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Review

REGγ, a proteasome activator and beyond?

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Abstract. REGγ, a member of the 11S proteasome activators, has been shown to bind and activate the 20S proteasome to promote proteasome-dependent degradation of important regulatory proteins, such as SRC-3 and cyclin-dependent kinase inhibitors p21, p16, and p19, in a ubiquitin- and ATP-independent manner. Furthermore, REGγ has been shown to facilitate the turnover of tumor suppressor p53 by promoting MDM2-mediated p53 ubiquitination. The discovery that REGγ regulates cell-cycle regulators is consistent with previous studies where REGγ-deficient mice have shown retardation in body growth, decreased cell proliferation and increased apoptosis, indicating a potential role of REGγ in cancer development. Additionally, REGγ's ability to promote viral protein degradation suggests its involvement in viral pathogenesis. This review presents an overview of the function of REGγ, a summary of the current literature, and insight into the possible biological function of REGγ relating to cancer, viral pathogenesis, and other diseases.

Keywords. Proteasome activator, REGγ, ubiquitin- and ATP-independent protein degradation, cancer, viral pathogenesis, SRC-3, p21, p53.

Introduction

REGγ (also known as PA28γ , 11Sγ, or PSME3) was first identified as the Ki antigen, a nuclear protein targeted by autoantibodies found in sera of patients with systemic lupus erythematosus [1]. The link between the Ki antigen and the autoimmune syndrome is yet to be elucidated, but the Ki antigen was later revealed to be a member of the REG family of proteasomal activators, including REGα and REGβ [2, 3]. REG is a unique family of proteasomal activators that has the ability to stimulate the proteolytic activity of the 20S core proteasome independent of ubiquitination and ATP [2, 3]. While REGα and REGβ are shown to function with the 20S core as an immunoproteasome to process antigens for MHC class I ligands presentation [4–6], the biological functions of REGγ have not been fully characterized. REGγ is implied to have a regulatory role in cell cycle transition and cell proliferation, as REGγ-deficient mice have significantly reduced body size and REGγ-deficient embryonic fibroblasts have impeded entry from G to S phase in the cell cycle [7, 8].

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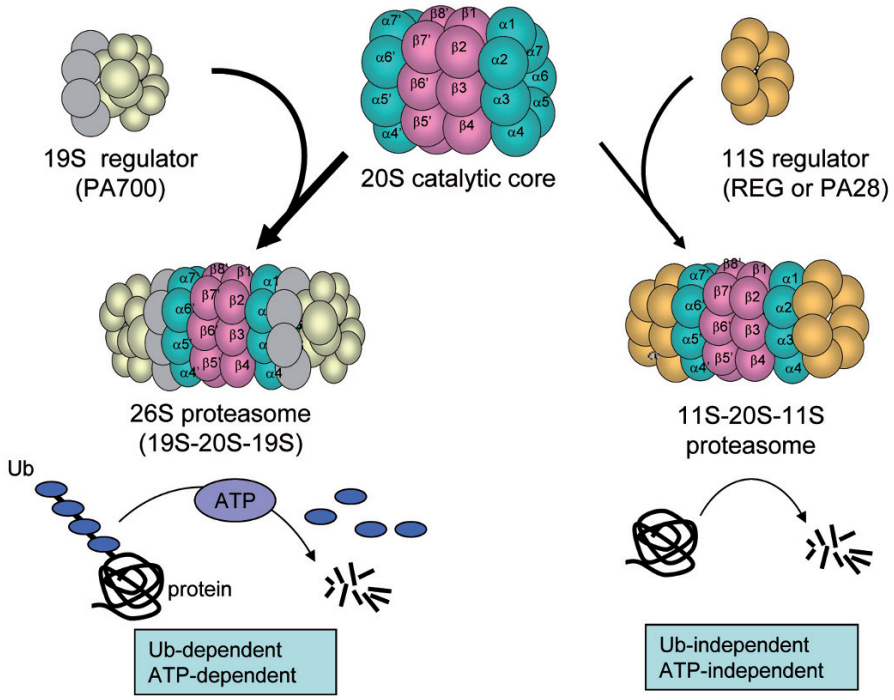

