDF15 as a marker of biological age has been further supported by a recent study reporting that GDF15 is expressed more in subjects with accelerated aging such as Down Syndrome persons, with respect to their siblings of similar age (Conte et al., 2019).

GDF15 is expressed in different types of tissues, such as placenta, skeletal muscle, brain, liver, heart, and it is found at circulating level, however, its pathophysiological role in the aging process is still poorly understood, as several studies suggested opposite functions for this protein. In particular, it is not yet clear whether increased levels of this mitokine in old age have detrimental or beneficial/protective effects on the organisms.

Many studies have proposed an anti-inflammatory role for GDF15. As an example, it has been demonstrated that GDF15 reduces the expression of pro-inflammatory cytokines and prevents the activation of T cells in liver of mice with fibrosis. In addition, GDF15 knockout (KO) induces in mice the production of TNF-α by T cells and the activation of CD4+ and CD8+ T cells, thus aggravating liver injury and fibrosis (Chung et al., 2017). In agreement, Abulizi and co-workers reported that GDF15 KO mice display elevated intensities of inflammatory responses and severe renal and cardiac damage in response to lipopolysaccharide (LPS), while GDF15 transgenic mice are protected from LPS-mediated organ injury (Abulizi et al., 2017). Moreover, an *in vitro* study on macrophages showed that GDF15 limits the action of TNF-α. These studies are in line with another finding in human prostate, where an inverse correlation between GDF15 levels, quantified by

immunohistochemistry image analysis, and CD3+, CD4+, CD8+, CD68+ and INOS+ leukocytes has been demonstrated. Moreover, the expression of IL-8 is downregulated by GDF-15 (Lambert et al., 2015). In agreement with these data, a recent study by Moon and colleagues identified a link between age-related induction of GDF15 and the protection of tissues from inflammation, in both humans and mouse models. In particular, these authors demonstrated that aged GDF15 KO mice presented higher levels of inflammatory markers in liver and adipose tissues, as well as impaired glucose homeostasis. Therefore, these data suggest that GDF15 is indispensable for attenuating aging-mediated local and systemic inflammation (Moon et al., 2020).

Similarly to inflammation, there are evidences indicating that GDF15 can have also anti-cancer properties, suggesting a tumour suppressor role for this protein. In a recent *in vitro* study, the overexpression of GDF15 in lung adenocarcinoma A549 cells inhibits the proliferation, migration and invasion of these cells through the activation of TGF-β/Smad signalling pathway (Duan et al., 2019). In agreement, another study indicates that the overexpression of GDF15 significantly suppresses non-small-cell lung cancer cell proliferation and induces apoptosis (Lu et a., 2017). Moreover, GDF15 overexpressing mice are protected from prostate cancer growth, thanks to the activation of CD8+ cytotoxic lymphocytes (Husaini et al., 2020).

In contrast to the above described protective role of GDF15, many other studies indicate that GDF15 can also play a pro-inflammatory role. For example, a study indicates that GDF15 is involved in the development of atherosclerosis by regulating apoptotic cell death and IL-6-dependent inflammatory response (Bonaterra et al., 2012). Another study on LDL-deficient mice has demonstrated that leukocyte-specific KO of GDF15 has beneficial effects against atherosclerosis by reducing macrophage plaque infiltration and decreasing necrotic core formation, suggesting a pro-inflammatory role of GDF15 in atherosclerosis (de Jager et al., 2011). In addition, other studies have identified GDF15 as a candidate biomarker of cellular senescence. In particular, GDF15 has been indicated as a component of the senescence-associated secretory phenotype (SASP) (Guo et al., 2019; Basisty et al., 2020; Di Micco et al., 2021), the pro-inflammatory secretome consisting of numerous cytokines, chemokines, growth factors and proteases released from senescent cells into the tissue microenvironment. Guo et al. have demonstrated that senescent fibroblasts secrete GDF15 as a SASP factor essential to promote cell proliferation, migration and invasion in colon adenoma and colorectal cancer cell lines *via* the MAPK and PI3K signalling pathways (Guo et al., 2019), suggesting that GDF15 may play an important role in promoting cancer progression. Moreover, several studies have found a strong link between GDF15 and presence of cancer. Circulating levels of GDF15 are in fact significantly higher in patients with different types of cancer compared to healthy controls (Kluger et al., 2011; Wang et al., 2014; Vocka et al., 2018; O'Neill et al., 2020), thus suggesting that GDF15 can

be considered as a marker to identify malignancies and a potential therapeutic target for the treatment of different types of cancer. In agreement, a very recent study demonstrated that circulating levels of GDF15 increase with tumour progression and are very high in patients with hepatocellular carcinoma (Myojin et al., 2021). Moreover, GDF15 KO in hepatic stellate cells suppresses liver tumour formation in mice (Myojin et al., 2021).

In the light of these contrasting findings, the understanding of the biological role of GDF15 appears much more complex than expected, especially in the aging process, where a number of stresses able to induce its expression can occur. Therefore, the analysis of its activities cannot be simple and straight-forward, but rather it has always to consider the biological context in which GDF15 acts. In particular, as it has been established that GDF15 is a stress-response molecule, the levels and nature of stress(es) that accompany GDF15 production should be considered. It is possible that, according to the type and duration of stress, a different role for this protein can be envisaged. In this review we will focus on the role of GDF15 during the aging process and will discuss different aspects of its double-sided nature and propose to consider GDF15 as a representative case of antagonistic pleiotropy. We will also discuss GDF15 in a unifying viewpoint based on the life-history theory, an ecological theory used in the study of aging (Selman et al., 2012; Maklakov and Chapman, 2019) that explains resource allocation during stress response through evolutionary concepts.

Evolutionary history of GDF15

GDF15 orthologues have been annotated in mammals, reptiles, amphibians, bony fish, and birds but there is no clear orthologue observed in the genomes of the other two lineages of craniata, hagfish, lampreys, or lower vertebrates (Lockart et al., 2020).

Phylogenetic analysis of the GDF15 proteins from different vertebrate species showed three main clusters, with one containing the mammalian species and another containing the other vertebrates. This second cluster also showed differentiation into two sub-clusters, one for the teleost species and another for birds, reptiles and amphibians (Pereiro et al., 2020).

Protein sequences data retrieved from Uniprot showed that human GDF15 has 90% identity with Ma's night monkey, Northern white-cheeked gibbon, Pygmy chimpanzee, Silvery gibbon, Bonobo, and Chimpanzee, while no other species present 100% identity (https://www.uniprot.org/uniprot/Q99988). A furine-like cleavage site, RXXR, needed for protein maturation, is conserved in human, mouse, rat, canine, and chimpanzee GDF15 (Baek and Eling, 2019).

To date the available data on the evolutionary history of GDF15 suggest an increasing importance of GDF15 in the primate evolution. Interestingly it has been observed that species-specific

expression of GDF15 is driven by a human-specific element and multiple alignment of 46 vertebrates shows that the underlying genomic sequence of the enhancer near GDF15 is conserved across most primates but absent from the mouse genome (Ulirsch et al 2014).

An evolutionary study performed across primates - based on a phylogenetic genome-phenome approach - has identified a correlation between the rate of protein evolution of GDF15 and several life-history traits such as maximum lifespan, weaning time, gestation and female age at maturity (Muntanè et al 2018).

GDF15 transcription regulation

The transcriptional regulation of GDF15 is very complex, since its promoter contains different cis- and trans-acting promoter elements. Various stresses and stimuli activate differently GDF15 through a number of transcriptional factors (TFs) and non-coding RNAs that converge to modulate its expression.

The mRNA expression of GDF15 is in part regulated by long non-coding RNAs (lncRNAs) and microRNAs (miRs), two classes of non-coding RNAs of about 200 nucleotides or 22 nucleotides in length, respectively. In particular these molecules may often act on GDF15 expression by activating other proteins which in turn regulate the expression levels of GDF15. There are several lncRNAs and miRs regulating GDF15, as observed in many tumours. For example, high levels of GDF15 in ovarian cancer are associated to the lncRNA GAS5, which acts on the transcription factor CEBPB blocking its transcription-promoting effect on GDF15 (Guo and Wang, 2019). Similarly, miR-34a modulates the regulation of the oncoprotein STMN1, that is involved in cancer progression also through the activation of GDF15 (Chakravarthi et al., 2018). Interestingly, GDF15 can be also regulated by lncRNAs and miRs acting together. In particular, the lncRNA PVT1, linked to malignancies, is negatively regulated by miR-214 and they both are involved in the regulation of GDF15 (Xiong et al., 2020).

