DOI: 10.11844/cjcb.2026.02.0027
中国细胞生物学学报 Chinese Journal of Cell Biology 2026, 48(2): 531–545 CSTR: 32200.14.cjcb.2026.02.0027

Scgn在神经系统中的研究进展

王东 陈卉丹 龚吉红* 阳小飞*
(中南民族大学生物医学工程学院认知科学重点实验室, 湖北省医学信息分析与肿瘤诊疗重点实验室, 膜离子通道与药物研发实验室, 武汉 430074)

摘要 Scgn是一种EF-hand钙结合蛋白, 在神经元特异性钙传感器家族中占据独特地位。作为钙信号转导的关键参与者, Scgn通过其六个EF-hand结构域参与多种神经过程的调控, 包括内分泌颗粒的分泌、突触囊泡释放, 并在神经发育与神经疾病中发挥重要功能。该文系统综述Scgn的结构特点、表达分布及其在神经系统中的多重作用, 并探讨其在神经精神疾病中的潜在病理意义与应用价值。基于现有研究, Scgn特异性分布于嗅球、海马等脑区, 与如SNAP-25和Doc2α等突触分泌关键分子发生Ca^{2+}依赖性相互作用, 调节神经突触传递与突触可塑性。此外, Scgn在阿尔茨海默病、帕金森病、癫痫等疾病中表现出的病理变化, 提示其可能作为早期生物标志物和潜在治疗靶点, 具有重要的转化研究前景。

关键词 促泌素; 钙结合蛋白; 神经系统疾病

Research Progress of Scgn in the Nervous System

WANG Dong, CHEN Huidan, GONG Jihong*, YANG Xiaofei*
(*Key Laboratory of Cognitive Science, Hubei Key Laboratory of Medical Information Analysis and Tumor Diagnosis & Treatment, Laboratory of Membrane Ion Channels and Medicine, College of Biomedical Engineering, South-Central Minzu University, Wuhan 430074, China*)

Abstract Scgn is an EF-hand calcium-binding protein occupying a unique position within the family of neuron-specific calcium sensors. As a key participant in calcium signaling, Scgn regulates diverse neural processes through its six EF-hand domains, including endocrine granule secretion, synaptic vesicle release, and plays crucial roles in neurodevelopment and neurological disorders. This review systematically summarizes Scgn's structural characteristics, expression patterns, and multifaceted roles within the nervous system, while exploring its potential pathological significance and therapeutic value in neuropsychiatric disorders. Existing studies indicate that Scgn is specifically distributed in brain regions such as the olfactory bulb and hippocampus. It engages in Ca^{2+}-dependent interactions with key synaptic secretion molecules like SNAP-25 and Doc2α, thereby regulating neurotransmission and synaptic plasticity. Furthermore, pathological alterations in Scgn observed in diseases like Alzheimer's disease, Parkinson's disease, and epilepsy suggest its potential as an early biomarker and therapeutic target, offering significant prospects for translational research.

Keywords Scgn; calcium-binding protein; nervous system disease

收稿日期: 2025-10-13 接受日期: 2025-12-01
国家自然科学基金(批准号: 32170699、32200560)和湖北省自然科学基金(批准号: 2022CFB906、2025AFA009)资助的课题
*通信作者。Tel: 027-67841902, E-mail: jihonggong@foxmail.com; Tel: 027-67843221, E-mail: sunlittlefly@hotmail.com
Received: October 13, 2025 Accepted: December 1, 2025
This work was supported by the National Natural Science Foundation of China (Grant No.32170699, 32200560) and the Hubei Provincial Natural Science Foundation of China (Grant No.2022CFB906, 2025AFA009)
*Corresponding authors. Tel: +86-27-67841902, E-mail: jihonggong@foxmail.com; Tel: +86-27-67843221, E-mail: sunlittlefly@hotmail.com

Scgn (secretagogin), as a member of CaBP (the calcium-binding protein) family, is also a crucial component of the nervous system. It plays a key role in regulating neurotransmission and neural development. In recent years, significant progress has been made in Scgn research, particularly in the fields of synaptic secretion and neurodegenerative diseases[1-2]. Research indicates that Scgn plays a vital role in neurodegenerative diseases such as Alzheimer's and Parkinson's disease, while its regulatory function in neural development is also gradually being elucidated[3]. These findings not only deepen our understanding of Scgn's biological functions but also provide novel therapeutic approaches and potential targets for neurological disorders. However, the precise mechanisms of Scgn in complex physiological and pathological contexts require further exploration, offering extensive scope and innovative opportunities for future research. This review synthesizes existing research on Scgn within the nervous system, focusing on its molecular structure, expression patterns, functional roles, and disease associations. It specifically compares Scgn sequences across different species, elucidating the significance of its evolutionary conservation and variations. We further discuss Scgn's involvement in neurodegenerative diseases, identifies future research directions, and offers novel perspectives for the treatment of neurological disorders.

1 An EF-hand calcium-binding protein Scgn

Within the nervous system, calcium ion signaling represents one of the core molecular events regulating neuronal function, playing a crucial role in processes such as excitability modulation, synaptic transmission, and synaptic plasticity[4-6]. The precise spatiotemporal dynamics of calcium ion concentration depend on the specific regulation of multiple calcium-binding proteins. These proteins bind calcium ions with high affinity, thereby mediating downstream signaling pathways and participating in diverse intracellular physiological activities[7]. Among numerous calcium-binding proteins, Scgn has garnered significant attention in recent years as a key member of this group.

Scgn was initially identified in 2000 by Austrian scientist WAGNER and colleagues[8] from a cDNA library of pancreatic β-cells, named for its ability to significantly promote insulin secretion. The *SCGN* gene is located on human chromosome 6 (GRCh38: 25652215-25701783), encoding a protein composed of 276 amino acids with a molecular weight of approximately 32 kDa. It belongs to the calcium-binding protein family.

Scgn is a calcium-binding protein that has garnered significant attention in recent years. Structurally, it exhibits a unique arrangement of six EF-hand domains and demonstrates distinct functional and tissue distribution characteristics compared with traditional CaBPs[9-10]. Recent studies indicate that Scgn plays a crucial role in various neurological disorders[11]. In Alzheimer's disease, studies indicate that Scgn-positive neurons may be associated with Aβ and tau pathology, exhibiting quantitative or morphological alterations in relevant brain regions, which suggests their involvement in the pathological processes of neurodegenerative diseases[11-12]. In Parkinson's disease animal models, Scgn has been linked to abnormal aggregation of α-synuclein[2]. Furthermore, Scgn co-expresses with CGRP (calcitonin gene-related peptide) in dorsal root ganglia, suggesting potential involvement in pain regulation pathways[13]. These findings indicate that Scgn serves not only as a crucial molecular tool for deciphering neural mechanisms but also as a novel therapeutic target for diagnosing and treating future neurological disorders.

This paper systematically elucidates the multifaceted roles of Scgn in the central nervous system from perspectives including molecular structure, expression patterns, physiological functions, evolutionary conservation, and disease associations. It further explores its potential research value in neurodevelopment and disease processes.

2 Structure, distribution, function, and evolution of Scgn

2.1 Molecular structure of Scgn

As a member of the calcium-binding protein

family, Scgn's molecular structure consists of six consecutive EF-hand domains arranged in a tandem configuration (Fig.1). It exhibits both the structural characteristics typical of Ca^{2+}-binding proteins and certain unique features[3]. The EF-hand domain was first identified by KRETSINGER et al[14] in PV (parvalbumin), with its name derived from the characteristic "helix-loop-helix" conformation of this structure[15]. The loop region within this domain typically comprises 12 amino acid residues, where residues bearing carboxyl side chains—such as Asp (aspartic acid) and Glu (glutamic acid)—mediate coordination with Ca^{2+}, enabling high-affinity calcium ion binding[15-16].

Calcium-binding proteins can be categorized based on their function, structure, and mechanism of action. Functionally, they are primarily divided into calcium buffer proteins and calcium sensor proteins[7,10]. Buffer proteins, such as Calbindin-D28k, regulate intracellular calcium concentration by reversibly binding and releasing Ca^{2+}, maintaining calcium homeostasis and preventing cellular damage caused by abnormal concentrations[7,17]. Sensor-type calcium-binding proteins undergo conformational changes upon Ca^{2+} binding, thereby activating or inhibiting the activity of downstream target proteins. This converts calcium ion concentration signals into intracellular signals, regulating corresponding physiological functions within the cell[18-19]. A typical example is CaM (calmodulin), which relies on its four EF-hand domains to achieve Ca^{2+} sensing and conformational conversion[20-21].

