Multidimensional Roles of GRK5 in Molecular Aging

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Considerable evidence now suggests that GRK5 can act as a molecular 'bridging' factor, allowing signaling regulation in pathophysiological settings that can control the connectivity between both the cardiovascular and neurophysiological complications of aging.

G-protein coupled receptor kinase 5 | aging | cardiovascular disease | neurodegeneration | GRK5 interactors

1. Role(s) of GRK5 in Molecular Aging

GRK5 (G protein-coupled receptor kinase 5) activity has been linked with multiple age-associated neoplastic, metabolic, neurodegenerative and cardiovascular ailments [1][2]. At the specific disease level, the expressional regulation and activity of GRK5 has been linked with multiple age-related diseases such as type 2 diabetes mellitus (T2DM) [3], cardiac hypertrophy [4], hypertension [5], Parkinson's disease [6][7], and Alzheimer's pathology in mice and humans [8]. As we age, a progressive dysfunction of multiple receptor signaling systems, across a broad range of tissues, takes place. In this context of age-related receptor system dysfunction, the loss of signaling system sensitivity has been most intensively studies for the insulinotropic signaling cascade. Disruption of the ability to effectively sense, uptake and eventually metabolize glucose has been identified as a pivotal regulator of the rate of aging in nearly every animal model tested [9]. Many of the first genes identified in lower species that control animal longevity were almost exclusively associated with the insulinotropic/insulin-like growth factor system [10]. The glycometabolic system, as well as the somatic sensitivity to insulin receptor functionality, is also strongly controlled through the functional status of adipose tissue in the body, e.g., adiponectin release from white adipose tissue is a potent insulin sensitizing factor [11]. Commensurate with a potentially important role of GRK5 in aging, it has been shown to be strongly expressed in adipose tissues, suggesting that its functionality may impact the glycoregulatory system. [12] demonstrated that GRK5 genomic deletion in murine models resulted in the generation of significant insulin resistance. In addition to this, genetic polymorphisms of GRK5 have been strongly associated with the generation of T2DM [13] and the efficacy profile of anti-diabetic therapeutic agents [14]. Furthermore, previous studies performed in GRK5 knock-out mice (GRK5-KO) reinforced the importance of GRK5 in metabolism as these animals displayed a decreased white adipose tissue mass, a lower weight gain, a decreased expression of adipogenic genes and a reduced adipocyte differentiation when fed a high-fat diet [12][15]. Although human data linking GRK5 to metabolism are sparse, a recent genome-wide association study found a robust association of two

single nucleotide polymorphisms (SNPs) in the GRK5 gene with apoB levels and total LDL-cholesterol, highlighting the role of GRK5 in cholesterol metabolism.

As well as long-term dysfunction of metabolic signaling systems in the aging process, significant disruptions of inflammatory mediator receptor systems are evident. This inflammatory signaling perturbation typically results in the creation of chronic low-grade inflammatory syndrome, recently codified as “inflammaging” [16][17][18]. Inflammaging, as a process, has been proposed to be functionally independent of exogenous systemic infection [19][20]. This chronic inflammatory condition has been linked to potentiated circulatory C-reactive peptide and IL-6 (interleukin 6) concentrations. Protracted exposure to these pro-inflammatory agents predisposes patients to an increased incidence of obesity, premature immunological aging, vascular sclerosis and neurodegenerative phenotypes [21][22]. The inflammaging process itself appears to be closely tied to the mechanisms of whole-somatic aging trajectory control. Hence, inflammaging has been strongly linked to the potentiation of nuclear factor-κB (NF-κB) activity – a process that at the hypothalamic level seems to act as an arbiter of the aging process [1][23].

At a fundamental level NF-κB has been shown possess the ability to regulate the expression of GRK5 [24] – therefore these two systems in fact potentiate each other’s activity in a feed-forward loop, a mode of signaling highly characteristic of the aging process itself. Demonstrating the intersection of GRK5 with the inflammatory aging process, GRK5 has been shown to antagonize TLR4 (Toll-like receptor 4) mediated phosphorylation of the NF-κB p105 protein. This action inhibits inflammatory mediator (lipopolysaccharide) sensitivity in macrophages [25]. Subsequent to the discovery of GRK5 regulation of p105, [26] reported that GRK5 binding to IκBα stabilizes this protein and facilitates the nuclear accumulation of IκBα by masking and thus inhibiting its nuclear export signal sequence. This nuclear accumulation of IκBα can then lead to decreased NF-κB activation in vascular endothelial cells. Research from [27] employing a GRK5 knockout (KO) murine model confirmed that endothelial GRK5 likely stabilizes IκBα in a manner reminiscent to previous studies [26][28]. Using this model, [24] further demonstrated an NF-κB inhibitory action of GRK5 in cardiac muscle cells.