The transcriptional modulation of GDF15 is even more complicated by the presence of several TFs acting to promote GDF15 expression. Among these TFs, there are p53, ATF3, ATF4, CHOP, XBP1, NF-κB, Sp1, KLF4, HIF1α, EGR1, AP1-2 (Fujita et al 2016). Literature data indicate that the main action of these TFs on GDF15 regulation is particularly associated with tumors and cellular stress, however, some of these transcription factors, such as Sp1, also regulate GDF15 basal transcription (Baek et al, 2001). Several studies indicate that some of these TFs, such as p53, ATF4, NF-κB, play important functions in aging, however, it is not known if and how they impinge upon GDF15 expression during aging. We will briefly describe here the main TFs that regulate GDF15 expression and, when possible, focusing on aging.

p53

p53 tumor suppressor plays a key role in mediating apoptosis upon various intracellular and extracellular signals. Several proteins are involved in p53 pathway, including GDF15. p53 induces GDF15 expression by acting on two binding sites of GDF15 promoter, p53-type response elements, RE1 and RE2. This latter confers p53-specific transactivation (Kannan et al., 2000; Li et al., 2000; Osada et al., 2007). Several studies have shown that p53 contributes to GDF15 up-regulation particularly in tumors, where GDF15 acts to reduce cell proliferation, invasion and tumorigenesis (Cheng et al., 2011; Knutson et al., 2012; Kang et al., 2013; Tsui et al., 2015; Kannan et al., 2000), suggesting that among the tumor suppressor activities of p53 there is also a paracrine activity mediated by GDF15.

The interaction of p53 and GDF15 during aging is at present unexplored. p53 is responsive to oxidative stress and plays a role in aging (Chatoo et al., 2011; Wu and Prives, 2018; Liu et al., 2018; Mijit et al., 2020). As mitochondrial dysfunction is reported to increase with age, thus causing an increased oxidative damage, it is plausible that an increased p53 activation occurs in response to such damage, also impinging upon GDF15 expression. Another possibility is that p53 can activate GDF15 transcription in response to inflammatory stimuli. It is in fact reported that C-Reactive Protein induces GDF15 *via* p53 binding to RE1 and RE2 (Kim et al., 2018). Since inflammatory mediators increase with age (the phenomenon of inflammaging), p53 could possibly represent the link between inflammaging and GDF15. Due to its anti-inflammatory activities, we proposed GDF15 to be a part of an anti-inflammaging response (Conte et al., 2020b).

ATF4 – ATF3 – CHOP – XBP1

The expression of GDF15 is strongly activated also by the integrated stress response (ISR) pathway, a sophisticate signalling pathway that aims to restore the physiological homeostasis of cells upon different stresses, such as oxidative stress, hypoxia, nutrient deprivation, and is generally triggered by an accumulation of misfolded proteins at the level of the endoplasmic reticulum (ER) (Harding et al., 2003; Wang et al., 2018; Costa-Mattioli and Walter, 2020). In response to these stresses, and in particular under chronic ER stress, ISR supports cells through the activation of a series of kinases that phosphorylate the eukaryotic translation initiation factor 2 (eIF2), which in turn activates the mRNA translation of the activating transcription factor 4 (ATF4). ATF4, together with ATF3, C/EBP homologous protein (CHOP) and functional spliced x-box binding protein 1 (XBP1s), are considered key transcriptional players of ISR, also involved in the expression of several UPR target genes. Moreover, they are directly involved in the up-regulation of GDF15 expression (Lee et al., 2010; Suzuki et al., 2017; Patel et al., 2019; Day et al., 2019; Kang et al., 2021). However, the

connection among ATF4, ATF3, CHOP, XBP1s and GDF15 in aging and age-related diseases is still unclear. Several findings indicate that ATF4, ATF3, CHOP and XBP1s play a key role also in the aging process. For example, several studies from simple model organisms to mammals have shown that XBP1s is fundamental in the maintenance of ER proteostasis to protect cells from damaged and misfolded proteins that progressively accumulate with aging and lead to the development of age-related diseases (Taylor and Dillin, 2013; Martinez et al., 2017). The increased expression of XBP1s extends health and lifespan in *C. elegans* (Martinez et al., 2017), while the loss of XBP1s accelerates age-related neurodegeneration (McLaughlin et al., 2018; Gerakis and Hetz, 2018). An important study by Zhang et al., (2018) has demonstrated that XBP1s activates the transcription of GDF15 in fasted liver cells thus reducing lipid accumulation and blocking the development of Non-Alcoholic Fatty Liver Disease in obese mice. This study suggests that the GDF15 activated by XBP1s is fundamental in regulating liver lipid metabolism, thus suggesting that XBP1s and GDF15 are important in the prevention of pathologies associated to lipid accumulation, which often occur during aging.

Regarding ATF3, ATF4 and CHOP during aging process, contrasting data are available. It has been reported that elevated protein levels of ATF4, ATF3 and CHOP are present in tissues of five slow-aging mouse models compared to wild-type (Li et al., 2014; Li et al., 2015). Moreover, in these mouse models the expression of ATF4 was even higher under stress conditions, suggesting that ATF4 pathway may help in regulating aging and age-related disease progress (Li et al., 2015). Conversely, other studies indicate that ATF4, ATF3 and CHOP are elevated in old mice and in cellular models of aging, suggesting that these molecules are important factors in the progression of aging (Ikeyama et al., 2003; Ghosh et al., 2015; Liu et al., 2020; Zhang et al., 2021). Furthermore, a study performed on human samples indicates that high expression levels of ATF4, CHOP and GDF15 are found in adipocytes of elderly women characterized by reduced lipogenic capacity that in turn is associated with mitochondrial dysfunction (Šrámková et al., 2019). These data suggest that these TFs could be responsible for the elevation of GDF15 levels observed during aging.

NF-κB

The activation of GDF15 is also regulated by NF-κB, a transcription factor well known for its involvement in the regulation of pro-inflammatory genes. NF-κB plays a key role in regulating inflammation, cell proliferation, cancer and immune response. Recent evidence indicates that high levels of GDF15, associated to NF-κB, act in the regulation of macrophage activity. In particular, a NF-κB-GDF15 axis seems to be involved in tumour cells escape from macrophage activity in the early stage of tumorigenesis (Bootcov et al, 1997; Ratnam et al, 2017).

NF-κB is also strongly associated with aging and cellular senescence, in both humans and rodents. For example, inducible genetic depletion of NF-κB in the skin of aged mice reverted gene expression signature to that of young mice, suggesting a fundamental role for NF-κB in the progression of aging degeneration (Adler et al, 2007). In agreement, genetic depletion of NF-κB, as well as the pharmacological inactivation of NF-κB-activating kinase, in progeroid mouse model attenuated the aging process and prolonged animal lifespan (Tilstra et al., 2012). In addition, NF-κB is associated with several age-related diseases through the secretion of SASP factors. In particular, NF-κB binds to the promoters of SASP genes and regulates their activation (Rovillain et al, 2011; Balistreri et al, 2013). As above mentioned, GDF15 has been recently added to the list of SASP factors (Di Micco et al., 2021) that may be regulated by NF-κB, although this hypothesis needs further confirmation.

Genetic variability effects on GDF15 concentrations

Recent data demonstrated that GDF15 protein concentration is also influenced by genetic variability. Folkersen and colleagues (Folkersen et al., 2020) have found four protein Quantitative Trail Loci (pQTLs) (rs2517481, rs1227734, rs60164552, rs112253475) that significantly affect (p-value < 5E-08) the plasma levels of GDF15 protein in individuals of European ancestry. rs1227734-T and rs112253475-A have a positive effect on the concentration of GDF15 protein, whereas rs2517481-C and rs60164552-C have a negative one (Table 1).

Another study (Sun et al., 2018) has revealed a significant positive effect (p-value < 1.5E-11) of a different SNP, rs45543339-T, on the protein level of GDF15 in three different cohorts of European descent, whereas a second SNP, rs1227734-T, showed a significant positive effect on the protein level of GDF15 only when conditioned to rs45543339 (Table 1).