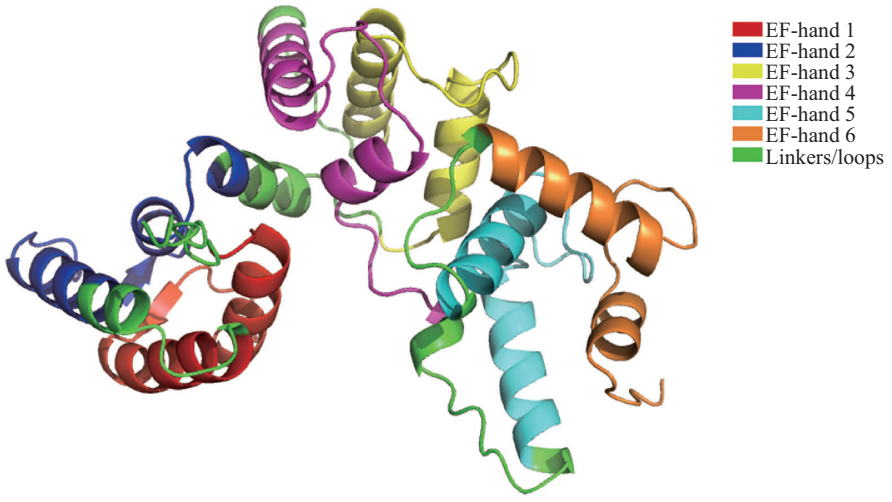
As a member of the calcium-binding protein family, Scgn is unique in possessing six EF-hand domains, a configuration uncommon among NCS (neuronal calcium sensor) proteins[22-23]. Sequence analysis reveals that at least four of Scgn's six EF-hands contain the conserved Ca^{2+}-binding motif (DxDxDG)[16], enabling stable Ca^{2+} binding. The remaining two represent "degenerate" EF-hands, potentially participating in protein stability maintenance or mediating protein interactions through conformational changes[10,24]. This coexistence of primitive EF-hands and "atypical EF-hands" endows Scgn with dual functions of calcium buffering and signal sensing[10,22].

Studies indicate strong synergistic interactions among Scgn's EF-hand modules: Ca^{2+} binding at one site enhances affinity at others, creating an "all-or-nothing" calcium signal conversion effect[15,24]. This structural feature enables Scgn to function both as a highly sensitive Ca^{2+} sensor and to exhibit multi-level complex functional regulation across different Ca^{2+} concentration thresholds.

Thus, Scgn demonstrates remarkable functional diversity and structural uniqueness in calcium signal transduction.

Compared with buffered calcium-binding proteins such as calbindin, calretinin, and parvalbumin, Scgn exhibits a molecular conformation more conducive to functioning as a calcium sensor[9,27-28]. Its structure contains multiple flexible regions, such as the highly plastic EF-hand 5 and EF-hand 6 domains, as well as partially disordered regions (e.g., between EF-hand 2 and EF-hand 3), which provide potential binding interfaces for protein interactions[24,29-30]. Experimental studies indicate that Scgn undergoes significant conformational changes upon Ca^{2+} binding: its C-terminus rearranges, causing domains I and II to rotate nearly 180° relative to domain III. Concurrently, EF-hand 5 and EF-hand 6 shift to form a hydrophobic surface, transforming the entire molecule from a "compact state" to an "open state." This transformation exposes binding sites for SNARE proteins (e.g., SNAP-25) and synaptic secretion regulatory proteins (e.g., Doc2α)[9,24,31].

This "conformation switch" mechanism exhibited by Scgn shares similarities with the function of Syt (synaptotagmin) in vesicle fusion. Upon Ca^{2+} binding, Syt1 undergoes conformational changes in its C2A and C2B domains, shifting from a cytoplasmic orientation to one inserted into the plasma membrane. This facilitates the formation of a "membrane bridge" structure, shortening the distance between vesicles and the plasma membrane, thereby promoting rapid vesicle-plasma membrane fusion and neurotransmitter release[32-35]. However, Scgn and Syt exhibit distinct differences in their Ca^{2+} kinetic ranges: Scgn activates within sub-mi-



图中按颜色区分结构域: EF-hand 1(红色)、EF-hand 2(深蓝色)、EF-hand 3(黄色)、EF-hand 4(紫色)、EF-hand 5(天蓝色)、EF-hand 6(橙色); 连接区linkers/loops为绿色。该结构由AlphaFold预测(UniProt ID: Q91WD9)。

The figure distinguishes structural domains by color: EF-hand 1 (red), EF-hand 2 (dark blue), EF-hand 3 (yellow), EF-hand 4 (purple), EF-hand 5 (sky blue), EF-hand 6 (orange); linkers/loops are green. The structure was predicted by AlphaFold (UniProt ID: Q91WD9).

图1 Scgn三维晶体结构示意图(根据参考文献[25-26]修改)

Fig.1 Schematic diagram of the three-dimensional structure of Scgn (modified from references [25-26])

cromolar to low micromolar Ca^{2+} concentrations, making it better suited for responding to low-frequency or sustained calcium signals[9-10,36]; whereas Syt primarily functions within the high-Ca^{2+} microdomains at synaptic terminals[37-39]. This distinction suggests that Scgn may play unique roles in specific synaptic activities and neural circuit regulation. Furthermore, compared with other NCS proteins, Scgn is distinguished by the unique arrangement of its six EF-hand domains and an extended C-terminal region, which is implicated in cell-specific localization and protein interactions[40-42]. These structural features collectively confer Scgn with unique functional diversity in calcium signaling perception and transduction.

In summary, Scgn's molecular structure combines a high-affinity Ca^{2+} binding site with protein-protein interaction interfaces. The unique architecture of its six EF-hand modules not only establishes its molecular basis as a Ca^{2+} sensor but also enables it to perform multiple critical functions within neurons. This structural property provides key insights into Scgn's role in neurotransmitter release, synaptic plasticity, and the pathogenesis of neurological disorders. Future studies utilizing cryo-electron microscopy, mass spectrometry, and computational 3D structural modeling may further elucidate the precise mechanisms underlying Scgn's calcium ion binding and signal decoding at the molecular level, thereby deepening our understanding of its multifunctional regulatory role.

2.2 Expression distribution of Scgn

Scgn was initially discovered in pancreatic beta cells and gained attention for its role in regulating insulin secretion[8]. Subsequent studies revealed that Scgn exhibited distinct brain region specificity and developmentally dependent expression patterns within the central nervous system. Rather than being broadly expressed across all neurons, this protein is highly concentrated in specific neuronal subtypes, making it a crucial molecular marker for identifying particular neural circuits.

In mammals, Scgn is widely expressed in key brain regions, including the olfactory bulb, hippocampus, hypothalamus, and thalamus. Within the olfactory bulb, Scgn primarily localizes to interneurons between the peribulbar and granular layers, potentially contributing to olfactory information processing[41,43]. Its expression in dentate gyrus granule cells and pyramidal neurons of the CA1-CA3 regions suggests involvement

in learning and memory functions[41,44]. In the PVN (paraventricular nucleus) and SON (suprachiasmatic nucleus) of the hypothalamus, Scgn co-expresses with OXT (oxytocin) and AVP (vasopressin) neurons, indicating participation in neuroendocrine regulation[9,27]. Within the thalamus, Scgn is specifically expressed in the lateral geniculate complex and adjacent regions, closely associated with sensory signal transmission[41,45]; in DRG (dorsal root ganglia), it colocalizes with CGRP (calcitonin gene-related peptide) and neuropeptide substance P, both implicated in nociception, suggesting involvement in pain transmission and modulation[9,13]. In primates and humans, Scgn expression further concentrates in regions closely linked to cognition and emotion, such as the neocortex, hippocampus, and olfactory bulb. It colocalizes with specific types of GABAergic and glutamatergic neurons, indicating its role in fine-tuning complex neural circuits[46-47].

In non-mammalian animals, Scgn distribution and function exhibit evolutionary differences. For example, in zebrafish brains, Scgn is widely distributed among motor-related neurons, reflecting its regulatory role in more primitive neural networks[24,48]. In amphibians and birds, Scgn is extensively expressed not only in the central nervous system but also in populations of neuroendocrine cells, suggesting its early function may be closely related to secretion regulation[49-50].