Taken together, GRK5 is clearly a vital component in both energy metabolism and chronic inflammation paradigms. It is interesting to note that both of these systems are known to strongly control molecular aging pathologies implicated in many different human disorders and consequently in inflammatory pathways [29]. These findings therefore make GRK5 a potentially important therapeutic target in the treatment of age-related diseases such as cardiovascular disease, neurological and metabolic disorders. In this review, we discuss the role of GRK5 in the context of cardiovascular and neurodegenerative disease to emphasize its function in inflammaging.

2. The Role of GRK5 in Cardiovascular Disease Pathology

Cardiovascular pathophysiologies, such as myocardial ischemia, myocardial infarction or hypertension involve the dysregulation of cardiac GPCR responsiveness, which in turn is partly induced by deleterious GRK signaling activity profiles [30][31]. The first cardiac GRK form identified was GRK2 [32], while the discovery of cardiac GRK5 came later [33]. GRK5 was found to be highly expressed in the myocardium through several studies employing genetically engineered mice with altered GRK5 levels [2][33][34]. Homozygous GRK5-KO mice are born with a

normal basal phenotype, although a loss of both GRK5 and GRK6 in mice results in lethality [1] [35]. Further studies in zebrafish lacking the GRK5 homolog Grk5l, suggested the importance of GRK5 fine tuning capacity in cardiac development through the mTOR pathway. Hence, these Grk5l deficient fish demonstrated altered cardiac tissue generation associated with premature loss of muscle cell progenitors leading to an imbalance of gross structure [1] [36]. Of note, GRK5 is shown to be up-regulated in heart failure [37]. It has been demonstrated that elevation of GRK5 expression in vascular smooth muscle cells (VSMCs) can also induce the development of high blood pressure [7] via altered β1-adrenergic receptor (β1-AR) and angiotensin II (Ang II) receptor signaling dynamics [38] [39]. GRK5 functionality also appears to be linked to the generation of atherosclerotic vascular pathophysiologies. Hence, the genomic deletion of GRK5 in an ApoE4-deficient murine background significantly accelerated the creation of aortic atherosclerosis compared to control mice [28].

2.1. Cardiac failure

GRK5 appears to exert a pivotal role in cardiac failure and several cardiomyopathies including cardiac hypertrophy [6][40]. Cardiac hypertrophy refers to the abnormal enlargement, or thickening, of cardiac muscle. This thickening can be caused by increases in cardiomyocyte size themselves or via changes in other cardiac muscular components, such as extracellular matrix. Cardiac hypertrophy can be induced via physiological effects (e.g., elevated cardiovascular exercise) or as the result of pathophysiology (e.g., hypertension or valvular disease) [41].

In humans, four non-synonymous SNPs of GRK5 with translational significance have been demonstrated. Of these known SNPs, the RH-domain resident Q41L polymorphism [leucine (L) converted to a glutamine (Q)] is highly enriched amongst African-American (A-A) individuals [42]. This divergent form of GRK5 possesses an augmented capacity to desensitize β2-adrenergic receptors (β2ARs) [43], thus engendering a population specific cardiovascular effect. The Q41L GRK5 variant appears to afford protection against congestive cardiac failure amongst A-A heart failure patients [1][44]. Reinforcing the potential protective capacity of GRK5 in the cardiac setting, increased GRK5 expression has been shown to attenuate cardiac burden in response to intense adrenergic stimulation [38][45]. As expected, a GRK5 activity blockade mediates the opposite effect, i.e., increased cardiac performance as well as improved resilience in the context of heart failure [46][47]. It has also been shown that functional GRK5 inhibition, performed by ectopic expression of an N-terminal GRK5 peptide fragment of GRK5, reduces the extent of cardiac muscle damage and attenuates the risk of heart failure [48].

During cardiac failure, the expression and activity of GRK5 are reflexively increased to enhance β-adrenergic receptor desensitization and thus attenuate contractility [38]. Activation of GPCRs by hypertrophic agonists, such as phenylephrine and/or Ang II, engages a number of intracellular signaling pathways, including calcineurin-nuclear factor of activated T cells (NFAT) [49], Ca^{2+}/CaM – dependent kinase II (CamK II) [50][51], MAPKs [52][53] and the Akt-mechanistic target of rapamycin (mTOR) pathway [54][55] among many others, that are important transducers of the hypertrophic response.