Figure 1. Proteasome activators and ubiquitin-dependent and -independent degradation. The 20S core is a barrel-shaped cylinder composed of two outer α-rings and two inner β-rings. The α-rings modulate the entrance of protein substrates, whereas the β-rings execute the action of proteolysis. There are at least two classes of proteasome activators in eukaryotic cells, which bind to the 20S proteasome and promote its catalytic function. The PA700 (or 19S) activator binds to proteasome in an ATP-dependent manner to form the 26S proteasome, which is primarily responsible for the degradation of ubiquitinated proteins. A second class of activators is ATP-independent and composed of a family of proteins known as REG (or 11S, PA28) which facilitates ubiquitin-independent protein degradation.

Recently, a number of advances have been made, suggesting the versatile function and role of REGγ in cells and human diseases. This review will cover the role of REGγ as a proteasomal activator, its potential roles in cancer, viral pathogenesis and other diseases.

REGγ and the Proteasome System

The proteasome system is one of the most important protein degradation systems in eukaryotes and has the ability to regulate cellular processes such as the cell cycle, transcription, cell signaling, cell death, and immune responses [9–11]. An enzymatically active proteasome is composed of a cylindrical 20S core and three proteasomal activators, PA700, PA28 and PA200 (The function of PA200 is less characterized and will not be discussed in this review). The 20S core is a stack of four heptameric rings, with two outer α rings and two inner β rings. The β rings contain active sites that have peptidylglutamyl-peptide hydrolase (PGPH), trypsin-like and chymotrypsin-like activities (β1, β2, β5, respectively), facing inward of the 20S [5, 12]. When protein substrates pass into the 20S lumen composed of the two β rings, the proteins are degraded into peptides. However, without proteasomal activators, protein substrates are barred from entering into the 20S, thus making the 20S latent.

Tertiary structural analysis shows that in the absence of proteasomal activators, the α rings of the 20S are normally closed, occluded by peptides from the amino termini of the α ring subunits [13]. However, when proteasomal activators bind to the α rings, the occlusion of the amino termini is removed and 13Å pores become available for protein substrates to enter into the 20S proteasome [12].

As illustrated in Figure 1, at least two classes of proteasome activators have been identified to bind to the 20S proteasome and enhance its catalytic function [14]. The 19S proteasomal activator (or PA700) is a well-studied proteasomal activator that binds to the 20S, forming the 26S proteasome, an ATP- and ubiquitin-dependent protease complex [15]. Most cellular proteins are degraded through the 26S proteasome after ubiquitination, a way for 26S to recognize proteins that need to be degraded. Six different ATPase subunits are found in the 19S proteasomal activator, and most likely produce ATP to unfold and deubiquitinate protein substrates before transferring them into the lumen of the 20S [16].

The alternative proteasomal activator, REG (also known as 11S proteasome), however, does not contain any ATPase activity and can mediate proteasomal degradation independent of ATP and ubiquitin. Among the three REG family members, REGα and REGβ share approximately 50 % amino acid identity, while REGγ shares only about 25 % amino acid identity with REGα and REGβ [17]. Although REGα/β is primarily located in the cytosol and together form heteroheptamer caps, REGγ is mainly found in the nucleus and forms homoheptamer caps. REGα/β is only found in the vertebrates while REGγ

is highly conserved between vertebrates and invertebrates [18]. REGα/β can be induced by interferon (IFN)-γ and play an important role in MHC class I antigen presentation [19, 20]. REGα/β has also been shown to be able to form a hybrid proteasome (11S-20S-19S) with 20S and 19S proteasome, which enhances the proteolytic efficiency of antigen processing in an ATP-dependent manner [21]. REGγ, on the other hand, is not responsive to IFNγ and does not appear to be heavily involved in the immune system. Mice deficient in REGγ, for example, do not show significant abnormalities in their immune system [8].