Two other genome-wide studies (Ho et al., 2012; Jiang et al., 2018), consisting of partially overlapping cohorts of European individuals, found eight SNPs (rs1227731-A, rs888663-T, rs3746181-A, rs1363120-C, rs749451-C, rs1054564-C, rs3195944-G, rs17725099-A) with a significant effect (p-value < 5E-08) on GDF15 blood concentration (Table 1). The most significant SNP was rs888663 in both analyses. In addition, a significant impact on GDF15 blood concentration was observed for other ten SNPs only after conditioning them on the top significant signal (rs888663) (Jiang et al., 2018).

Among the above-mentioned SNPs, four were reported as pQTL (rs2517481, rs1227734, rs60164552, rs112253475), and four as eQTL – expression Quantitative Trait Loci (rs3746181, rs1363120,

rs888663, rs1054564). For the remaining five SNPs (rs3195944, rs749451, rs17725099, rs1227731, rs45543339) other studies are needed in order to investigate their role in the molecular mechanisms affecting the GDF15 protein levels.

Furthermore, GDF15 blood concentration is not only associated to genetic variability of unique SNPs but also to genetic variability of whole genes that are analysed combining several SNPs retrieved from Illumina microarray. A gene-based association analysis discovered a significant association (p-value < 1E-05) between seven genes (GDF15, LRRC25, MIR3189, PGPEP1, which are located on chromosome 19, and B3GALT6, SDF4, TNFRSF4, which are located on chromosome 1), and GDF15 blood concentration (Jiang et al., 2018).

TABLE 1: SNPs with significant effect on GDF15 blood level, ordered by chromosomic position.

SNP	Chr	Bp	Gene Name	Effect Allele	Effect on GDF15 protein blood concentration	SNP function (GDF15)	Reference
rs2517481	6	31043931	-	C	↓	pQTL	Folkersen et al., 2020
rs112253475	19	18841757	CRTC1	A	↑	pQTL	Folkersen et al., 2020
rs3195944	19	18476711	PGPEP1	G	↑	unknown	Ho et al., 2012; Jiang et al., 2018
rs3746181	19	18477017	PGPEP1	A	↓	eQTL	Ho et al., 2012; Jiang et al., 2018
rs749451	19	18479647	PGPEP1	C	↑	unknown	Ho et al., 2012; Jiang et al., 2018
rs1363120	19	18482304	intergenic	C	↓	eQTL	Ho et al., 2012; Jiang et al., 2018
rs17725099	19	18482358	intergenic	A	↑	unknown	Ho et al., 2012; Jiang et al., 2018
rs888663	19	18484922	intergenic	T	↑	eQTL	Ho et al., 2012; Jiang et al., 2018
rs60164552	19	18488285	intergenic	C	↓	pQTL	Folkersen et al., 2020
rs1227731	19	18497903	GDF15	A	↑	unknown	Ho et al., 2012; Jiang et al., 2018
rs1054564	19	18499815	GDF15	C	↑	eQTL	Ho et al., 2012; Jiang et al., 2018
rs1227734	19	18501034	intergenic	T	↑	pQTL	Sun et al., 2018; Folkersen et al., 2020;

rs45543339	19	18503194	LRRC25	T	↑	unknown	Sun et al., 2018

SNP ID, chromosome, genomic position in hg19, gene name, effect allele, effect on GDF15 protein blood concentration, SNP function on GDF15 and references are reported for each SNP.

GDF15 regulation at protein level

In addition to the transcriptional regulation, GDF15 is also regulated at translational and maturation levels. GDF15 is translated into a 308 amino acid protein, including a pro-peptide of 167 amino acids and a mature form of 112 amino acids. GDF15 is at first synthesized as GDF15 precursor (pro-GDF15) that then dimerizes to form the pro-GDF15 dimer. The dimeric form is subsequently cleaved at the furine-like cleavage site, RXXR, forming the mature GFD15 form of 112 amino acids that is secreted as mature homodimer bound together by a disulphide bond (Baek and Eling, 2019; Wang et al., 2021).

Pro-GDF15 is mainly cleaved by three proteases belonging to the family of the proprotein convertase subtilisin/kexin (PCSK) serine protease, PCSK3, PCSK5 and PCSK6, which act specifically at the RXXR cleavage site (Couture et al., 2017; Li et al., 2018; Baek and Eling, 2019; Wang et al., 2021). These proteases are widely expressed in different tissues and their essential role in the maturation of GDF15 has been demonstrated in *in vitro* experiments, where cells were treated with different classes of protease inhibitors. PCSK inhibitions in fact led to the decrease of extracellular levels of mature GDF15 and the consequent increase of intracellular levels of pro-GDF15 (Li et al., 2018). In addition to PCSK enzymes, during placental development GDF15 is also modified by the matrix metalloprotease 26 (MMP26) (Li et al., 2014; Wang et al., 2021). Moreover, very recently it has been observed that also β-arrestin 1 (ARRB1) plays a fundamental role in the maturation of GDF15 (Zhang et al., 2020; Wang et al., 2021). In particular, in hepatocytes ARRB1 binds the pro-GDF15 and facilitates its transport to the Golgi apparatus to promote the subsequent GDF15 cleavage and maturation through PCSK enzymes (Zhang et al., 2020; Wang et al., 2021).

However, to date it is not yet clear what kind of stimuli (physiological or pathological) activate PCSK enzymes to regulate the maturation of GDF15 and their specific biological function in the aging process. Literature data suggest a role of these proteases in several age-related diseases (Choi and Korstanje, 2013; Turpeinen et al., 2013; Chen et al., 2019; Tong et al., 2021). Therefore, it is plausible that pathological conditions associated to aging may promote PCSK expression/activation thus affecting GDF15 maturation.

GDF15 receptor(s)

One of the reasons why the role of GDF15 is not yet totally clear is due to the limited knowledge on the receptors by which GDF15 binds to target cells. In 2017, four groups

simultaneously identified the GDNF α-like receptor (GFRAL) as the only known GDF15 receptor so far, acting through the REarranged during Transfection (RET) co-receptor. To date, it seems that GFRAL expression is limited to the area postrema (AP) and the nucleus of the solitary tract (NTS), two important hindbrain centres involved in the control of energy and regulation of appetite (Tsai et al., 2019). These areas are considered as the target of GDF15 activity (Emmerson et al., 2017; Hsu et al., 2017; Mullican et al., 2017; Yang et al., 2017), therefore it is not yet clear how GDF15 can act on other peripheral tissues in the absence of known GDF15-specific receptors.

GDF15-GFRAL signalling is involved in energy metabolism and body weight regulation, through a non-homeostatic pathway (Berthoud, 2006; Hsu et al., 2017) that is not regulated by hormones related to metabolism, physical activity or food intake, but rather by stress-related responses that induce the expression of GDF15. High levels of GDF15 lead to loss of body weight in numerous chronic human diseases through the activation of GFRAL-expressing neurons. GFRAL KO mice are resistant to the anorexigenic effects of elevated GDF15 levels, both under stress conditions and after chemotherapy, a treatment that usually induces weight loss (Hsu et al., 2017; Patel et al., 2019; Worth et al., 2020). In agreement, monoclonal antibodies against GDF15 can block the engagement of GFRAL and inhibit tumour cachexia (Suriben et al., 2020).

While there are several studies on the effects of the GDF15-GFRAL signalling pathway in mice following pharmacological stimuli or in pathological conditions, no one has clarified the physiological role of GDF15-GFRAL in healthy conditions and during aging. We and others demonstrated that in healthy conditions, physiological and metabolic stressors, such as physical exercise, fasting or high fat diet, increase the circulating levels of GDF15 (Galliera et al., 2014; Kleinert et al., 2018; Conte et al., 2020a; Klein et al., 2021), suggesting a physiological role for this mitokine in the regulation of energy metabolism to protect the organisms from stressful conditions (i.e. intense exercise, starvation or overnutrition). However, it is not yet clear whether this possibility is linked to the activation of GFRAL. Klein and co-workers demonstrated that the increased plasma levels of GDF15 after vigorous exercise are comparable to those found in pathological conditions, in both humans and mice. However, they demonstrated that both wild-type and GFRAL KO mice after vigorous exercise had similar body weights, fat and lean mass, suggesting that, unlike the pharmacological administration of GDF15, high levels of endogenous GDF15 may induce a GFRAL-independent and peripheral pathway of activity (Klein et al., 2021).