During nervous system development, Scgn expression exhibits distinct temporal dynamics. In embryonic and neonatal stages, Scgn is broadly expressed in neural progenitor cells and migrating neurons, suggesting a potential role in neurogenesis and neural circuit formation. As development progresses, Scgn expression gradually becomes restricted to specific neuronal types, shifting toward more refined regulatory functions[3,51-52]. For instance, studies reveal high Scgn expression in GABAergic interneurons of the human embryonic neocortex, but its levels decline postnatally, persisting only at low levels into adulthood[46,51]. Further studies indicate that in brain regions such as the hippocampus, Scgn is frequently co-expressed with neuropeptides like SST (somatostatin) and CRH (corticotropin releasing hormone). This suggests that Scgn may serve as a “bridge” between multiple neurotransmitter systems, thereby participating in the coordination of different neural signaling pathways[27,53-54].

In summary, Scgn expression exhibits high specificity across species, brain regions, and developmental stages. In mammals, it is primarily distributed in key brain areas such as the olfactory bulb, hippocampus, hypothalamus, and thalamus—regions extensively involved in cognition, emotional regulation, and neuroendocrine control. In non-mammalian animals, Scgn is more involved in regulating fundamental neural networks. From a developmental perspective, Scgn expression patterns undergo a transition from broad involvement during neurogenesis to specific targeting of distinct neuronal subtypes, reflecting its multifaceted roles in neural circuit construction and fine-tuning.

2.3 Multidimensional functions of Scgn in the central nervous system

As a member of the EF-hand calcium-binding protein family, Scgn possesses a unique molecular structure, particularly its six EF-hand calcium-binding domains. This structure not only endows the protein with highly efficient calcium ion binding capacity but also provides the structural foundation for its multifunctional roles in the nervous and endocrine systems. Previous studies have systematically demonstrated Scgn’s tissue-specific and developmental stage-specific expression patterns, suggesting its potential significance in various physiological processes. However, Scgn’s functional execution depends not only on its own structural characteristics but also critically on its dynamic interactions with other proteins. These interactions directly influence Scgn’s subcellular localization, activity state, and its role in key processes such as neurotransmitter release, regulation of neuronal excitability, and modulation of synaptic plasticity. Therefore, we will continue to explore Scgn’s molecular structural features, focusing on elucidating its interactions with several key proteins and its multifunctional roles.

2.3.1 Interaction between Scgn and SNAP-25

SNAP-25 (synaptosomal-associated protein of 25 kDa)

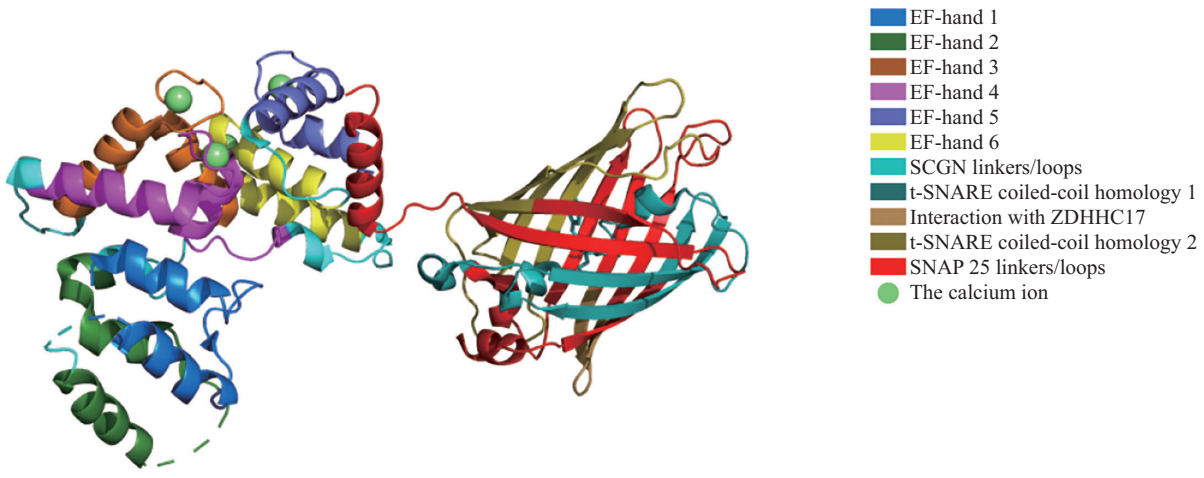
is a crucial component of the SNARE protein complex. Together with Syntaxin-1 and VAMP, it forms the core complex that mediates the fusion of synaptic vesicles with the plasma membrane[55]. Studies reveal that Scgn directly binds to SNAP-25 in a Ca^{2+}-dependent manner (Fig.2)[56-57]. This interaction extends beyond structural association to functionally regulate vesicle release, highlighting its significant biological importance.

Experimental studies indicate that following neuronal stimulation, calcium ion influx binds to Scgn, inducing a conformational change that allows it to interact with SNAP-25. This interaction blocks the interaction between Syntaxin-1 and SNAP-25. Syntaxin-1 subsequently binds to Munc18-1, exposing its SNARE domain and laying the foundation for complex assembly. The Scgn-SNAP-25 complex migrates toward the plasma membrane. Upon elevated calcium ion concentration, Scgn undergoes another conformational change, releasing SNAP-25 to participate in SNARE complex formation. This drives fusion between synaptic vesicles and the plasma membrane, releasing neurotransmitters. Finally, SNAPs (soluble NSF attachment proteins) facilitate SNARE complex dissociation, recycling components for subsequent vesicle fusion.

This process highlights the critical role of the Scgn-SNAP-25 interaction in regulating synaptic secretion. Scgn enhances binding efficiency with SNAP-25 under high Ca^{2+} conditions, accelerating SNARE complex assembly and thereby speeding up neurotransmitter release. Notably, this interaction exhibits distinct calcium-dependent dynamics: binding is weak at resting Ca^{2+} levels but significantly enhanced during action potential-induced Ca^{2+} transients. This suggests that Scgn may function as a fast calcium sensor, selectively fine-tuning the temporal and spatial precision of synaptic transmission during high-frequency firing or intense stimulation[27,59].

In vivo functional studies further confirm that Scgn deficiency reduces synaptic release probability in cortical and hippocampal neurons, with markedly diminished evoked neurotransmitter release. This phenotype is closely associated with dysregulated SNAP-25 function[27,57]. Collectively, these findings demonstrate that Scgn plays an indispensable role in regulating efficient neurotransmitter release through its specific interaction with SNAP-25.

2.3.2 Interaction between Scgn and Doc2α Doc2α (double C2-like domain-containing protein alpha) is a



左侧为Scgn蛋白结构示意图, 右侧为SNAP-25蛋白结构示意图。在Ca^{2+}存在条件下, Scgn的第三结构域(EF-hand 5和EF-hand 6)与SNAP-25的C末端SNARE基序的一段α-螺旋区域结合。该结构数据源自RCSB PDB数据库(PDB ID: 8BAN)。

The left panel shows the structural diagram of the Scgn protein, while the right panel depicts the structural diagram of the SNAP-25 protein. In the presence of Ca^{2+}, the third domain of Scgn (EF-hand 5 and EF-hand 6) binds to an α-helical region within the C-terminal SNARE motif of SNAP-25. This structure retrieved from the RCSB PDB (PDB ID: 8BAN).

图2 Scgn与SNAP-25复合物的三维晶体结构示意图(根据参考文献[58]修改)

Fig.2 Schematic diagram of the three-dimensional crystal structure of the Scgn-SNAP-25 complex (modified from reference [58])

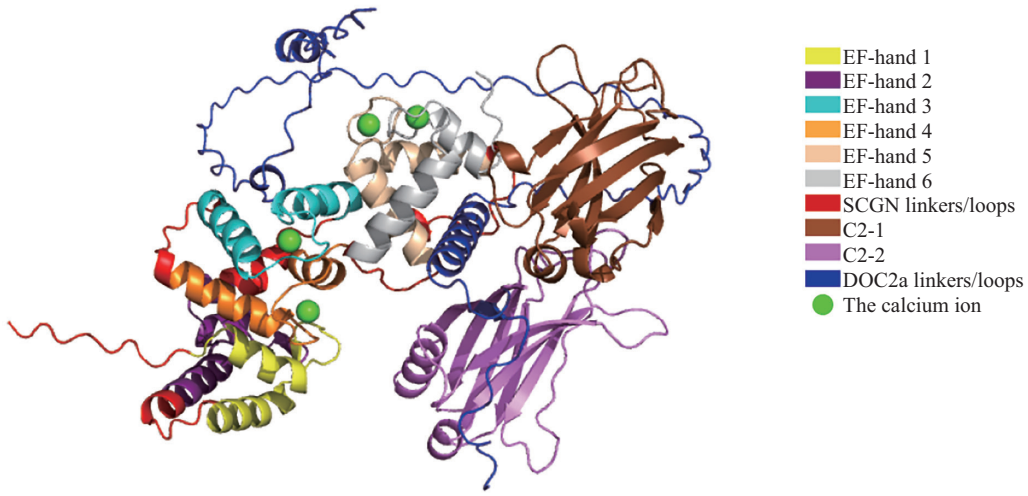
Ca^{2+}-binding protein containing two C2 domains that plays a crucial role in regulating spontaneous synaptic release and activity-dependent vesicle fusion. It promotes synaptic vesicle release by sensing intracellular Ca^{2+} concentration changes and interacting with SNARE proteins[60]. Recent studies indicate that the interaction between Scgn and Doc2α plays a crucial role in both release mechanisms, jointly coordinating the coupling between calcium signaling and SNARE complex assembly (Fig.3)[1,61].