Biochemical Properties of REGγ

The presence of the REG proteasome activators, including α, β, and γ homologs, is shown to increase the proteasome activity and alter the cleavage pattern and substrate-specificity of the proteasome [22]. The overall secondary structure of REGγ, similar to that of REGα/β, is composed of four 33-45 residues long α-helices with one linker sequence between helix 2 and 3 called the "activation loop" [17]. A point mutation (N151Y) within the activation loop results in the inability of REGγ to activate the proteasome, although it can still bind tightly with the proteasome, demonstrating a critical role of the activation loop in proteasome activation [23–25]. Unlike REGα and REGβ, which activate proteasome-mediated cleavage after hydrophobic, acidic or basic amino acid residues and enhance all three proteasome activities, REGγ only enhances the cleavage after basic amino acid residues and selectively activates the trypsin-like catalytic subunit of the 20S proteasome, but suppresses the chymotrypsin-like and PGPH catalytic subunits of the 20S proteasome *in vitro* [26, 27].

Which region(s) make the REG homologs unique remains an intriguing question. The divergent regions between the three homologs of REG in the general secondary structure include the N-terminal and C-terminal sequences and the amino acids flanking the activation loop. Chimera studies show that the N-terminus region and the activation loop flanking sequences participate in REG oligomerization, whereas the C-terminus region, located on the surface of the REG homologs, is important for the stability of heptamer and proteasome binding [28]. None of these divergent regions were found to contribute to selective REGγ activation. However, a mutant form of REGγ (K188E/D) displayed changes to its activation properties and had the ability to activate all three proteasome activities [27]. In addition, the K188E/D mutant was observed to reduce the stability of the REGγ heptamer [27]. Interestingly, during protein purification, recombinant REGγ gains the ability to activate all three proteasome activities after ammonium sulfate precipitation [29]. These treated REGγ heptamers were also less stabilized. This implies an inverse correlation between the stability of the REGγ heptamer and REGγ's ability to expand its activation properties. Instead of failing to activate the chymotrypsin-like and PGPH active sites, REGγ may be inhibiting these active sites by changing the conformation of the proteasome. Whether this selective activation of proteasome catalytic activity holds physiologically significance is still unknown.

Previously it was thought that REGγ only degrades short peptides [2]. Recent evidence demonstrates that intact intracellular proteins can also be targets of REGγ [23, 24, 30]. However, how intact proteins are unfolded and translocated into the 20S proteasom in an ATP-independent manner is poorly understood. The 20S proteasome has been shown to possess endoproteolytic activities [31]. It is thus speculated that REGγ promotes proteasomal cleavage of the internal peptide bonds of unstructured or naturally unfolded proteins for entry into the 20S proteasome, a process known not to require ATP [32]. In addition, physical interaction between REGγ and its substrate protein may function as a Brownian ratchet to prevent the backward movement of the substrate molecule within the 20S proteasomal channel, allowing for its efficient degradation [33, 34].

Biological Functions of REGγ

A casual relationship between REGγ and cell growth regulation had been suggested in an earlier study [35]; the exact biological function of REGγ, however, remained unclear until the generation of REGγ-deficient mice and the subsequent identification of REGγ target proteins. REGγ knockout mice were generated by two independent groups and both reported that loss of REGγ expression resulted in decreased body size and defects in cell-specific mitosis, suggesting a role of REGγ in the regulation of cell growth and proliferation [7, 8]. Furthermore, mouse embryonic fibroblasts (MEFs) lacking REGγ displayed slower cell cycle transition from G1 to S phase. A similar finding was observed in Drosophila cells depleted of REGγ, suggesting a conserved function of REGγ in cell cycle regulation [36]. In addition, REGγ has been implicated to be involved in the regulation of apoptosis. REGγ-deficient MEFs had markedly increased levels of apoptosis compared to the wild-type counterparts [8]. Interestingly, several REGγ binding partners related to the initiation or regulation of apoptosis have been identified, including