In this regard, there are two possible hypotheses to explain the mechanisms of action of GDF15 that, however, are still to be investigated. The first is that GDF15 acts through a soluble form of GFRAL. There are in fact two splice variants of GFRAL: the full-length form (A) of 393 amino acids with a transmembrane sequence, and a short form (B) of 238 amino acids, that misses the

transmembrane sequence, but contains the GDF15-binding domain and thus might act as a soluble receptor (Li et al., 2005; Breit et al., 2017; Tsai et al., 2018). At present there are no data on the action of the soluble complex GDF15-GFRAL, however, the coreceptor RET is widely expressed also in tissues different from the CNS, so it is possible that the soluble GDF15-GFRAL complex may activate the GDF15 signalling pathways in these tissues by interacting with RET, as it is known to occur for the IL-6 trans-signalling (Breit et al., 2017; Tsai et al., 2018).

The second hypothesis is that GDF15 might act through TGF-β receptors (type 1 and 2) in the TGF-β/SMAD signalling pathway (Lu et al., 2017; Li et al., 2020). In particular, ALK5 and TGF-β type 2 receptors seem to be involved in GDF15 signalling (Artz et al., 2016), while the involvement of TGF-β type 1 is still debated, as it has been reported that commercial sources of recombinant GDF15 may be contaminated with low levels of TGF-β (Olsen et al., 2017).

While it is known that GDF15 is up-regulated during aging, to date little is known about possible age-related changes in the expression of GFRAL and other putative GDF15 receptors. It has been proposed that the rise in GDF15 concentrations during aging could be a compensatory phenomenon for a decreased expression or sensitivity of these receptors. This is partly contradicted by the fact that exogenous GDF15 administration in old animals is able to induce a response, thus indicating that GDF15 receptors are still working (Lockhart et al., 2020).

GDF15 effects

As mentioned, GDF15 has many diverse effects, both at systemic and local level. The discovery of GFRAL receptor in the brain suggested that GDF15 acts centrally to control appetite, body weight and energy balance. This was later confirmed by studies in mice where the ablation of GDF15 led to diet-induced obesity (Tran et al., 2018; Patel et al., 2019), demonstrating the fundamental role of GDF15 in the regulation of energy homeostasis. Moreover, GDF15 acts centrally to cause emesis and nausea, two effects that lead to disease-related anorexia.

GDF15 acts also directly in peripheral tissues by increasing lipolysis, oxidative metabolism and thermogenesis, cellular processes associated with reduction of insulin resistance and inflammation. To this regard, several studies on transgenic mice overexpressing human GDF15 showed reduced adipose tissue, lower weight and resistance to obesity, as well as lower serum level of insulin, leptin and IGF-1, with respect to WT mice fed with the same diet (Macia et al., 2012; Kim et al., 2013; Chrysovergis et al., 2014; Lertpatipanpong et al., 2021). These effects seem to be due to the increased expression of key genes involved in the regulation of thermogenesis, lipolysis, and oxidative metabolism. In particular, the relative expression levels of gene related to lipolysis, such as ATGL and HSL, and thermogenesis, such as UCP1 and PGC1α, were higher in the white adipose

tissue of GDF15 overexpressing mice compared to WT (Chrysovergis et al., 2014). Similarly, in mice fasting-induced high levels of GDF15 reduced hepatosteatosis associated to obesity due to the increased expression of hepatic genes of lipid catabolism (Zhang et al., 2018). In agreement, the genetic ablation of GDF15 in UCP1 transgenic mice, with compromised muscle-specific OXPHOS capacity, promotes a progressive increase in body fat mass, induces elevated plasma leptin levels and compromises the systemic insulin sensitivity as a metabolic response to muscle mitochondrial dysfunction (Ost et al., 2020). These data suggest that GDF15 plays a crucial role as an endocrine metabolic cytokine acting in response to mitochondrial dysfunction (Ost et al., 2020).

As already mentioned, GDF15 plays roles as anti-inflammatory mediator in the adaptation of tissues to stress and protection against injury, as well as to prevent cell apoptosis (Abulizi et al., 2017; Zhang et al., 2017; Moon et al., 2020; Rochette et al., 2021a). In particular, GDF15 treatment increased the cell proliferation rate of human umbilical vein endothelial cells (HUVECs) by enhancing the expression of G1 cyclins, cyclins D1 and E, through the PI3K/Akt, ERK, and JNK pathways, involved in cell growth and survival, and inhibition of apoptosis (Jin et al., 2012). These data were confirmed by other studies suggesting that GDF15 plays a mitogenic role in endothelial cells and promotes angiogenesis (Jin et al., 2012; Wang et al., 2017; Ha et al., 2019). The anti-apoptotic role of GDF15 was also demonstrated in another study in heart grafts, where it has been shown that the overexpression of human GDF15 in transgenic mice protects hearts from ischemia reperfusion injury through the inhibition of Foxo3a and Rel A p65, a member of NF-κB family (Zhang et al., 2017). The cardioprotective role of GDF15 was also confirmed in another study showing that GDF15 protects cardiomyocytes against different apoptotic stimuli and induces hypertrophy via the kinases PI3K and ERK and the transcription factor R-SMAD1 (Heger et al., 2010).

Considering the biological complexity of GDF15 and the involvement of several TFs on its regulation, and the number of different activities that it exerts on many tissues and organs that have been briefly described, GDF15 could be seen as the knot of a bow tie architectural module playing a role in the aging process (Figure 1). The "bow tie" model was introduced to describe ordered and complex biological systems characterized by several and distinct input signals (or fan in) that converge into a core, the knot, where they are organized, processed and elaborated according to precise protocols, and then propagated as multiple output signals (or fan out) (Csete and Doyle, 2004; Tieri et al., 2010; Tieri et al., 2012; Friedlander et al., 2015). According to the evidence described above, GDF15 could represent the core of the bow tie module. In particular, during aging many stress stimuli (fan in) can activate transcription factors converging on GDF15 production regulation (knot), which in turn has a number of different activities, leading to different downstream effects in different tissues (fan out). Little is known on how bow tie architectures evolve, however in the case of GDF15

in aging system, this biological module might be a flexible, robust, efficient and economical system, equipped with a regulatory feedback loop, able to convey different effects in response to different stimuli to which the organism may be exposed, thus reducing the number of central molecular mediators, and the relative energy expenditure, that would otherwise necessary to respond to the myriad of stimuli associated with aging (Csete and Doyle, 2004; Tieri et al., 2012).

GDF15 in aging and age-related diseases

According to its definition of mitokine, circulating GDF15 is elevated in animal models with mitochondrial dysfunctions, in patients with mitochondrial diseases, as well as in subjects characterized by mitochondrial impairment. Mitochondrial dysfunction is considered a driver of the aging process across several species, from worms to mammals, however, a mild mitochondrial defect can actually contribute to activate an adaptive and beneficial response in all species. This phenomenon, known as mitohormesis, is an adaptive stress response that increases stress resistance and promotes longevity (Ristow and Zarse, 2010). We and other authors have proposed that GDF15 can be a promoter of mitohormesis (Conte et al 2019, 2020b; Klaus and Ost, 2020). However, many studies reported an association of GDF15 levels with different diseases, therefore the role of this mitokine is still debated. As mitochondrial DNA (mtDNA) mutations, oxidative stress and increased reactive oxygen species (ROS) production occur with aging, it does not come as a surprise that GDF15 levels are elevated in old people, and, as mentioned, it recently emerged as one of the most up-regulated proteins during aging, reaching the highest levels in centenarians. Therefore, GDF15 looks like a *trait d'union* among aging, mitochondrial dysfunction and ARDs. Such connections and associations will be briefly summarized in this chapter.

Expression levels of GDF15 are elevated in various ARDs, and the plasma levels of GDF15 appear to reflect the severity and progression of a disease. For this reason, GDF15 is considered as both a clinical biomarker and a target to counteract several ARDs. In addition, GDF15 is also considered a marker of all-cause mortality (Wiklund et al., 2010; Fujita et al., 2016) and in agreement we found that high GDF15 levels correlate with lower survival in old age (Conte et al., 2019). In contrast with these results, a study performed in transgenic GDF15 mice suggested that GDF15 is an important regulator of mammalian longevity and may act as a survival factor (Wang et al., 2014). However, it is to note that any other study confirming this finding is present in the literature.