GRK5 can undergo nuclear translocation in a calmodulin-dependent manner following $G\alpha_q$-based signals emanating from α-adrenergic and Ang II receptors. This nuclear translocation of GRK5 has been shown to be

mutually exclusive with its interaction with plasma membrane GPCRs – thus distinguishing canonical and non-canonical GRK5 functions [7]. This cellular redistribution is proposed to help mitigate the deleterious functions of cardiac hypertrophy [56][57][58][59][60]. Nuclear GRK5 migration is assisted through a productive interaction with calcium sensing proteins (CSP) [61] – thus GRK5 is specifically sensitive to the presence of Ca^{2+}/CaM [62][63]. Indeed, GRK5, possessing a high affinity for CaM, is rapidly inactivated in cells upon elevations in cytosolic calcium. This aspect of GRK5 biology reinforces its pivotal role in the modulation of calcium-associated muscular contractility [64][65].

It has been demonstrated that nuclear GRK5 acts as a class II histone deacetylase kinase (HDAC). In this scenario it has been reported that GRK5 is able to phosphorylate HDAC5 (histone deactylase 5) [66]. This GRK5-mediated phosphorylation causes redistribution of HDCA5 out of the nucleus resulting in a function alleviation of its MEF2 (myocyte enhancer factor 2) transcription factor repression – leading to “de-repression” of MEF2. Demonstrating the important role of GRK5 in cardiovascular aging this GRK5-mediated MEF2 activation transcribes multiple genes associated with cardiac hypertrophy [59][66]. GRK5 activity has further been shown to control hypertrophic responses via its interaction in the nucleus with components of the NFAT pathway [67]. GRK5 interacts with the NFAT-pathway in the nucleus during pathological hypertrophy. In addition, it is clear that GRK5 is strongly connected with the NF-κB signaling cascade [26][27][28][29][26][68][69][70] as an NF-κB binding element has been identified within the GRK5 DNA promoter region. This functional signaling region has subsequently been demonstrated to orchestrate the expression pattern of GRK5 in cardiac muscle cells [70].

Physiological hypertrophy does not only occur naturally in the heart due to augmented exercise regimens but also during pregnancy [71] Non-pathological cardiac hypertrophy is a process typified by relatively normal and proportionate myocyte growth – this reflexive response increases the capacity for cytoprotective cardiac activity [72] [73]. In contrast, pathological hypertrophy involves a disruption of the proportions of the new myocytes that causes an eventual diminution of heart chamber volume with a concomitant augmentation of septal wall thickness [73]. Recent research has suggested that GRK5 is only a controller of non-pathological hypertrophy [74]. In this research, using TgGRK5 mice, it was shown that physical exercise induced a classical physiological cardiac hypertrophy response. With specific respect to the nuclear functionality of GRK5 in cardiac hypertrophy it was shown in this exercise context that minimal nuclear GRK5 activity was found [74]. This corresponds with a study demonstrating that NFAT was not shown to regulate physiological hypertrophy [75]. While elevated levels of intracellular Ca^{2+} levels are common to both physiological and pathological cardiac hypertrophy, it has been proposed that pathological hypertrophic effects are differentially controlled through distinct intracellular calcium stores. Thus differential sources of “activating” calcium may allow the specific stimulation of the GRK5-related hallmarks of pathological hypertrophy, i.e., nuclear GRK5 accumulation, HDAC kinase activity and increased NFAT activity. Reinforcing the concept of differential hypertrophic mechanisms, none of these selective events are routinely found in standard exercise-induced hypertrophic paradigms [74].

While GRK5 is evidently associated with deleterious cardiac signaling and cell growth, GRK5 does appear to possess additional non-pathological roles in heart functionality. For example, GRK5 has been shown to be an important intermediate in the mitogenic and pro-survival signaling cascades emanating from the β1-adrenergic

receptor-mediated transactivation [76] of the epidermal growth factor receptor (EGFR) [77]. Therefore, it appears that GRK5 possesses a dual functionality with respect to cardiac activity, i.e., GRK5 is involved in both protective and detrimental signaling events that are delineated via differential subcellular compartmentalization between nuclear and non-nuclear sites.