At rest, the EF-hand domain of Scgn remains closed, inhibiting SNARE complex assembly and neurotransmitter release. An action potential triggers a rise in Ca^{2+} concentration, which binds to the EF-hand domain, causing it to open and expose the pore site. Doc2α binds to membrane phospholipids via its C2 domain, forming the Scgn-Doc2α complex. This complex releases SNAP-25, initiating SNARE assembly and facilitating neurotransmitter release. When Ca^{2+} levels decrease, Scgn and Doc2α return to their resting state, preparing for the next signal.

This dynamic interaction demonstrates that Scgn can form complexes with Doc2α in the perimembrane region under low-to-moderate Ca^{2+} concentrations, thereby regulating the basal spontaneous release activity of neurons. Unlike mechanisms primarily involved in action potential-induced rapid release, the Scgn-Doc2α system focuses on modulating low-frequency, sustained neurotransmitter release, playing a crucial role in maintaining the baseline activity and synaptic homeostasis of neural circuits.

Notably, Scgn-Doc2α interactions may play a critical role in synaptic development during neurogenesis[9,62]. Spontaneous release is implicated in synaptic pruning and stability regulation; Scgn may indirectly modulate neural circuit development and plasticity by influencing Doc2α function[1]. Experimental evidence indicates that Scgn deletion or downregulation disrupts Doc2α function, manifesting as reduced microsynaptic current frequency. This phenomenon provides crucial insights into Scgn's potential mechanisms in developmental neurological disorders such as autism and epilepsy[61-62].

2.3.3 Multidimensional functions and cross-system regulation of Scgn in the nervous system As a multifunctional calcium-sensing protein, Scgn's biological roles extend beyond classical neurotransmitter release regulation to encompass multiple critical physiological



左侧面板展示了Scgn蛋白质结构的示意图。右侧面板展示了Doc2α蛋白结构示意图。在Ca^{2+}存在下, Scgn第三结构域(EF-hand 5与EF-hand 6)与Doc2α两个C-端C2结构域之间的连接区发生相互作用。该结构由AlphaFold预测获得(UniProt ID: Q91WD9 & Q7TNF0)。

The left panel shows a schematic diagram of the Scgn protein structure. The right panel shows a schematic diagram of the Doc2α protein structure. In the presence of Ca^{2+}, the linker region between Scgn's third domain (EF-hand 5 and EF-hand 6) and the two C-terminal C2 domains of Doc2α interacts. The structure was predicted by AlphaFold (UniProt ID: Q91WD9 & Q7TNF0).

图3 Scgn与Doc2α复合物的三维晶体结构(根据参考文献[25-26]修改)

Fig.3 Three-dimensional structure of the Scgn-Doc2α complex (modified from references [25-26])

and pathological processes, including neuroendocrine function, neurodevelopment, and cell protection. Its functions within the nervous system can be systematically summarized as follows.

Beyond modulating classical neurotransmitters, Scgn participates in neuropeptide secretion. In the hypothalamus, Scgn co-expresses with OXT and AVP neurons, promoting the release of both neuropeptides upon calcium signal activation. Studies indicate that Scgn deficiency or functional inhibition reduces OXT and AVP secretion efficiency, thereby impairing physiological functions such as stress responses, social behavior, and fluid homeostasis[9,27]. These findings demonstrate Scgn's indispensable role in neuroendocrine regulation.

Scgn regulates neurodevelopment and synaptic plasticity. During embryonic and neonatal stages, Scgn is widely distributed among neural stem cells and migrating neuronal populations, suggesting potential involvement in neuronal migration, axon guidance, and synaptogenesis[63]. Functional studies demonstrate that Scgn overexpression restores integration and synapse formation in newborn neurons, while its absence leads to abnormal neural network development[48]. This finding offers a novel molecular perspective for understanding neurodevelopmental disorders such as autism spectrum disorder and epilepsy.

Growing evidence indicates Scgn also possesses neuroprotective functions. In models of oxidative stress, glutamate excitotoxicity, and neurodegenerative diseases, Scgn-positive neurons often exhibit enhanced anti-apoptotic capacity[64-65]. This property may relate to its regulation of Ca^{2+} dynamics, maintenance of mitochondrial function, and stabilization of intracellular homeostasis. For example, in Alzheimer's disease animal models, the P301L tau transgenic mouse model was utilized to simulate the tau pathological features of AD. At the cellular level, Scgn-positive neurons showed almost no tau expression, and vice versa. Furthermore, at the tissue level, Scgn expression was found to negatively correlate with tau pathology severity. Downregulation of Scgn protein was observed only in areas with active tau expression, while non-expressing regions remained largely unchanged[65], further supporting Scgn's neuroprotective role.

Scgn possesses cross-system regulation capabilities. Although this review focuses on the central nervous system, it is noteworthy that Scgn was initially discovered in pancreatic β-cells and also plays a crucial role in regulating insulin secretion[66]. Given that insulin protects against β-amyloid-induced synaptic loss in AD models[67], the presence of Scgn in pancreatic β-cells points to shared endocrine and neural functions, potentially underpinning the pathogenesis of Alzheimer's disease and diabetes. This suggests that Scgn's functions may span the nervous and endocrine systems, forming a key molecular link in neuro-endocrine-metabolic cross-regulation. Growing evidence indicates that Scgn in the nervous system may be linked to metabolic regulation, stress responses, and endocrine disorders such as diabetes[40,68].

In summary, the core functions of Scgn can be summarized as follows: firstly, Scgn acts as a highly efficient calcium ion sensor, enabling precise decoding of intracellular calcium signals. Secondly, Scgn plays a key regulatory role in the release of neurotransmitters and neuropeptides. Furthermore, during neurodevelopment, Scgn participates in neuronal migration, axon guidance, and synaptogenesis; under pathological conditions, it exerts neuroprotective effects; finally, Scgn's functions extend beyond the nervous system to the endocrine system, where it contributes to metabolic regulation. These functional characteristics underscore Scgn's significance in neuroscience and provide a foundation for further research into its role in both neurological health and disease.

2.4 Scgn cross-species sequence alignment analysis

The functional complexity of Scgn, along with its brain region distribution specificity and developmental stage differences across species, suggests that this protein's critical role in neurogenesis, neural circuit formation, and neurotransmitter system coordination may depend on its highly conserved structure. Therefore, conducting sequence conservation analysis of Scgn

holds significant scientific importance. By comparing Scgn amino acid sequences across species, we can identify key residues and functional domains that have remained stable throughout evolution, thereby providing a basis for elucidating its mechanisms in complex nervous system functions. Consequently, we performed sequence alignment analysis of Scgn from six different species.

As shown in Fig.4, homology analysis of Scgn amino acid sequences from human, mouse, rat, pig, cow, and zebrafish revealed significant conservation. Across the entire protein, 180 amino acids were identical among all six species, accounting for 65.2% of the total sequence. This high level of conservation indicates that Scgn possesses important biological functions that have been preserved throughout evolution. However, when analyzing the sequence homology of the six EF-hand domains within the Scgn protein, we found significant differences in conservation among species. Specifically, EF-hand 1 and EF-hand 2 exhibited relatively low conservation at 55.6% and 25.0%, respectively, suggesting these domains may possess greater evolutionary flexibility. In contrast, EF-hand 3, EF-hand 4, and EF-hand 6 showed higher conservation at 83.3%, while EF-hand 5 demonstrated the highest conservation at 94.4%. This high conservation suggests that EF-hand 3 to EF-hand 6 may perform more critical functions across species, particularly in calcium ion binding and signaling, consistent with their documented calcium-binding capabilities. These conservation differences likely reflect adaptive evolutionary traits of Scgn proteins across species while also hinting at the potential significance of EF-hand domains in nervous system functions.