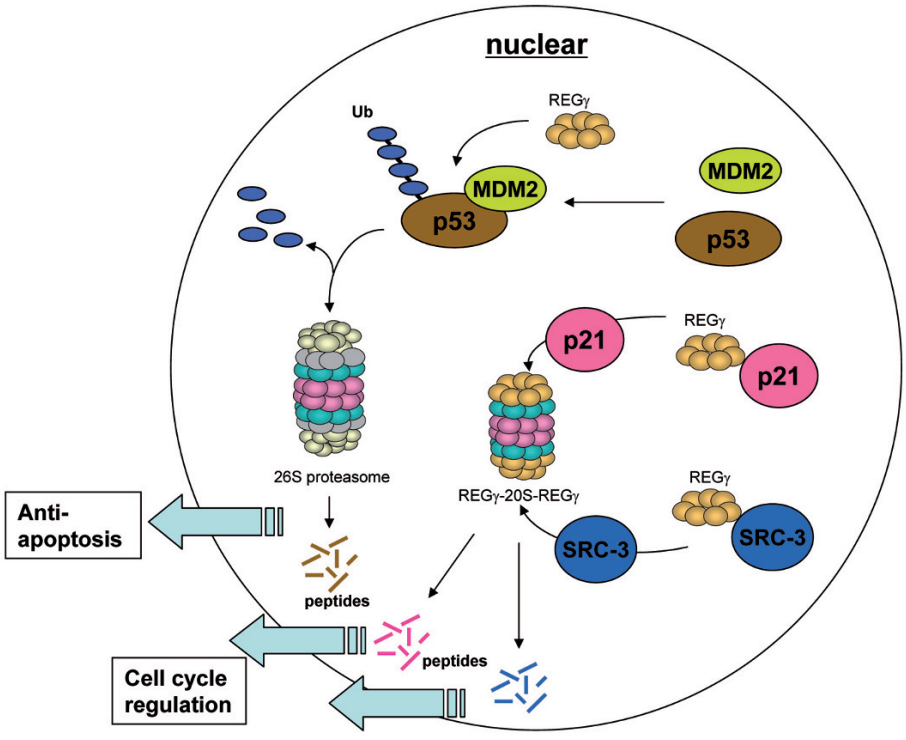

Figure 2. Intracellular substrates of REGγ and their roles in cell growth and apoptosis regulation. REGγ binds with and facilitates the degradation of p21 and SRC-3 by the 20S proteasome in an ATP- and ubiquitin-independent manner. REGγ also assists the turnover of p53 as a co-activator to promote MDM2-mediated p53 ubiquitination to promote MDM2-mediated ubiquitination and subsequent degradation of p53 via the 26S proteasome. Aberrant degradation of these proteins is linked to inappropriate cell cycle progression, apoptosis, and ultimate cell growth abnormality. MDM2, murine double minute-2; Ub, ubiquitin; SRC-3, steroid receptor coactiator-3

caspase-7, MEKK3, FLASH, Daxx, RanBPM, and PIAS [14, 37, 38].

More recently, the identification of the cellular targets of REGγ has reinforced its important functions in the regulation of cell proliferation and apoptosis. REGγ was reported to facilitate the degradation of the steroid receptor coactivator-3 (SRC-3/AIB1) and cyclin-dependent kinase inhibitor p21 by the 20S proteasome in an ATP- and ubiquitin-independent manner [23, 24, 30]. SRC-3 is considered as an oncogene often found amplified in breast cancer and plays an important role in cell growth [39]. The cell cycle inhibitor p21 is an important regulator which prevents the G1/S transition [40].