Increased circulating levels of GDF15 have been associated with cachexia, sarcopenia, cancer, cardiovascular diseases, hypertension, metabolic disorders and type 2 diabetes, renal dysfunction and chronic inflammatory diseases. Moreover, in very recent studies, a link between high levels of GDF15 and COVID-19 was observed. In particular, GDF15 serum levels resulted elevated in hospitalized

COVID-19 patients (mean 12.4 ng/ml in patients *versus* <2 ng/ml in controls) and, among these, non-survivors had higher GDF15 serum levels after intensive care unit admission with respect to survivors, supporting the idea that GDF15 is associated to mortality (Myhre et al., 2020; Notz et al., 2020; García de Guadiana Romualdo et al., 2021; Rochette et al., 2021).

The involvement of GDF15 in different age-related diseases is summarized in Table 2, though the molecular mechanisms of GDF15 in the progression of aging remain still largely unknown. A detailed description of GDF15 involvement in every single disease is outside the scope of this review, as an example of the involvement of GDF15 in ARDs, a specific focus on cachexia and sarcopenia is provided in Box 1.

TABLE 2: Effects of GDF15 in different age-related diseases

Disease	*Model system*	*Studies proposing a positive/neutral effect of GDF15*	*Studies proposing a negative effect of GDF15*	*References*
Sarcopenia	Humans	1. No differences are found in GDF15 serum levels in sarcopenic patients compared to non-sarcopenic.	2. GDF15 serum levels and muscle mRNA expression are negatively correlated with muscle mass. 3. GDF15 serum levels are increased in patients with lower limb mobility impairment.	1. Nga et al., 2021; Seo et al, 2020 2. Kim et al., 2020; Patel et al., 2016 3. Conte et al., 2020a
	Mice		1. Circulating levels and muscle mRNA expression of GDF15 are significantly higher in a model of accelerated skeletal muscle aging. 2. Endurance exercise in old mice suppresses the age-related increase of GDF15 expression in muscle. 3. GDF15 overexpression in mice muscle causes atrophy.	1. Ito et al., 2018 2. Kim et al., 2020 3. Patel et al., 2016
	Myoblasts	1. GDF15 knockdown in myoblasts results in reduced fusion and myotube size.	2. Treatment of C2C12 myotubes with GDF15 increases the expression of two atrophy-related genes.	1. Bloch et al., 2015 2. Ge et al., 2013
Cachexia	Humans		1. Circulating levels of GDF15 correlate with cachexia and reduced survival in patients with cancer. 2. GDF15 serum levels of individuals with prostate cancer show a direct relationship with cancer-associated weight loss.	1. Lerner et al., 2015 2. Johnen et al., 2007
	Mice		1. Antibody-mediated inhibition of GDF15-GFRAL activity inhibits weight loss in mice carrying GDF15-expressing tumors. 2. In mice with xenografted prostate cancer GDF15 levels are associated with reduced food intake and weight loss.	1. Suriben et al., 2020 2. Johnen et al., 2007

CVD	Humans		1. GDF15 shows a strong association with future sudden cardiac death. 2. Elevated GDF15 plasma levels are found in patients at highest risk of cardiovascular events.	1. Andersson et al., 2020 2. Baggen et al., 2017
	Mice	1. Transgenic mice with cardiac-specific overexpression of GDF15 are protected from cardiac hypertrophy while GDF15 *null* mice display cardiac hypertrophy after pressure overload stimulation. 2. ApoE deficient mice overexpressing GDF15 in macrophages have smaller lesions in aortic sinus and thoracic aorta. 3. Overexpression of GDF15 in ischemia/reperfusion injury heart grafts inhibits cell death and reduces pro-inflammatory cytokines production.		1. Xu et al., 2006 2. Johnen et al., 2012 3. Zhang et al, 2017
	Cardio-myocytes	1. Rat neonatal cardiomyocytes overexpressing GDF15 show reduced induction of hypertrophy after treatment with Angiotensin II. 2. Overexpression of GDF15 in rat cardiomyocytes exposed to cold hypoxia followed by reperfusion protects from apoptosis.		1. Xu et al., 2006 2. Zhang et al, 2017
T2D, Insulin resistance	Humans	1. Circulating levels of GDF15 are significantly higher in T2D patients treated with Metformin with respect to non-treated patients.	2. GDF15 plasma levels are significantly increased in T2D patients compared to healthy controls. Patients with complications, such as micro- and macrovascular disease, show higher levels of GDF15. 3. Changes in GDF15 plasma levels from baseline to 4 years are associated with HOMA-IR.	1. Conte et al., 2021; Natali et al, 2019; Gerstein et al, 2017 2. Conte et al., 2021; Carlsson et al., 2020; 3. Kempf et al., 2012
	Mice	1. Mice with induced diabetes and a transgenic overexpression of GDF15 display reduced fasting blood glucose levels and serum insulin levels. 2. IL-13-induced GDF15 expression reduces serum glucose level and this effect is abolished in GDF15 KO mice. 3. Genetic deletion of GDF15 in type 1 and type 2 diabetes mice models worsens diabetic kidney damage.		1. Lertpatipanpong et al., 2021 2. Lee et al, 2017 3. Mazagova et al, 2013
ND	Humans	1. GDF15 plasma levels in Alzheimer's disease patients are similar to those of non-demented controls.	2. GDF15 cerebrospinal fluid levels are higher in patients with Lewy body disorders compared to controls.	1. Conte et al., 2021 2. Maetzler et al., 2016 3. Chai et al., 2016

			3. Higher circulating GDF15 levels are associated with dementia and cerebrovascular disease. 4. GDF15 circulating levels are associated with worsening cognitive function and decline from normal cognitive status to dementia.	4. Jiang et al, 2016
	Mice	1. GDF15 KO affects dopaminergic neuron survival in a Parkinson's disease model.	2. GDF15 expression is increased in the hippocampus of kainic acid-treated mice.	1. Machado et al., 2016 2. Yi et al., 2015
	Microglial cells	Treatment with exogenous recombinant GDF15 promotes Aβ clearance ability of microglial cells.		Kim et al., 2018
Renal diseases	Humans		1. Plasma GDF15 levels are higher in elderly with cronic kidney disease and are negatively associated with eGFR. 2. Preoperative GDF15 plasma levels predict acute kidney injury in patients undergoing cardiac surgery.	1. Kim et al., 2019 2. Heringlake et al., 2016
	Mice	GDF15 KO in kidneys enhances inflammatory response after ischemia-reperfusion injury.		Liu et al., 2020
Cancer	Humans		1. In elderly men GDF15 plasma levels improve prognostication of cancer morbidity and mortality. 2. GDF15 expression increases during the progression of cervical carcinogenesis. 3. GDF15 is overexpressed in a large range of cancer types at transcript and circulating level.	1. Wallentin et al., 2013 2. Li et al., 2018 3. Welsh et al., 2013
	Mice	1. In prostate cancer prone mice GDF15 overexpression protects from tumor growth by modulating CD8+ T cell mediated anti-tumor immunity. 2. GDF15 overexpression suppresses chemically induced carcinogenesis in colon.	3. GDF15 overexpression in prostate cancer prone-mice reduces local tumor growth but promotes metastasis. 4. siRNA-mediated downregulation of GDF15 reduces tumorigenesis of melanoma cells by a retardation of tumor vascular development.	1. Husaini et al, 2020 2. Baek et al, 2006 3. Husaini et al, 2012 4. Huh et al, 2010
	Fibroblasts		GDF15 secreted from senescent fibroblasts has pro-tumorigenic effects on colorectal cancer cell lines.	Guo et al., 2019
	Bladder cancer cells	Treatment with recombinant GDF15 attenuates tumor cell proliferation. Tumors derived from carcinoma cells overexpressing GDF15 shows reduced size.		Tsui et al, 2015

Note: CVD = cardiovascular diseases; ND = neurodegenerative diseases; T2D = type 2 diabetes.