When performing homology alignment of Scgn amino acid sequences across five mammalian species (human, mouse, rat, pig, and cow), we observed significantly higher conservation compared to the cross-phylum alignment including zebrafish. Overall, 219 amino acids were completely identical across these five mammals, accounting for 79.3% of the total sequence. This result indicates that Scgn proteins exhibit high sequence conservation across mammals and suggests that they perform similar biological functions in these spe-

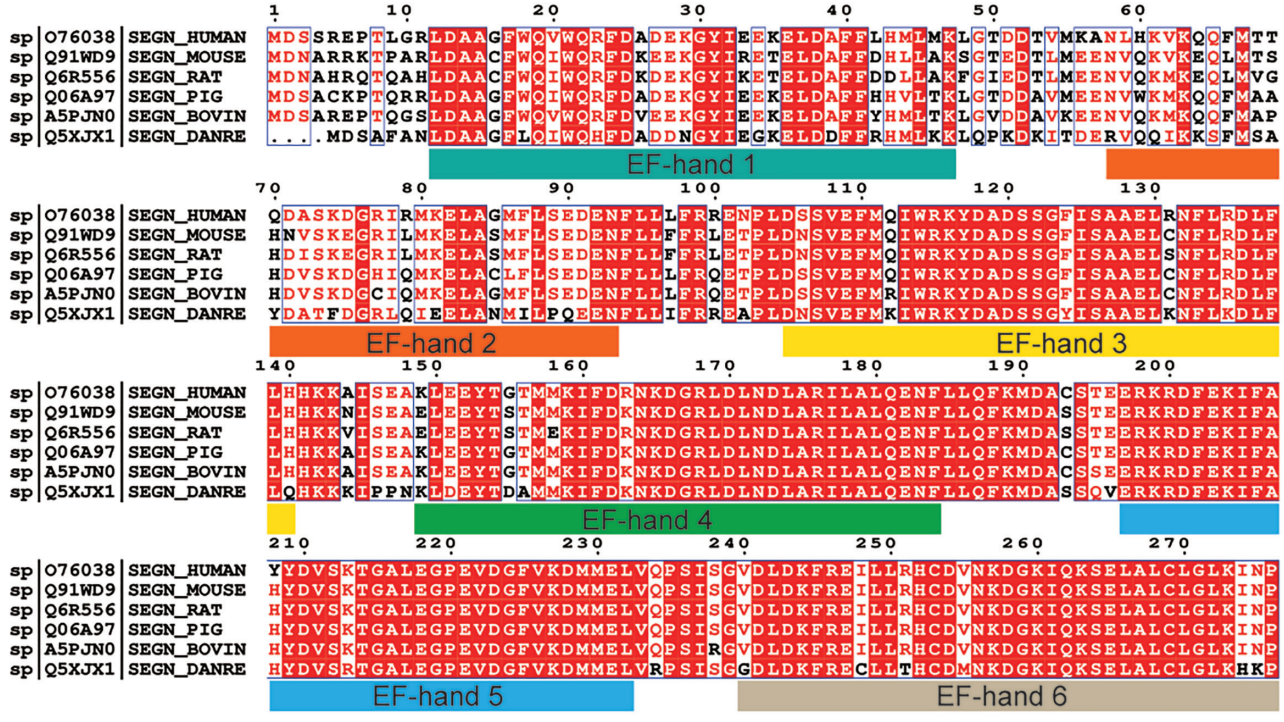


图4 不同物种Scgn氨基酸序列同源性比对

Fig.4 Homology comparison of Scgn amino acid sequences across species

cies. Homology analysis of the six EF-hand domains in the Scgn proteins from the five mammals also revealed significantly higher conservation than in the cross-class comparison. Specifically, EF-hand 1 showed 72.2% conservation, EF-hand 2 58.3%, while EF-hand 3 to EF-hand 6 exhibited higher conservation rates of 91.7%, 88.9%, 97.2%, and 100%, respectively. This indicates that the EF-hand domains of Scgn proteins in mammals, particularly EF-hand 3 to EF-hand 6, exhibit extremely high sequence conservation, with EF-hand 6 domains being completely identical. This suggests a high degree of conservation in their calcium ion binding and signaling functions. Such high conservation further supports the evolutionary conservation of Scgn's critical functions in the mammalian nervous system.

In summary, through homology alignment of Scgn amino acid sequences from humans, mice, rats, pigs, cattle, and zebrafish, we have revealed the characteristics of conservation and flexibility in Scgn protein evolution. The overall Scgn protein sequence exhibits significant conservation across different species, with this conservation being particularly pronounced in mammals. GARTNER et al[69] demonstrated the high sequence homology and similar tissue expression patterns of human and rat secretin through sequence comparison analysis, immunostaining, and immunoblotting. BASU et al[49] investigated Scgn in the brain and pituitary gland of the catfish (*Clarias batrachus*), revealing that Scgn is highly conserved evolutionarily and plays a crucial role in neuroendocrine regulation. This aligns with our findings, and such high sequence conservation indicates that Scgn has maintained its core function throughout evolution. Furthermore, variations in the conservation of EF-hand domains suggest potential adaptive evolution of Scgn proteins across species. The high conservation of EF-hand 3 to EF-hand 6, particularly the complete identity of EF-hand 6, suggests these domains perform critical and conserved functions in calcium ion binding and signaling. In contrast, the lower conservation of EF-hand 1 and EF-hand 2 suggests these regions may exhibit greater flexibility across species to adapt to diverse physiological demands. This balance between conservation and flexibility likely reflects Scgn's ability to retain core functions while adapting to specific biological requirements across different species.

3 Scgn is closely associated with multiple neuropsychiatric disorders

Scgn is a calcium-binding protein containing six EF-hand domains, widely distributed throughout the neuroendocrine system and specific regions of the central nervous system. In recent years, Scgn has been increasingly recognized as playing a crucial role in the pathogenesis and progression of various neuropsychiatric disorders due to its functions in calcium signaling regulation, neurotransmitter release, stress modulation, and intervention in protein aggregation. These disorders include AD (Alzheimer's disease), PD (Parkinson's disease), ASD (autism spectrum disorder), and SRD (stress-related disorders).

In Alzheimer's disease research, the olfactory pathway is considered one of the earliest affected regions[70]. DOTY et al[71] observed a selective reduction of a population of undifferentiated Scgn-positive bipolar neurons in the olfactory system of elderly humans during early AD stages, suggesting a potential link to early olfactory deficits. Further studies indicate that Scgn expression in the hippocampus is closely associated with tau protein pathology. MAJ et al[72] demonstrated that Scgn interacts with tau protein via a Ca^{2+}-dependent mechanism, influencing its conformational stability and aggregation tendency. CHIDANANDA et al[40] reported that Scgn functions as a calcium-dependent stress response molecule, exhibiting upregulation under thermal and oxidative stress conditions. It possesses chaperone-like properties and may participate in the pathological processes of protein aggregation disorders. ZAHOLA et al[73] systematically mapped Scgn distribution within the brainstem noradrenergic system, highlighting its expression in regions like the locus coeruleus. This finding suggests that a potential link to noradrenergic system degeneration associated with AD, indicating Scgn may contribute to the vulner-

ability of disease-related neuronal populations.

Regarding PD, Scgn also exhibits unique biological connections. LACHÉN-MONTES et al[74] identified abnormal expression of Scgn-associated networks in the olfactory bulb of PD patients through proteomics, consistent with early olfactory dysfunction in PD. More crucially, CHIDANANDA et al[2] reported that Scgn can directly bind to α-synuclein via its C-terminal region in the presence of Ca^{2+}. This interaction induces a conformational change in Scgn, stabilizing the soluble pool of α-synuclein and thereby effectively preventing its aggregation and fibrillation. Moreover, this direct interaction between Scgn and α-SNPA alters the conformation of α-SNPA, shifting it from the stable state required for membrane binding to an unstable state. Consequently, α-SNPA is prevented from binding to the membrane, thereby reducing its toxic effects on dopaminergic neurons. This function positions Scgn as a potential "chaperone-like" protein, demonstrating significant value in regulating protein homeostasis.

In the realm of neurodevelopmental disorders, Scgn has emerged as a novel risk gene for ASD. LIU et al.[48] demonstrated through integrated human mutation screening and animal model studies that Scgn loss-of-function causes social behavior deficits, hippocampal developmental abnormalities, and oxytocin signaling pathway disruption. Notably, WANG et al[61] revealed that Scgn regulates excitatory synaptic transmission and social behavior by interacting with the Doc2a protein located at 16p11.2. Disruption of this interaction axis replicates ASD-like behavioral phenotypes. The discovery of this "Scgn-Doc2a" molecular pathway expands our understanding of ASD pathogenesis.