In addition, proteasome-independent functions of REGγ have also been reported recently. For example, REGγ has been found to promote the degradation of p53 by acting as a co-activator to promote MDM2-mediated p53 ubiquitination [41]. The tumor suppressor protein p53 is an important transcription factor that plays a critical role in cell cycle arrest and apoptosis by activating several target genes including bax, p21 and gadd45 [42]. Decreased levels of p53 allow cells to pass through the G1/S checkpoint during cell cycle progression. Other studies have shown that REGγ may play a key role in chromosomal stability during mitosis [43] and in the organization of nuclear speckles [44]. Furthermore, there was a report implicating a potential function of REGγ in regulating the activity of G protein-coupled receptors through binding with the C-terminus of thromboxane A_2 receptor [45].

Together, the available evidence strongly supports critical physiological roles of REGγ in the regulation of several fundamental cellular processes. A summary of the intracellular substrates and biological functions of REGγ related to cell growth regulation and apoptosis is illustrated in Figure 2. Future studies are required to identify the additional intracellular targets of REGγ contributing to its pro-proliferative and anti-apoptotic actions.

Regulation of REGγ

Like the majority of intracellular proteins, REGγ can be regulated at different levels, including post-translational modification. However, the regulatory mechanisms are largely undefined. Unlike REGα/β which is induced by IFNγ and various infections, REGγ expression is not affected. Nonetheless, it was shown that IFNγ treatment results in a complete loss of REGγ protein in human colon cancer cells without affecting its mRNA levels [46]. In addition, lymphocytic choriomeningitis virus infection in mice caused a marked reduction in REGγ protein expression in the liver [47].

Recent studies on post-translational modification of REGγ revealed an important regulatory mechanism for its activities. An early report showed that REG can

be phosphorylated *in vitro* [48]. A recent study has further identified the upstream kinase responsible for REGγ phosphorylation. It was found that MEKK3, a mitogen-activated protein kinase (MAPK) kinase kinase that activates JNK and p38 MAPKs, directly binds with and phosphorylates REGγ [38]. Another MAPK kinase kinase, B-RAF, which activates ERK1/2 MAPK, has also been shown to physically interact with REGγ and phosphorylate REGγ *in vitro* [38, 49]. Although the functional significance of REGγ phosphorylation remains to be determined, it was shown that MEKK3 increases the expression level of REGγ in the cell [38]. The possibility of REGγ possessing other functions after phosphorylation, however, is not excluded. For instance, phosphorylation may also be involved in substrate specificity by the REGγ-proteasome. Phosphorylation of REGγ provides one of the regulatory mechanisms through which extracellular signaling can activate the REGγ-dependent proteasome.

It is noted that REGγ is mostly restricted to the nucleus while MEKK3 is in the cytoplasm. Thus the interaction between REGγ and MEKK3 can only occur during the mitotic phase of the cell cycle in which the nuclear envelope is broken down and REGγ is redistributed throughout the cell and has a chance to interact with MEKK3 [38]. This REGγ redistribution and interaction with MEKK3 may be significant in the context of mitosis progression and exit [38]. Interestingly, it was reported that REGγ undergoes an intranuclear redistribution at mitosis [43]. During telophase, REGγ was found to be localized on the chromosomes [43]. Overexpression of REGγ has been shown to weaken spindle damage-induced mitotic arrest and allow cells to escape, leading to a premature exit of mitosis [43]. The underlying mechanism of REGγ subcellular redistribution is unclear; deletion studies, however, show that the N-terminal putative nuclear localization signal of REGγ may play a critical role in its nuclear localization and binding with chromosomes during telophase [43]. It is also speculated that post-translational modification of REGγ may be involved in its redistribution in the nucleus. For example, the function of monoubiquitination and sumoylation in the regulation of subcellular localization has been well-documented [50].