GDF15 as a mediator of a life history program

As discussed above, GDF15 is emerging as a key player in aging and ARDs, but the interpretation of its biological role is still an open issue. Considering the role of GDF15 in the evolutionary history of our species, as mentioned at the beginning of this review, we adopt an ecological perspective to gather the huge amount of (sometimes contrasting) data on GDF15. One of the most successful ecological theory used in the study of aging is the life history theory that argues that organisms allocate limited resources into separate biological programs that can be broadly identify as i) growth, ii) reproduction, and iii) maintenance to maximize reproductive success (Stearns 1992; Maklakov and Chapman 2019). The life history theory explains patterns of resource allocation in different environment and in response to diverse stimuli and stresses.

Recently Wang and colleagues (2019) provided new evidence for the division of the maintenance program in two subfields: 1) the defense program and 2) the dormancy program, both relying on different metabolic programs regulated by the hypothalamus and its axes. The defense program is activated by factors that the organism must face, such as pathogens, and it is a program that requires a high amount of energy and relies on anabolic metabolism to mount protective responses. The dormancy program is activated by absence of resources or by adverse environment (food shortage, extreme temperatures) that promote energy conservation and relies on catabolic metabolism. Interestingly these programs can "work" separately, however, the inflammatory response activates many components of dormancy programs without the stimulus of adverse environment. Surviving an infection requires pathogen clearance but also tissue protection from both pathogens and inflammatory damage that is achieved through a defense-induced dormancy program. Among the molecules that play a role in the dormancy programs, FGF21 has been described as a fundamental signal that coordinate organ-specific activities that allow tissue protection for surviving inflammatory conditions. Similarly, GDF15 displays similar features that suggest a role of this molecule in the dormancy program such as the capability to mediate tissue tolerance during inflammation (Luan et al 2019). Luan and colleagues (2019) demonstrated that in mice models GDF15 coordinates physiological response to inflammation and induces tolerance to inflammatory damage by modulating systemic levels of plasma triglycerides. Other than the resistance to inflammatory damage, GDF15 has other activities and features that support the idea that is part of a dormancy program. In particular, as previously mentioned, GDF15 is known since many years for promoting cell survival from different type of insults by protecting from apoptosis (Subramaniam et al., 2003; Heger et al., 2010; Abulizi et al., 2017; Zhang et al., 2017). GDF15 also promotes fatty acid beta-oxidation and catabolism in the liver upon starvation (Zhang et al., 2018). GDF15 maintains the

body temperature in mice and, if blocked, mice suffered of hypothermia (Luan et al 2019). However, the molecular mechanisms that confer tolerance to stress and inflammatory insults in hibernating animals are still under investigation and the role of GDF15 is an open research question. Moreover, it is strongly expressed by cardiac and skeletal muscle fibers during strenuous exercise (Galliera et al., 2014; Gil et al., 2019; Laurens et al., 2020), where it can offer protection against myocyte apoptosis (Heger et al., 2010; Zhang et al., 2017). Recent data suggest that GDF15 may also have neuroprotective effects, as it is able to prevent retinal ganglion cells loss upon retinal nerve crush in mice (Iwata et al., 2021). As a whole, these data support the idea that GDF15 may be an integral component of a program of cell/organismal passive protection that can be concealed within the concept of dormancy program (Figure 2).

Conclusions

GDF15 is emerging not only as an important stress response protein involved in many fundamental biological processes, but also as a key player in the aging process. In fact, it results one of the most up-regulated proteins in old age (Tanaka et al., 2018; Conte et al., 2019; Lehallier et al. 2019), a biomarker of many ARDs and a factor associated with decreased survival at old age (Wiklund et al., 2010; Fujita et al., 2016; Conte et al., 2019; 2020a; 2021). The multiple processes it is involved in, and the many stimuli and transcription factors impinging upon its activation led us to speculate that it may be considered at the centre of a bow tie architecture, a very robust and flexible way to organize complex biological phenomena. As discussed all along the text and as illustrated in Fig. 1, GDF15 expression can be activated by a number of TFs triggered by different stresses and signals. The balancing of the activities of these TFs (including regulatory ones) constitutes the knot of the bow tie, where processing and elaboration of the signals occur, resulting in different levels of GDF15 production, in turn having many different biological effects. It is possible that another layer of signal elaboration does exist, as GDF15 must be cleaved in its mature form, secreted and then bound to its receptor, and so far, little is known on the factors involved in this processing, and on the possible age-related modifications they can undergo. However, there is no doubt that it has an important, beneficial role for human biology, as indicated by many studies and evolutionary considerations. When coming to its role in the aging process, however, things get complicated, and the association with many ARDs and mortality led to the idea that it may have detrimental roles in advanced age and in different pathologies. It is more than likely that the age-associated rise in GDF15 concentrations is an adaptive reaction to increasing stresses that however can turn to be detrimental in itself if not correctly regulated/turned off (Conte et al., 2019) (Figure 3), according to the antagonistic pleiotropy theory of aging. In particular, stresses can be more frequent and unresolved

(due to impairment of the repair or homeostatic systems), leading to a chronic, progressive elevation of GDF15 levels. Accordingly, the association of GDF15 with pathologies is observed in conditions of chronically elevated levels of GDF15. In agreement with the idea of the *continuum* between aging and ARDs (Franceschi et al., 2018), the same stresses that can cause chronic elevation of GDF15 may be the same that in the end lead to aging and ARDs. Therefore, the apparent involvement of GDF15 in both processes may be possibly due to unwanted effects on metabolism and immune defences (*e.g.* cachexia, immune depression). Finally, the possibility also exists that GDF15 effects remain always beneficial, but the intensity of the stresses is so high that GDF15 fails in restoring the homeostasis and the net result is the onset of pathology, so that the association between the level of GDF15 and the pathology could be indirect or even spurious.

As a whole, the role of GDF15 is not totally clarified, despite the huge efforts made so far. We surmise that, in an ecological perspective, it may be considered as an important mediator of defence processes where, according to the life history theory, catabolic reactions are prevailing over anabolic ones. These reactions are used during periods of resource paucity and are collectively indicated as dormancy programs (Wang et al., 2019). As discussed all along the text, GDF15 seems to have all the characteristics for being a factor involved in these dormancy programs, including food shortage, as well as protection from inflammatory injury and acute physical exercise. For a correct functioning, the organism needs a tight balancing between catabolic (dormancy) and anabolic defence reactions, and then the association of GDF15 with aging and ARDs could be also due to an impairment of such balancing, with an excessive tilting toward dormancy possibly induced by chronic inflammation (inflammaging).

Notwithstanding the data on the beneficial role of GDF15, the association with many ARDs have led many researchers to consider GDF15 as a potential therapeutic target to reduce ARDs. Pharmaceutical approaches to modulate the activity of GDF15 have been tested in several animal disease models. Just as an example, anti-GDF15 monoclonal antibodies have been successfully tested to protect from cancer-induced cachexia, as mentioned (Suriben et al., 2020). However, it must be considered that in some cases an increase in GDF15 production/activity may be desirable, as demonstrated by the case of type 2 diabetes, where GDF15 levels are increased upon metformin treatment, suggesting that the beneficial role of this drug is mediated by GDF15. As a whole, GDF15 holds promises as a target for both modulatory and activatory drugs, suggesting once again its important, yet underestimated, role in human aging and ARDs.

BOX 1 Focus: GDF15 in muscle wasting, sarcopenia and cachexia

Muscle wasting is a phenomenon associated with many pathophysiological conditions, including aging and cancer. Old subjects and cancer patients may suffer from sarcopenia and cachexia, respectively, two conditions characterized by muscle atrophy and weakness. Both sarcopenia and cachexia are multifactorial syndromes in which a fundamental role is played by inflammation, oxidative stress and mitochondrial dysfunction (Sartori et al., 2021). However, despite these two syndromes have several aspects in common, it is not yet clear whether the molecular mechanisms leading to muscle wasting are exactly the same. In other words, whether the molecular mechanisms of sarcopenia, associated to aging, and those of cachexia, associated to cancer, have a common denominator.