Furthermore, in stress disorders (such as anxiety, depression, and post-traumatic stress disorder), Scgn functions as a "calcium signaling switch" within the HPA (hypothalamic-pituitary-adrenal) axis[9,53]. Romanov et al[75] confirmed that Scgn is an essential Ca^{2+} sensor for CRH neuron ACTH (adrenocorticotropic-hormone) release in the hypothalamic paraventricular nucleus. Scgn deficiency significantly reduces ACTH and corticosterone levels, impairing the endocrine response to acute stress[75]. This finding reveals that Scgn not only participates in neural function regulation but may also be involved in the neuroendocrine basis of psychiatric disorders.

In summary, Scgn, as a key calcium signaling regulator, is increasingly being revealed to have multiple roles in neurodegeneration, developmental disorders, and stress responses. It not only holds potential as an early disease biomarker but also serves as a critical target for intervening in protein aggregation, regulating synaptic function, and restoring endocrine balance. However, most current research remains confined to animal models or *in vitro* experiments. Future studies require large-scale human clinical validation and longitudinal investigations to further clarify its pathological role and therapeutic potential across various neuropsychiatric disorders.

4 Discussion

Scgn, a calcium-binding protein containing six EF-hand domains, plays a crucial role in the nervous system. Its unique molecular structure enables dual functions of calcium buffering and signal sensing, extensively participating in diverse physiological processes including neurotransmitter release, synaptic plasticity regulation, neuroendocrine activity, and neurodevelopment. Within the central nervous system, Scgn expression exhibits distinct brain region specificity and developmental stage-specificity, primarily concentrated in key areas such as the olfactory bulb, hippocampus, and hypothalamus. This suggests its critical role in learning and memory, emotional regulation, and maintaining neuroendocrine homeostasis.

In recent years, the association between Scgn and various neuropsychiatric disorders has been progressively revealed, including AD, PD, ASD, and SRD. Research indicates that Scgn exerts potential protective effects by modulating calcium signaling transduction and protein interactions, thereby alleviating neurodegenerative lesions, improving synaptic function, and regulating neural network development. However, the specific molecular mechanisms underlying Scgn's role

in these diseases require further investigation.

Overall, as a multifunctional calcium signaling regulator, Scgn plays an indispensable role in maintaining physiological functions and influencing pathological processes within the nervous system. Future research should focus on its precise functions within distinct neural circuits, disease-associated molecular mechanisms, and feasibility as a therapeutic target to advance diagnostic and treatment strategies for neurological disorders. Furthermore, Scgn's high evolutionary conservation suggests universal core functions, and cross-species studies will provide a more comprehensive perspective on its biological significance.

Research on Scgn within the nervous system has progressively revealed its multidimensional biological significance, yet existing findings still exhibit certain limitations that warrant further exploration. Nevertheless, existing findings exhibit certain characteristics and limitations warranting deeper consideration. Firstly, Scgn exhibits marked species-specific variations in distribution and function. For instance, it is widely expressed in GABAergic neurons of the human neocortex but absent in mice[76]. This suggests Scgn may be linked to the evolution of higher-order functions in primate brains, though systematic cross-species functional comparisons remain lacking. Using gene editing technology, the human Scgn gene was introduced into mouse models to observe its expression patterns and functional changes. Concurrently, brain-like organoids from both human and mouse sources were constructed to compare Scgn expression and functional differences across species. Molecular docking and AlphaFold technologies were employed to investigate Scgn's interaction networks with other proteins across species, revealing the molecular basis for functional variations. Additionally, behavioral experiments validated Scgn's role in higher-order primate functions.

Secondly, Scgn functions span both vesicle exocytosis and neurotransmitter release[24] while also participating in stress hormone regulation[27], indicating dual neuroendocrine regulatory roles. This cross-system regulatory capacity underscores Scgn's biological importance but also complicates elucidating its mechanisms. In neurodegenerative disease research, the olfactory bulb is recognized as a common "entry point" for multiple pathological processes[70]. Notably, this brain region exhibits the highest expression abundance of the calcium-binding protein Scgn throughout the entire brain[43]. Since Scgn maintains neuronal homeostasis by regulating intracellular Ca^{2+} signaling, its functional impairment can directly induce calcium imbalance[24]. Extensive research has confirmed that disrupted calcium homeostasis is a core driver of neurodegeneration in diseases like Alzheimer's and Parkinson's[77-79]. Consequently, alterations in Scgn levels or function within the olfactory bulb emerge as a pivotal molecular link connecting "localized calcium homeostasis disruption" to the onset of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases[73,80]. However, whether Scgn alterations represent causation, compensation, or a concomitant phenomenon remains difficult to distinguish and warrants further investigation.We can then utilize relevant disease models to generate mouse models, employing omics analysis methods such as transcriptomics and proteomics to conduct detailed sampling and documentation of diseased mice at different stages. Concurrently, by integrating calcium imaging technology, we can elucidate the true role of Scgn in these diseases.

Moreover, Scgn exhibits specific distribution in cognitive-emotional-endocrine core brain regions such as the olfactory bulb, hippocampus, and hypothalamus, making it a potent biomarker for distinguishing neuronal subtypes[47,81]. This raises a critical question: while serving as a biomarker, what is its true functional role? Current studies have clarified Scgn expression patterns across brain regions[82], yet its specific functional mechanisms remain unexplored. This suggests that future research should not only consider Scgn's role as a marker but also delve into its dynamic functional mechanisms within neuronal network homeostasis and synaptic plasticity. Firstly, at the cellular level, we will use gene editing technology to study the effects of Scgn knockout on synaptic transmission and synaptic

plasticity through electrophysiological recordings. Secondly, we will employ calcium imaging to observe dynamic signal changes in Scgn-positive neurons *in vivo*, validating their function through optogenetic stimulation. Next, we can use optogenetics and chemogenetics to specifically manipulate Scgn-positive neurons and observe their impact on individual behavior. Finally, we will employ immunofluorescence to visualize the dynamic expression patterns of Scgn in wild-type mice. These experiments will contribute to a deeper understanding of the dynamic functional mechanisms of Scgn in neuronal network homeostasis and synaptic plasticity.

In summary, Scgn research is transitioning from "descriptive discovery" to "mechanistic explanation" and "clinical translation." While descriptive findings regarding Scgn's expression patterns and evolutionary conservation are relatively well-established, its specific functions within particular tissues remain unclear. The physiological roles and mechanisms underlying Scgn's evolutionary variations across species require further investigation. Additionally, although Scgn is currently associated with numerous neuropsychiatric disorders, its causal effects and temporal relationships remain undefined.

Future research should advance in three key areas: Firstly, utilize cross-species comparisons and multi-omics technologies to further elucidate its functional counterparts across species. Secondly, conduct experiments to clarify its specific mechanisms within the nervous system. Thirdly, explore its causal role and intervention potential in neurodegenerative diseases and psychiatric disorders. Multifaceted research is essential for understanding Scgn's role in the nervous system.

参考文献 (References)

[1] TU Y, QIN J, ZHANG Q M, et al. Secretagogin regulates asynchronous and spontaneous glutamate release in hippocampal neurons through interaction with Doc2α [J]. Life Med, 2023, 2(5): lnad041.

[2] CHIDANANDA A H, SHARMA A K, KHANDELWAL R, et al. Secretagogin binding prevents α-Synuclein fibrillation [J]. Biochemistry, 2019, 58(46): 4585-9.

[3] HANICS J, TRETIAKOV E O, ROMANOV R A, et al. Neuronal activity modulates the expression of secretagogin, a Ca^{2+} sensor protein, during mammalian forebrain development [J]. Acta Physiol (Oxf), 2025, 241(5): e70031.

[4] BADING H. Therapeutic targeting of the pathological triad of extrasynaptic NMDA receptor signaling in neurodegenerations [J]. J Exp Med, 2017, 214(3): 569-78.

[5] TÖNNIES E, TRUSHINA E. Oxidative stress, synaptic dysfunction, and Alzheimer's disease [J]. J Alzheimers Dis, 2017, 57(4): 1105-21.

[6] BRINI M, CARAFOLI E. Calcium signalling: a historical account, recent developments and future perspectives [J]. Cell Mol Life Sci, 2000, 57(3): 354-70.

[7] SCHWALLER B. Cytosolic Ca^{2+} buffers [J]. Cold Spring Harb Perspect Biol, 2010, 2(11): a004051.