2.2. Hypertension

The maintenance of well-controlled vascular blood pressure is imperative for effective and reliable delivery of oxygenated blood to all major life-preserving organs. Significantly and chronically elevated blood pressure, i.e., hypertension, is a prominent risk-determining player in the etiological profile of multiple chronic conditions including ischemic heart disease with associated subsequent cardiac and renal failure [78][79]. The major organs and processes that endogenously regulate vascular pressure include the kidney, heart and the contractile state of VSMCs which regulates radial changes of blood vessels, thus modulating peripheral vascular resistance.

High blood pressure, with its associated stressful effects on vascular wall integrity, can result in the potentiation of GRK5 expression within VSMCs. Associated with these observations it has been shown that Ang II stimulation of VSMCs can also increase GRK5 expression levels in a calcium dependent manner [80]. This association between VSMC-based GRK5 expression and hypertension was again studied by [40] in which an ectopic increase of GRK5 expression in vessels was genetically engineered. GRK5 overexpression was subsequently found to induce a gender-specific hypertensive response, i.e., blood pressure increases were much more profound in males compared to females [40]. Both male and female hypertension in these GRK5-overexpressing mice was ablated upon treatment with the inhibitor of $G\alpha_i$ signaling, pertussis toxin. Further gender-specific effects on the cardiovascular parameters of these GRK5-overexpressing mice were also apparent, e.g., β1-adrenergi receptor signaling in males was altered while Ang II-mediated increased vascular tone was only found in females [40]. Interestingly, and in contrast to the reported overexpression of GRK2 in VSMCs, the elevation of GRK5 expression failed to induce any significant cardiac hypertrophy [39].

2.3. Atherosclerosis

Atherosclerosis presents as a long-term inflammatory disease found primarily in the major arteries. This condition is typified by the accumulation of oxidized low-density lipoproteins (LDL) within the arterial wall and a progressive inflammatory cell infiltration into the vessel [81][82]. The recruitment of inflammatory cells to these lesions is triggered by the production of chemokines within the plaque microenvironment [82]. Chemokine-stimulated GPCRs initiate several downstream effectors, promoting actin polarization, shape changes and directed cell movement which ultimately leads to atherosclerotic plaque formation [83].

GRK5 possesses the capacity to regulate signaling through multiple heptahelical receptors [4][84] including multiple types that have been strongly linked to etiological activities in the atherosclerotic process [85][86][87][88][89][90]. Interestingly GRK5 has also been shown to phosphorylate other signal transduction proteins that can influence the atherosclerotic process too, including p53 [91], IκBα [68][92], platelet derived growth factor receptor-β (PDGFRβ) [93]

[94] and HDCA5, via MEF2 activation [59]. GRK5 can also stimulate anti-atherogenic signaling activity in model systems. For example, GRK5-KO mice have an increase in lesion area when compared to wildtype mice through two different cell-type regulatory mechanisms in monocyte/macrophages and VSMCs [29]. In VSMCs, GRK5 is able to promote the degradation of the pro-atherogenic platelet-derived growth factor receptor-β in lysosomes which is thought to reduce platelet-derived growth factor-mediated VSMC proliferation and migration [29]. GRK5 also regulates monocyte chemotaxis; i.e., *in vitro* GRK5-KO monocytes possess increased migration capacity in response to C-C chemokine ligand 2 (CCL2) (a ligand for the C-C chemokine receptor type 2 (CCR2) receptor) and colony stimulating factor-1 (CSF1) (a ligand for the colony stimulating factor 1 receptor (CSF1R) tyrosine kinase) [29]. CCL2-mediated leukocyte migration is instrumental in atherosclerotic lesion progression and responsible for the increased macrophage content in lesions from GRK5-KO mice. These findings highlight the potential mechanisms in both monocyte retention and emigration after their migration across the endothelium and present new strategies to limit atherosclerotic lesion progression.

3. GRK5 in Neurodegeneration

In contrast to its expression profile in cardiovascular organs, central nervous system (CNS) expression of GRK5 is comparatively sparse [36][35] because of a low GRK5 expression in the majority of cortical areas, except for the limbic system [95]. As we have outlined previously there is emerging evidence that demonstrates the multiple non-canonical roles of GRK5 outside of GPCR activity regulation. These novel effects of GRK5 are also associated with multiple important neurophysiological functions. For example, GRK5 deficient mice display a specific and nuanced subtype-specific muscarinic receptor dysfunction while closely-associated adrenergic and opioid receptor activity was not altered [96][97][98]. CNS muscarinic receptor activity has long been associated with the maintenance of learning and memory behavior [99]. Thus, it is unsurprising that GRK5-KO mice present with cognitive dysfunction shown to correlate with hippocampal neurosynaptic failure [98]. Again, as with the cardiovascular effects, gender differences in GRK5 activity were seen with respect to neurodegenerative phenotypes, i.e., augmented axonal defects and synaptic degenerative changes, were shown to be greater in female experimental animals as opposed to males. In addition, at the molecular signaling level, hippocampal levels of the synaptosomal-associated protein 25 (SNAP25) and synaptophysin were significantly lower in females compared to males [98].