GDF15 is elevated in conditions of muscle wasting and weakness, and it is suggested to contribute to loss of muscle mass and function (Bloch et al., 2013; Patel et al., 2016). We and others showed that GDF15 is associated with decreased muscle performance and increased inflammation, and it is elevated in patients with lower limb mobility impairment (Conte, et al., 2019; Conte et al., 2020a; Semba et al., 2020; Alcazar et al., 2021). GDF15 is also proposed as a biomarker for age-related sarcopenia in aging humans and mice (Kim et al., 2020; Herpich et al., 2020). Kim et al. (2020) analysed the levels of GDF15 in muscle and serum of both mice and humans across a wide age range, and they found that GDF15 positively correlates with deterioration of skeletal muscle quality. Moreover, only in old mice, endurance exercise suppressed the age-related increase of GDF15 (Kim et al., 2020), proposing exercise as a treatment to decrease GDF15 and possibly counteract sarcopenia. Despite the growing evidence indicating the association between GDF15 and sarcopenia, the exact role of GDF15 in the decline of muscle mass and function is still unclear. To this regard, there is also a study suggesting that GDF15 may not predict the risk for sarcopenia, at least in older Asian adults. In this study, authors observed that serum levels of GDF15 in sarcopenic subjects are similar to that found in control non-sarcopenic group (Nga et al., 2021). However, at present, this is the only study indicating the absence of association between sarcopenia and GDF15. Conversely, there are several studies suggesting a possible action of GDF15 on skeletal muscle. For example, an *in vitro* study indicated that the GDF15 treatment in C2C12 myotubes leads to an increased expression of two atrophy-related genes, MuRF-1 and Atrogin, and a reduction in the expression of muscle specific microRNAs (Bloch et al., 2015). In agreement, GDF15 was remarkably higher in skeletal muscle tissue and at serum levels in a mouse model characterized by an accelerated skeletal muscle aging (Ito et al., 2018).

As above mentioned, GDF15 is considered a critical mediator of disease-related anorexia-cachexia, through the GDF15-mediated activation of hindbrain GFRAL-RET receptors. Elevated

circulating levels of GDF15 are present in patients with cancer and cachexia wasting syndrome and positively correlate with reduced survival in these patients (Johnen et al., 2007; Tsai et al., 2014; Lerner et al., 2015; Suriben et al., 2020; Ahmed et al., 2021). The molecular mechanisms mediating cachexia remain poorly understood, however, Allan and co-workers recently demonstrated that an antagonist monoclonal antibody of GFRAL reverses cancer cachexia in mice by preventing the GDF15-driven interaction of RET with GFRAL and thus inhibiting the RET signalling (Suriben et al., 2020). In particular, the administration of this GFRAL antagonist inhibited tumour-related weight loss in mouse models carrying GDF15-expressing tumours. Moreover, mice with tumour that had lost significant body weight, after the administration of the GFRAL antagonist, regained almost the entire amount of lost body weight, also without relevant changes in the food intake (Suriben et al., 2020), suggesting that the inhibition of GDF15-GFRAL-RET signalling may be an approach to treating cancer cachexia.

Although these studies suggest an association between GDF15 and muscle dysfunction, it is not yet clear whether the age-related skeletal muscle decline is due to a direct action of GDF15 on skeletal muscle causing sarcopenia, or whether the increase of GDF15 associated to aging causes anorexia and body weight loss, and thus indirectly leads to the decline of muscle mass and function. However, all the data described indicate that when GDF15 is produced in excess, as during aging or cancer, it can have an acute effect on appetite. In this regard, it is not clear whether GDF15 plays a role in the decrease in appetite also in the elderly, in other words whether GDF15 is involved in the phenomenon known as "anorexia of aging". Many old people suffer from this phenomenon, a condition that has serious consequences for health. In particular, anorexic elderly have an increased risk of muscle weakness, sarcopenia, osteoporosis, and hip fracture (Martone et al., 2013; Tsutsumimoto et al., 2020). Therefore, it seems likely that GDF15 plays a role in the anorexia of aging with a mechanism similar to that of cachexia, although no data are yet available to support this hypothesis. However, centenarians, who are characterized by poor appetite and low BMI, have circulating GDF15 levels similar to those of cachectic patients (Conte et al., 2019; Lerner et al., 2015; Lerner et al 2016; Vaes et al., 2020). In particular, in centenarians we found an average level of GDF15 of 3,000 pg/ml, with a range from 590 to 7,600 pg/ml, while in cachectic patients several studies showed an average level of about 2,000-5,000 pg/ml, up to even 10,000 pg/ml (Conte et al., 2019; Johnen et al., 2007; Lerner et al., 2015; Lerner et al 2016; Vaes et al., 2020). Therefore, it is possible that chronically elevated levels of GDF15 as those observed in elderly people can lead to a progressive decrease in BMI and muscle mass similar to those observed in cachectic patients, even though with a less dramatic speed, and possibly through multiple mechanisms that include not only central anorexia but also peripheral modulation of lipolysis and apoptosis.

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Declaration of Competing Interest:

The authors declare no conflict of interest.

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Figure legend

Figure 1. GDF15 as knot of a bow tie module. Due to its great number of triggers and downstream effects, GDF15 may be considered as the pivotal knot of a bow tie-structured module. In this kind of modules, the core (in this case GDF15 and its regulatory machinery) accepts a wide range of age-related input (fan in: stress stimuli that activate transcription factors) and then produces a wide variety of outputs (fan out: downstream detrimental or beneficial effects induced by GDF15). This architecture can also be equipped with a regulatory feedback loop, capable of modulating the knot.

Figure 2. Hypothetical involvement of GDF15 in the dormancy program. GDF15 is proposed as a mediator of dormancy responses, considered as one arm of the maintenance mechanisms, the other being active defense, according to the life history theory. Defence mechanisms can be themselves a trigger for dormancy, and dormancy mechanisms can modulate defence response in order not to harm the organism.

Figure 3. Schematic hypothesis of GDF15 changes during lifetime. GDF15 is usually expressed at low levels in young age, with transient peaks corresponding to acute stress that GDF15 contribute to solve. As the stress response machinery (such as ISR, UPR) gets progressively impaired with age, GDF15 rises become likely more intense and prolonged, leading to a situation of chronic elevation, associated with ARDs, comorbidity and mortality. According to the steepness of this rise, ARDs will appear early in life or much later.