[8] WAGNER L, OLIYARNYK O, GARTNER W, et al. Cloning and expression of secretagogin, a novel neuroendocrine- and pancreatic islet of Langerhans-specific Ca^{2+}-binding protein [J]. J Biol Chem, 2000, 275(32): 24740-51.

[9] MAJ M, WAGNER L, TRETTER V. 20 years of secretagogin: exocytosis and beyond [J]. Front Mol Neurosci, 2019, 12: 29.

[10] ALPÁR A, ATTEMS J, MULDER J, et al. The renaissance of Ca^{2+}-binding proteins in the nervous system: secretagogin takes center stage [J]. Cell Signal, 2012, 24(2): 378-87.

[11] KUMAR D, SHARMA A, SHARMA L. A comprehensive review of Alzheimer's association with related proteins: pathological role and therapeutic significance [J]. Curr Neuropharmacol, 2020, 18(8): 674-95.

[12] ATTEMS J, ALPAR A, SPENCE L, et al. Clusters of secretagogin-expressing neurons in the aged human olfactory tract lack terminal differentiation [J]. Proc Natl Acad Sci USA, 2012, 109(16): 6259-64.

[13] SHI T J, XIANG Q, ZHANG M D, et al. Secretagogin is expressed in sensory CGRP neurons and in spinal cord of mouse and complements other calcium-binding proteins, with a note on rat and human [J]. Mol Pain, 2012, 8: 80.

[14] KRETSINGER R H, NOCKOLDS C E. Carp muscle calcium-binding protein. II. Structure determination and general description [J]. J Biol Chem, 1973, 248(9): 3313-26.

[15] GIFFORD J L, WALSH M P, VOGEL H J. Structures and metal-ion-binding properties of the Ca^{2+}-binding helix-loop-helix EF-hand motifs [J]. Biochem J, 2007, 405(2): 199-221.

[16] DENESSIOUK K, PERMYAKOV S, DENESYUK A, et al. Two structural motifs within canonical EF-hand calcium-binding domains identify five different classes of calcium buffers and sensors [J]. PLoS One, 2014, 9(10): e109287.

[17] AIRAKSINEN M S, EILERS J, GARASCHUK O, et al. Ataxia and altered dendritic calcium signaling in mice carrying a targeted null mutation of the calbindin D28k gene [J]. Proc Natl Acad Sci USA, 1997, 94(4): 1488-93.

[18] CHIN D, MEANS A R. Calmodulin: a prototypical calcium sensor [J]. Trends Cell Biol, 2000, 10(8): 322-8.

[19] BAGUR R, HAJNÓCZKY G. Intracellular Ca^{2+} sensing: its role in calcium homeostasis and signaling [J]. Mol Cell, 2017, 66(6): 780-8.

[20] KHALEEL Z H, NO Y H, KIM N H, et al. Design of a light and Ca^{2+} switchable organic-peptide hybrid [J]. Proc Natl Acad Sci

USA, 2025, 122(5): e2411316122.
[21] VILLALOBO A, BERCHTOLD M W. The role of calmodulin in tumor cell migration, invasiveness, and metastasis [J]. Int J Mol Sci, 2020, 21(3): 765.
[22] MIKHAYLOVA M, HRADSKY J, KREUTZ M R. Between promiscuity and specificity: novel roles of EF-hand calcium sensors in neuronal Ca^{2+} signalling [J]. J Neurochem, 2011, 118(5): 695-713.
[23] BAKSHEEVA V E, BALDIN A V, ZALEVSKY A O, et al. Disulfide dimerization of neuronal calcium Sensor-1: implications for Zinc and Redox signaling [J]. Int J Mol Sci, 2021, 22(22): 12602.
[24] QIN J, LIU Q, LIU Z, et al. Structural and mechanistic insights into secretagogin-mediated exocytosis [J]. Proc Natl Acad Sci USA, 2020, 117(12): 6559-70.
[25] JUMPER J, EVANS R, PRITZEL A, et al. Highly accurate protein structure prediction with AlphaFold [J]. Nature, 2021, 596(7873): 583-9.
[26] FLEMING J, MAGANA P, NAIR S, et al. AlphaFold protein structure database and 3D-Beacons: new data and capabilities [J]. J Mol Biol, 2025, 437(15): 168967.
[27] ROMANOV R A, ALPÁR A, ZHANG M D, et al. A secretagogin locus of the mammalian hypothalamus controls stress hormone release [J]. EMBO J, 2015, 34(1): 36-54.
[28] MULDER J, SPENCE L, TORTORIELLO G, et al. Secretagogin is a Ca^{2+}-binding protein identifying prospective extended amygdala neurons in the developing mammalian telencephalon [J]. Eur J Neurosci, 2010, 31(12): 2166-77.
[29] BITTO E, BINGMAN C A, BITTOVA L, et al. X-ray structure of *Danio rerio* secretagogin: a hexa-EF-hand calcium sensor [J]. Proteins, 2009, 76(2): 477-83.
[30] KAWASAKI H, KRETSINGER R H. Structural and functional diversity of EF-hand proteins: evolutionary perspectives [J]. Protein Sci, 2017, 26(10): 1898-920.
[31] BAUER M C, O'CONNELL D J, MAJ M, et al. Identification of a high-affinity network of secretagogin-binding proteins involved in vesicle secretion [J]. Mol Biosyst, 2011, 7(7): 2196-204.
[32] KIESSLING V, KREUTZBERGER A J B, LIANG B, et al. A molecular mechanism for calcium-mediated synaptotagmin-triggered exocytosis [J]. Nat Struct Mol Biol, 2018, 25(10): 911-7.
[33] TRAN H T, ANDERSON L H, KNIGHT J D. Membrane-binding cooperativity and coinsertion by C2AB tandem domains of synaptotagmins 1 and 7 [J]. Biophys J, 2019, 116(6): 1025-36.
[34] WANG S, LI Y, MA C. Synaptotagmin-1 C2B domain interacts simultaneously with SNAREs and membranes to promote membrane fusion [J]. eLife, 2016, 5: e14211.
[35] BENDAHMANE M, BOHANNON K P, BRADBERRY M M, et al. The synaptotagmin C2B domain calcium-binding loops modulate the rate of fusion pore expansion [J]. Mol Biol Cell, 2018, 29(7): 834-45.
[36] ROGSTAM A, LINSE S, LINDQVIST A, et al. Binding of calcium ions and SNAP-25 to the hexa EF-hand protein secretagogin [J]. Biochem J, 2007, 401(1): 353-63.
[37] SÜDHOF T C. Calcium control of neurotransmitter release [J]. Cold Spring Harb Perspect Biol, 2012, 4(1): a011353.
[38] CHAPMAN E R. How does synaptotagmin trigger neurotransmitter release [J]? Annu Rev Biochem, 2008, 77: 615-41.
[39] KAESER P S, REGEHR W G. Molecular mechanisms for synchronous, asynchronous, and spontaneous neurotransmitter release [J]. Annu Rev Physiol, 2014, 76: 333-63.
[40] CHIDANANDA A H, KHANDELWAL R, JAMKHINDIKAR A, et al. Secretagogin is a Ca^{2+}-dependent stress-responsive chaperone that may also play a role in aggregation-based proteinopathies [J]. J Biol Chem, 2022, 298(9): 102285.
[41] TÉLLEZ DE MENESES P G, PÉREZ-REVUELTA L, CANAL-ALONSO Á, et al. Immunohistochemical distribution of secretagogin in the mouse brain [J]. Front Neuroanat, 2023, 17: 1224342.
[42] HANICS J, SZODORAI E, TORTORIELLO G, et al. Secretagogin-dependent matrix metalloprotease-2 release from neurons regulates neuroblast migration [J]. Proc Natl Acad Sci USA, 2017, 114(10): e2006-15.
[43] PÉREZ-REVUELTA L, TÉLLEZ DE MENESES P G, LÓPEZ M, et al. Secretagogin expression in the mouse olfactory bulb under sensory impairments [J]. Sci Rep, 2020, 10(1): 21533.
[44] TAPIA-GONZÁLEZ S, INSAUSTI R, DEFELIPE J. Differential expression of secretagogin immunostaining in the hippocampal formation and the entorhinal and perirhinal cortices of humans, rats, and mice [J]. J Comp Neurol, 2020, 528(4): 523-41.
[45] GEZELIUS H, MORENO-JUAN V, MEZZERA C, et al. Genetic labeling of nuclei-specific thalamocortical neurons reveals putative sensory-modality specific genes [J]. Cereb Cortex, 2017, 27(11): 5054-69.
[46] KIM J Y, PAREDES M F. Implications of extended inhibitory neuron development [J]. Int J Mol Sci, 2021, 22(10): 5113.
[47] TAPIA-GONZÁLEZ S, DEFELIPE J. Secretagogin as a marker to distinguish between different neuron types in human frontal and temporal cortex [J]. Front Neuroanat, 2023, 17: 1210502.
[48] LIU Z, TAN S, ZHOU L, et al. SCGN deficiency is a risk factor for autism spectrum disorder [J]. Signal Transduct Target Ther, 2023, 8(1): 3.
[49] BASU S, MITRA S, SINGH O, et al. Secretagogin in the brain and pituitary of the catfish, *Clarias batrachus*: molecular characterization and regulation by insulin [J]. J Comp Neurol, 2022, 530(11): 1743-72.
[50] VÉLEZ E J, UNNIAPPAN S. A comparative update on the neuroendocrine regulation of growth hormone in vertebrates [J]. Front Endocrinol, 2020, 11: 614981.
[51] ALZU'BI A, CLOWRY G J. Multiple origins of secretagogin expressing cortical GABAergic neuron precursors in the early human fetal telencephalon [J]. Front Neuroanat, 2020, 14: 61.
[52] NASCIMENTO M A, BIAGIOTTI S, HERRANZ-PÉREZ V, et al. Protracted neuronal recruitment in the temporal lobes of young children [J]. Nature, 2024, 626(8001): 1056-65.
[53] ALPÁR A, ZAHOLA P, HANICS J, et al. Hypothalamic CNTF volume transmission shapes cortical noradrenergic excitability upon acute stress [J]. EMBO J, 2018, 37(21): e10087.
[54] ZEISEL A, HOCHGERNER H, LÖNNERBERG P, et al. Molecular architecture of the mouse nervous system [J]. Cell, 2018, 174(4): 999-1014,e22.
[55] POZZI D, CORRADINI I, MATTEOLI M. The control of neuronal calcium homeostasis by SNAP-25 and its impact on neurotransmitter release [J]. Neuroscience, 2019, 420: 72-8.