Moreover, REGγ has been identified as a caspase-7 binding protein [37]. Subsequent studies demonstrate direct cleavage of REGγ by caspase-3 and -7, both *in vitro* and *in vivo* [37]. However, the functional significance of the cleavage of REGγ during apoptosis has not yet been elucidated, as overexpression of a non-cleavable form of REGγ resulted in no observable effect on apoptosis induced by multiple stimuli [37].

REGγ and Cancer

REGγ has been reported to be highly expressed in thyroid cancer [51] and in colorectal cancer serum [52], and was proposed to be a potential cancer marker [52]. Immunohistochemical staining revealed elevated expression of REGγ expression in both colonic adenoma and invasive cancer, suggesting that REGγ may play an important role during all phases of carcinogenesis [52].

The first mammalian target of REGγ was discovered by Li et al. in an effort to analyze the homeostasis of nuclear receptor coactivators [24]. REGγ has thus been linked to cancer by its ability to specifically degrade SRC-3, an oncogenic protein which is often overexpressed in hormone-sensitive tumors such as breast, prostate and ovarian cancer, as well as in hormone-independent cancers such as pancreatic and gastric cancers [39, 53–56]. SRC-3 is a member of the SRC family of transcriptional coactivators that associates not only with nuclear receptors such as estrogen receptor, progesterone receptor, and thyroid receptor, but also with transcription factors such as activator protein-1, nuclear factor κB, signal transducer and activator of transcription and E2F1 [57]. Through these interactions, overexpressed SRC-3 is able to affect many signaling pathways involved in cell proliferation, survival and migration. The ability of REGγ to degrade other oncogenic proteins, such as hepatitis C virus (HCV) core protein [58] and pituitary tumor-transforming 1 (PTTG1) [56], provides additional examples for its role in cancer development.

The cell cycle inhibitor p21 has also been identified to be a REGγ-proteasome target [23, 30]. It was demonstrated that the ubiquitin-independent REGγ-proteasome pathway is responsible for the degradation of p21 *in vivo* and *in vitro*. As a broad-specificity inhibitor of cyclin-dependent kinases and a regulator of apoptosis, p21 plays an essential role in regulating cell cycle progression and cell death [40]. Defects or downregulation of p21 have been linked to the development of various cancers and contribution to tumour progression [40].

Interestingly, in addition to p21, another two cyclin-dependent kinase inhibitors, p16 and p14 (p19 in mouse), have also been identified to be targets of REGγ [30]. Both p16 and p14 are tumor suppressors and are encoded by the *Ink4a/Arf* locus which is frequently deleted in human cancers [59]. Mice lacking p16 and p19, in combination or individually, are all prone to spontaneous tumor formation and are sensitive to carcinogens [59].

The tumor suppressor protein p53 is well-documented to have the ability to stimulate apoptosis and cell cycle

arrest in the event of DNA damage and strongly suppress oncogenesis [42]. MDM2, the negative regulator of p53, is an E3 ligase that can bind to p53 and promote degradation of p53 through direct ubiquitination [42] . REGγ has been found to be a cofactor that assists the interaction between p53 and MDM2 by specifically binding to both proteins and promoting the ubiquitin-dependent proteasomal degradation of p53 [41]. Absence of REGγ has been shown to lead to increased p53 protein levels in several cancer cell lines. Elimination of REGγ can abrogate the degradation of p53 mediated by MDM2 and induce increased levels of p21, and as a result, prevent cell cycle progression and enhance apoptosis [41].

Taken together, REGγ has been shown to be involved in the degradation of oncogenic proteins such as SRC-3, HCV core protein, and PTTG1, while it also targets tumor suppressors, including p21, p16, p19, and p53, for degradation. The overall pathological outcome of REGγ-proteasomal activity is complicated by the fact that it may play either tumor-promoting or tumor-suppressive roles. Likewise, the 26S proteasome is required for the degradation of numerous oncogenic proteins and tumor suppressors. The distinct function of REGγ in cancer development is likely determined by multiple factors, including cell specificity, which is best illustrated by the proteasome inhibitor, Bortezomib, for the successful treatment of multiple myeloma [60]. Despite the myriad of positive and negative context-specific functions influenced by different targets of REGγ, it is evident that REGγ has a dynamic and dominant role in regulating cell growth and apoptosis. Future studies to generate transgenic animal models with overexpression of REGγ will undoubtedly provide further insights into the contribution of the REGγ in cancer development.