It has also been proposed that the involvement of GRK5 in dementia-related conditions is likely associated with its potent role in regulating neurite outgrowth that is required c [100].

Obstructive sleep apnea (OSA) occurs in approximately 2 to 4% of middle-aged women and men, respectively. Among these, OSA is also observed to be more common in obese patients, potentially due to increased tracheal occlusion caused by excessive cervical adipose deposits. While OSA can induce health concerns with respect to lack of effective sleep patterns, it is evident that OSA is also closely associated with intermittent cerebral hypoxia. Considering this deleterious hemodynamic effect it is unsurprising that OSA has been shown to be a potent risk factor for associated cognitive impairment in nearly a quarter of diagnosed OSA patients [101]. At the molecular level CNS hypoxic episodes can often result in the increased production rate of ROS – these oxygen species can rapidly interact and modify a broad range of CNS lipids, nucleic acids and proteins. Enhanced CNS ROS production has

therefore been associated vascular endothelial dysfunction, perturbations of blood-brain barrier integrity and eventual neurosynaptic signal transduction dysfunction. Rodent models of intermittent hypoxia have been developed to effectively replicate the OSA found in human patients [1][102]. Using these, it has been demonstrated that intermittent hypoxia effects upon behavioral rodent activity (anxiety, balance, short-term memory) are acutely sensitive to, and potently augmented by, the genetic deletion of GRK5 [1][102]. Such research suggests that part of the CNS functionality of GRK5 may be associated with oxygen sensation neurochemistry, potentially via controlling astrocytic functions.

3.1. GRK5 and Alzheimer's disease (AD) pathology

For a significant period of time, undue focus on amyloid pathologies and their subsequent association with Alzheimer's disease (AD) has been in effect [103][104][105][106]. However, and from a more therapeutically important aspect, there has long been known to be an extant cholinergic receptor (post-synaptic nicotinic and M1 muscarinic acetylcholine) hypofunction evident in AD [107]). In AD it has been demonstrated that augmented presynaptic cholinergic activity results in the reflexive attenuation of synaptic acetylcholine release. This reduced release therefore results in diminished level of activity at the post-synaptic muscarinic M1 GPCRs. Indicating the importance of muscarinic signaling in AD pathophysiology, muscarinic M1 receptor signaling cascades can inhibit β-amyloidogenic (Aβ) amyloid precursor protein (APP) processing, resulting in a decreased level of cytotoxic β-amyloid accumulation [108]. From genetic deletion mouse models (i.e., GRK5-KO) it has been shown that GRK5 functionality is associated with severe hippocampal dysfunction (loss of neurosynaptic proteins and axonal swelling) as well as increased amyloidosis [13][109].

When combined with murine AD models (Tg2576) GRK5 deficiency was found to cause increased inflammatory astrogliosis in both hippocampal and cortical brain areas [110]. In addition to this effect, the GRK5 deficiency was also linked with both increased soluble Aβ levels as well as increased insoluble Aβ plaque load [111]. These findings were proposed to be due to a GRK5-induced potentiation of presynaptic muscarinic M2 receptor activity that resulted in a significant reduction of synaptic acetylcholine transmission levels [100][111]. This GRK5-associated alteration of synaptic receptor activity in murine models of AD has been shown to be linked to disruptions in sub-cellular compartmentalization of GRK5. Hence, [112] were able to demonstrate that aged AD model mice possess a highly specific plasma membrane deficiency of GRK5 [112]. A paucity of pre-synaptic GRK5, with its concomitant detrimental effect on M2-acetylcholine receptor-controlled acetylcholine release, has been subsequently linked to an exacerbation of tau hyperphosphorylation and further neuronal dysfunction. Using chemical blockade of these hyperactivated M2 receptors [112] were able to attenuate this tau hyperphosphorylation in a GSK3β-dependent manner.