[56] MULDER J, ZILBERTER M, SPENCE L, et al. Secretagogin is a Ca^{2+}-binding protein specifying subpopulations of telencephalic neurons [J]. Proc Natl Acad Sci USA, 2009, 106(52): 22492-7.

[57] ROMANOV R A, ZEISEL A, BAKKER J, et al. Molecular interrogation of hypothalamic organization reveals distinct dopamine neuronal subtypes [J]. Nat Neurosci, 2017, 20(2): 176-88.

[58] SZODORAI E, HEVESI Z, WAGNER L, et al. A hydrophobic groove in secretagogin allows for alternate interactions with SNAP-25 and syntaxin-4 in endocrine tissues [J]. Proc Natl Acad Sci USA, 2024, 121(16): e2309211121.

[59] MERINEY S D, UMBACH J A, GUNDERSEN C B. Fast, Ca^{2+}-dependent exocytosis at nerve terminals: shortcomings of SNARE-based models [J]. Prog Neurobiol, 2014, 121: 55-90.

[60] YEO X Y, LIM Y T, CHAE W R, et al. Alterations of presynaptic proteins in autism spectrum disorder [J]. Front Mol Neurosci, 2022, 15: 1062878.

[61] WANG Q W, QIN J, CHEN Y F, et al. 16p11.2 CNV gene Doc2α functions in neurodevelopment and social behaviors through interaction with Secretagogin [J]. Cell Rep, 2023, 42(7): 112691.

[62] LEONE R, ZUGLIAN C, BRAMBILLA R, et al. Understanding copy number variations through their genes: a molecular view on 16p11.2 deletion and duplication syndromes [J]. Front Pharmacol, 2024, 15: 1407865.

[63] CHUNG C, GIRGISS J, GLEESON J G. A comparative view of human and mouse telencephalon inhibitory neuron development [J]. Development, 2025, 152(1): dev204306.

[64] GYENGESI E, ANDREWS Z B, PAXINOS G, et al. Distribution of secretagogin-containing neurons in the basal forebrain of mice, with special reference to the cholinergic corticopetal system [J]. Brain Res Bull, 2013, 94: 1-8.

[65] ATTEMS J, ITTNER A, JELLINGER K, et al. Reduced secretagogin expression in the hippocampus of P301L tau transgenic mice [J]. J Neural Transm, 2011, 118(5): 737-45.

[66] YANG S Y, LEE J J, LEE J H, et al. Secretagogin affects insulin secretion in pancreatic β-cells by regulating actin dynamics and focal adhesion [J]. Biochem J, 2016, 473(12): 1791-803.

[67] DE FELICE F G, VIEIRA M N, BOMFIM T R, et al. Protection of synapses against Alzheimer's-linked toxins: insulin signaling prevents the pathogenic binding of Abeta oligomers [J]. Proc Natl Acad Sci USA, 2009, 106(6): 1971-6.

[68] GYENGESI E, PAXINOS G, ANDREWS Z B. Oxidative stress in the hypothalamus: the importance of calcium signaling and mitochondrial ROS in body weight regulation [J]. Curr Neuropharmacol, 2012, 10(4): 344-53.

[69] GARTNER W, VILA G, DANEVA T, et al. New functional aspects of the neuroendocrine marker secretagogin based on the characterization of its rat homolog [J]. Am J Physiol Endocrinol Metab, 2007, 293(1): e347-54.

[70] MOON H S, HAN Z Y, ANDERSON R J, et al. Olfactory-guided behavior uncovers imaging and molecular signatures of Alzheimer's disease risk [J]. Brain Sci, 2025, 15(8): 863.

[71] DOTY R L. Olfactory dysfunction in neurodegenerative diseases: is there a common pathological substrate [J]? Lancet Neurol, 2017, 16(6): 478-88.

[72] MAJ M, GARTNER W, ILHAN A, et al. Expression of TAU in insulin-secreting cells and its interaction with the calcium-binding protein secretagogin [J]. J Endocrinol, 2010, 205(1): 25-36.

[73] ZAHOLA P, HANICS J, PINTÉR A, et al. Secretagogin expression in the vertebrate brainstem with focus on the noradrenergic system and implications for Alzheimer's disease [J]. Brain Struct Funct, 2019, 224(6): 2061-78.

[74] LACHÉN-MONTES M, GONZÁLEZ-MORALES A, ILORO I, et al. Unveiling the olfactory proteostatic disarrangement in Parkinson's disease by proteome-wide profiling [J]. Neurobiol Aging, 2019, 73: 123-34.

[75] ROMANOV R A, ALPÁR A, HÖKFELT T, et al. Molecular diversity of corticotropin-releasing hormone mRNA-containing neurons in the hypothalamus [J]. J Endocrinol, 2017, 232(3): r161-72.

[76] RAJU C S, SPATAZZA J, STANCO A, et al. Secretagogin is expressed by developing neocortical gabaergic neurons in humans but not mice and increases neurite arbor size and complexity [J]. Cereb Cortex, 2018, 28(6): 1946-58.

[77] ALVAREZ J, ALVAREZ-ILLERA P, GARCÍA-CASAS P, et al. The role of Ca^{2+} signaling in aging and neurodegeneration: insights from caenorhabditis elegans models [J]. Cells, 2020, 9(1): 204.

[78] BORBOLIS F, PLOUMI C, PALIKARAS K. Calcium-mediated regulation of mitophagy: implications in neurodegenerative diseases [J]. NPJ Metab Health Dis, 2025, 3(1): 4.

[79] SCHRANK S, BARRINGTON N, STUTZMANN G E. Calcium-handling defects and neurodegenerative disease [J]. Cold Spring Harb Perspect Biol, 2020, 12(7): a035212.

[80] UBEDA-BAÑON I, SAIZ-SANCHEZ D, FLORES-CUADRADO A, et al. The human olfactory system in two proteinopathies: Alzheimer's and Parkinson's diseases [J]. Transl Neurodegener, 2020, 9(1): 22.

[81] GARAS F N, SHAH R S, KORMANN E, et al. Secretagogin expression delineates functionally-specialized populations of striatal parvalbumin-containing interneurons [J]. eLife, 2016, 5: e16088.

[82] 刘琴, 来茂德. 促泌素蛋白的分布和功能[J]. 浙江大学学报(医学版)(LIU Q, LAI M D. Location and functions of secretagogin protein [J]. Journal of Zhejiang University, Medical Sciences), 2016, 45(1): 56-60.