REGγ and Viral Pathogenesis

Increasing numbers of studies have suggested that viruses can evolve different strategies to utilize the host ubiquitin-proteasome system to promote viral infection [61]. Proteasome-mediated proteolysis has been reported to play a critical role in various steps in the viral lifecycle by increasing degradation of intracellular proteins and/or excess viral proteins that may perturb the efficiency of virus replication. Recent studies have suggested that degradation of excess viral proteins may be required by some viruses to achieve optimal viral replication and virus-mediated pathogenesis. The interaction between HCV core protein and REGγ is an example of this.

The HCV core protein is responsible for the development of steatosis, insulin resistance and hepatocarcinoma in the liver. It has been shown that REGγ binds directly to and regulates the stability and nuclear retention of the HCV core protein and mediates its ubiquitin-independent, proteasomal degradation [58]. This interaction has proved to be critical for HCV pathogenesis as REGγ knockout not only resulted in accumulation of HCV core protein in the nucleus, but also abrogation of liver pathology induced by HCV core protein [62]. It was further demonstrated that REGγ plays a critical role in HCV core protein-induced insulin resistance and hepatocarcinoma [63]. These findings suggest that the products of the REGγ-dependent degradation of HCV core protein may be a key in the development of HCV pathological symptoms. In addition, REGγ may also be involved in viral pathogenesis in a different perspective, as viral proteins may manipulate the REGγ-proteasome complex to degrade cellular proteins. This area is currently unexplored, providing an exciting opportunity to examine virus-mediated regulation of host proteins.

As many viruses utilize cell cycle regulation and apoptosis manipulation as strategies to control their infection cycles, the implied role of REGγ in promoting cell cycle progression and inhibiting apoptosis provides a novel avenue for further investigation. Our recent studies suggest an important role of REGγ in coxsackievirus replication. Coxsackievirus is an important human pathogen associated with myocarditis and subsequently dilated cardiomyopathy [64]. We have shown that viral protein synthesis and viral replication are significantly increased in HEK293 REGγ-overexpressing cells. Knockdown of REGγ sensitizes cells to coxsackievirus-induced apoptosis and leads to a reduction of viral replication (unpublished data). The regulation of REGγ during coxsackievirus infection and the mechanisms through which REGγ may regulate viral infection are currently under investigation.

REGγ and Other Diseases

Neurodegenerative diseases are commonly characterized by deposits of aggregated toxic proteins in the cytosol and the nuclei of neurons [65]. These aggregated proteins are often polyubiquitinated, implying that the function of the ubiquitin-proteasome system is impaired or inhibited. Indeed, reduced proteasomal activity has been associated with several neurodegenerative diseases such as Alzheimer's disease, Huntington's disease and Parkinson's disease [65].

Huntington's disease (HD) is caused by the expansion of a CAG repeat in the huntingtin gene, which results