Figure 1

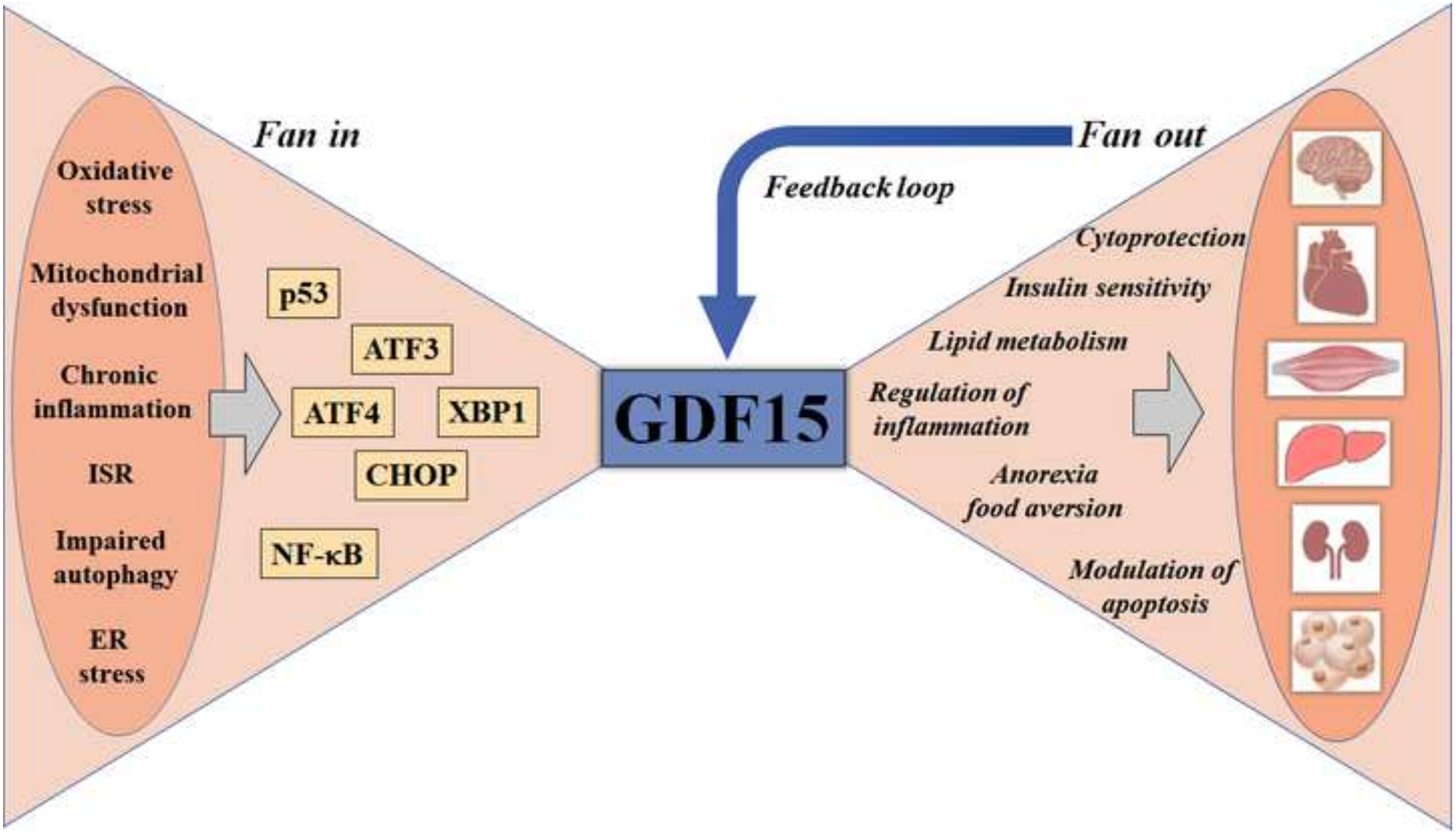


Figure 2

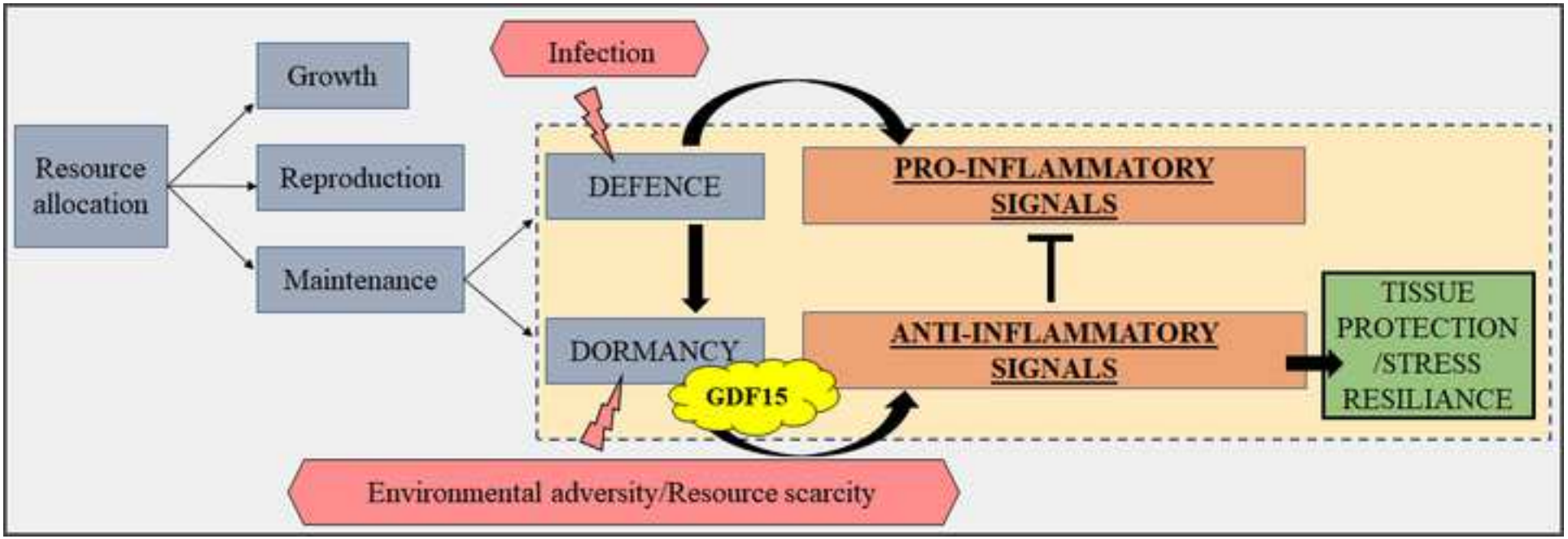
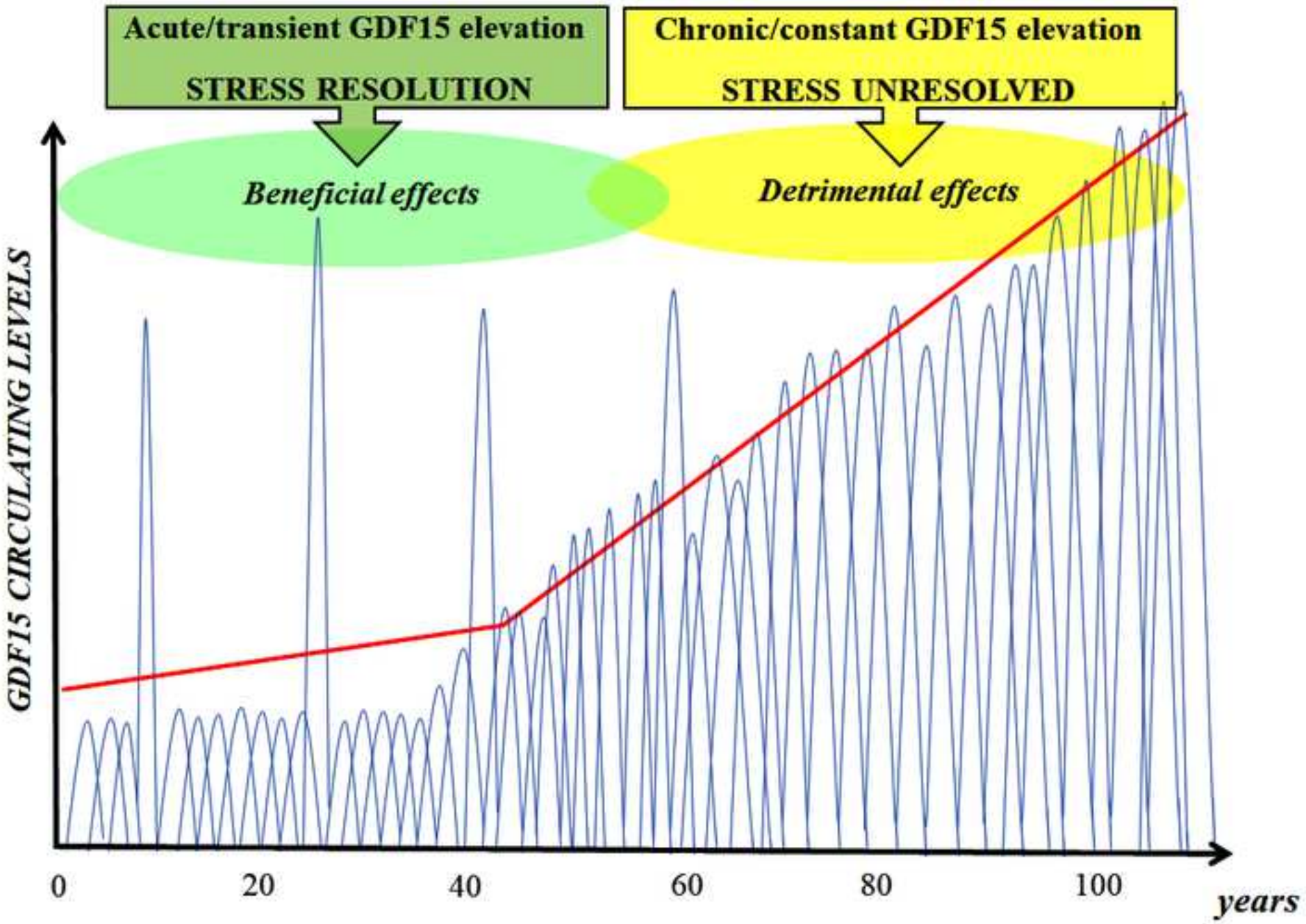


Figure 3



GDF15, an emerging key player in human aging

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