It is thus apparent that GRK5 may indeed hold the key to the connection between the current major theories of AD, i.e., the amyloid and the cholinergic hypotheses. The cholinergic hypothesis suggests that cholinergic CNS dysfunction is responsible for the cognitive decline [113] while the amyloid hypothesis proposes that Aβ is the AD-causative factor [114][115][116][117][118]. Interestingly, as we have previously outlined, Aβ is thought to be one of the driving forces for alterations of membrane associated GRK5 in AD [119]. GRK5 plasma membrane deficiencies can

mediate presynaptic M2 acetylcholine autoreceptor hyperactivation that, in turn, causes post-synaptic cholinergic hypoactivity through the functional attenuation of cholinergic neurotransmission. This disrupted cholinergic transmission then serves to augment Aβ amyloid production leading to a “feed-forward” process of progressive neurosynaptic dysfunction and amyloid toxicity. In this recursive process both amyloid deposition and cholinergic dysfunction each can serve as a cause and/or consequence of each other, with the extant GRK5 dysfunction as the pivotal mediator. Given the present interest in these hypotheses in AD pharmacotherapy, the importance of GRK5 as a drug target in this system may increase significantly in the future.

As a prelude to our next section, it is intriguing to note that GRK5 can be further connected with AD through its ability to phosphorylate α-synuclein (SNCA) [12][120][121], tubulin as well as the AD-associated tau protein [112]. This pathological effect has been proposed to occur through GRK5-mediated phosphorylation causing increased SNCA polymerization and eventual aggregation – in a similar manner to that seen with Aβ in the context of AD [122].

3.2. Parkinson’s disease (PD)

Parkinson’s disease (PD) is one of the most commonly encountered neurodegenerative diseases at the present time, just behind AD with respect to world prevalence. The pathological effects of PD impact the primary fine motor systems of the body. PD is clinically typified by progressive deterioration of tremor, rigidity, bradykinesia/akinesia, gait disturbance, and postural instability. The major defining neuropathological feature of PD has long been considered to be the loss of neurons in the *substantia nigra* that provide dopaminergic innervation to the striatum, the CNS region most heavily implicated in fine motor control. Since the molecular mechanism causing dopaminergic neuron dysfunction are yet to be comprehensively defined, there are unfortunately no effective current pharmacotherapeutic interventions capable of retarding, or reversing, the disease [123]. One of the lesser known aspects of PD is the fact that advancing age is arguably the strongest risk factor for its generation [124]. In this light it is unsurprising that PD is typically is presented after the age of 60.

With respect to the functional intersection between GRK5 and PD pathology, it has been demonstrated by multiple research groups that GRK5 represents one of the major kinases that can phosphorylate SNCA. This classical function of GRK5 results in the promotion of the oligomerization of PD (with actual co-localization of GRK5 and SNCA), facilitating the creation of pathological Lewy bodies in the *substantia nigra* and *locus coeruleus* of PD patients [12][120]. The nuclear functionality of GRK5 is one of its defining functional features among GRK proteins – GRK5 activity itself has also been shown to promote the nuclear translocation of SNCA and its associated factors PLK2 and 3 (Polo-like kinase 2 and 3) [125][126]. While the full ramifications of nuclear SNCA remain currently cryptic, it has been proposed that this aspect of SNCA biology may be independent of the classically-pathological SNCA aggregation modality. It is important to note, especially with respect to aging pathomechanisms, that oxidative stress environments promote the enhanced nuclear localization of SNCA [127][128][129]. Within the nuclear domain SNCA has been shown to functionally antagonize histone acetylation, resulting in increased neurotoxicity [130][131]). Nuclear SNCA has also been found to be a transcriptional regulator capable of binding to PGC1-α (Peroxisome proliferator activated receptor gamma coactivator 1-alpha) promoter regions, and in doing so, potentially regulate mitochondrial gene transcription and thus neurometabolic ROS-associated activity [129]. In

addition to these cell signaling-based analyses, genetic association studies have proposed a haplotypic association of GRK5 gene with the clinical presentation of sporadic PD. These pathological haplotypes associated with functional GRK5 SNPs that can control multiple transcription factors (Yin Yang-1 (YY1) and cAMP response element-binding protein (CREB-1)) that together are capable of potentiating SNCA transcription [121]. Unfortunately, and as is quite common with genetic association studies, subsequent studies have failed to reproduce some of these propositions. Hence, studies employing GRK5 deletion in cells have failed to find a resultant attenuation of SNCA phosphorylation[132][133]. In addition, further studies have not observed a strong localization of GRK5 in Lewy bodies [134] or a firm association of GRK5 SNPs with PD [135].

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