in the expression of expanded polyglutamine huntingtin protein that is neurotoxic. In the striatal neurons of an HD model, it was found that overexpression of REGγ significantly increases cell viability following proteasome inhibition and quinolinic acid excitotoxic stimulation [66]. The neuroprotective role of REGγ is significant as it has the potential for protecting the neurons from cell damage and death associated with proteasomal dysfunction and excitotoxicity, which are often observed in HD. Interestingly, brain also expresses the highest level of REGγ as compared to other organs [14]. The pathological significance of REGγ in HD remains debatable. Based on its biochemical properties in the suppression of chymotrypsin-like proteasome activities [27], REGγ was proposed to contribute to proteasomal impairment in polyglutamine disease by inhibiting the cleavage between Gln-Gln bonds, for which chymotrysin-like activities are mainly responsible. But transgenic animal studies seem not to support this assumption. It was shown that knockout of REGγ in R6/2 HD mice does not attenuate HD pathology in the mouse brain [67]. Moreover, the proteasomal activity was unchanged in the brain of R6/2 HD mice as compared to wild-type counterparts [67]. A recent study from the same research groups challenged the previous view that the proteasome only cleaves the Gln-Gln bonds between the first two N-terminal glutamine [68]. They reported that the proteasome is capable of cleaving every Gln-Gln bonds within the polyglutamine tract and overexpression of REGγ mutant (K188E) promotes such degradation [69]. This study raises the possibility of proteasome-targeted therapeutic avenues for HD. Future investigation is required to elucidate the pathological contribution of REGγ in neurodegenerative diseases and the precise molecular mechanisms involved.

Proteasomal dysfunction has also been implicated recently in heart disease [70–75]. Cardiac hypertrophy is a compensatory response to a variety of physiological or pathological stimuli. However, sustained hypertrophic responses may eventually lead to heart failure, arrhythmia, and sudden death [76]. Down regulation of proteasomal activity has been shown to stop and even reverse hypertrophy of the heart [72–74]. Work in our laboratory found that patients with end-stage heart failure have increased levels of REGγ as compared to those patients who passed away without indication of cardiac complications (unpublished data). In addition, using a rat model of myocardial infarction, we found that the expression levels of REGγ are significantly increased in ischemic hearts, but only in the infarcted region, not the non-infarcted myocardium (unpublished data). Importantly, the identified substrates of REGγ, including SRC-3, p21, and p53, have been shown to play a role in the pathogenesis of heart diseases [77, 78]. Together, these findings may indicate a key function of REGγ in conjunction with the proteasome in cardiac remodeling.

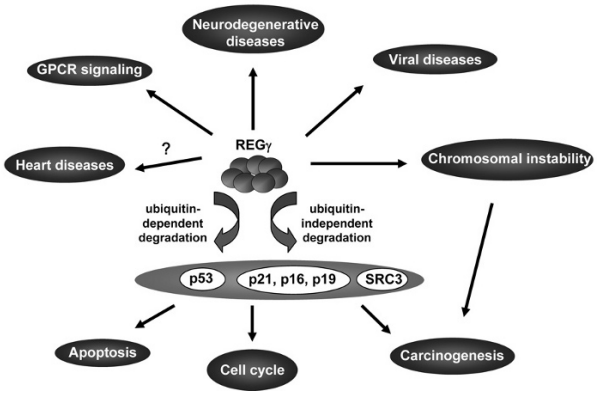

Figure 3. Biological functions of REGγ. The validated and potential biological functions of REGγ are illustrated. In addition to its cell growth related function and therefore a potential role in cancer development, REGγ is also likely to be involved in neurodegenerative diseases, viral diseases, GPCR signaling events, etc., by regulating downstream target proteins directly or indirectly.

Conclusion

REGγ is a unique biological molecule with multiple implicated roles in ubiquitin-, and ATP-independent nuclear protein degradation and cell cycle progression, which may contribute to numerous pathological developments such as cancer, viral diseases and neurodegenerative diseases. As of now, REGγ's biological functions are still unclear, but, undeniably, the functions that have been discovered weave closely into important cellular processes. As presented in this review, REGγ has a great potential to be a therapeutic target in the treatment of cancer, viral pathogenesis, and neurodegenerative diseases. It can act not only as a proteasome activator but also as a cofactor, nuclear speckle organizer, G-protein-coupled receptor activity regulator and chromosome stabilizer during mitosis (Fig. 3). The biological role of REGγ has proven to be important and warrants further investigations.

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