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Current Dilemma on Granin Proteins: Proteins Involved in Various Cellular Functions without Known Mechanisms

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Mini Review

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Regulated secretion empowers stimulus-controlled release of bioactive molecules in all endocrine cells. Chromogranins are known to play an important role in all the steps of the regulated secretion *viz.* granulogenesis, acidification and maturation of granular matrix of the secretory cells. Over-expression of the granin proteins in the non-secretory cells can induce granulogenesis. Chromogranins modulates the open probability of the IP3Rs (IP_3 Receptor type 1) with several folds and hence involved in the calcium homeostasis, involved in the cargo maturation and are processed by prohormone convertase to produce multiple bioactive peptides. Thought researcher accumulated plenty of data about their functional involment in different processes but how chromogranins facilitate these functions is still a point of discussion. In this mini review we are going to discuss about the current perspective of the Chromogranins and the lack of the complete information about their mode of involment in different cellular functions.

Chromogranins are first identified in the mid of 1960s in the chromaffin granules that were aimed to study the physiology of the catecholamine in mammals [1,2]. The name Chromogranin was proposed by the Schneider, et al. in 1967 [3]. First member of the family was chromogranin A followed by other members of the family as chromogranin B (SgI), Chromogranin C (SgII), 1B1075, HISL-19, 7B2 and NESP55. The Chromogranins are distributed ubiquitously regulated secretory pathway of the endocrine, neuroendocrine and neuronal cells [3-10]. Primary structure analysis demonstrates that granins are acidic in nature and encompasses many pairs of the basic amino acids which are potential cutting sites for the prohormone convertases in the acidic environment.

Chromogranins A and B involved in secretory granule biogenesis of secretory cells [11-13]. Immunostaining studies have demonstrated the granulogenic roles of chromogranins in both neuroendocrine and endocrine cells [12]. Expression of the granins in non-neuroendocrine cells, such as NIH3T3 or COS cells that do not normally contain secretory granules, induce formation of secretory granules in these cells, whereas suppression of granin expression in neuroendocrine cells substantially reduce the number of secretory granules formed in these cells [11-13]. It was initially reported that only CHGA, but not CHGB, is capable of inducing granule formations [13], which was proved to be wrong in later studies [11,13]. The granulogenic capability of CHGB is, in fact, shown to be greater than that of CGA in certain conditions [12]. All these studies are based on the suppression/knockout of the specific granin protein in the particular secretory cells or animals. The granulogenic function of the chromogranin was specific for the cells types. Due to that it was difficult to generalize even though it is true for many cases. The research to explain the mechanism involved the in granulogenic function of the Chromogranin proteins has not been focused yet.

The calcium was highly concentrated in the secretory granules which was thought to be because of the presence of large content of acidic chromogranins that have a high-capacity, low-affinity Ca^{2+}-binding ability. Chromogranin A binds 32–55 mol of Ca^2/mol, with dissociation constants (Kd) of 2.7–4 mM [14], whereas chromogranin B binds 50–93 mol of Ca^2/mol, with Kd of 1.5–3.1 mM [15,16]. As a result, most (99.9%) of the intragranular

calcium stays bound to chromogranins [14,17-21]. Chromogranins are also known to bind catecholamines [22] and ATP [23] that exist in secretory granules at 600 mM and 150 mM, respectively [24,25]. Chromogranin A is reported to bind 32 mol of norepinephrine/mol, with a Kd of 2.1 mM [22]. The intragranular content released from the chromaffin cells of CHGA-knockout mice, were shown to be reduced 30% [26], suggesting the role of chromogranin A in the storage of catecholamines. It was also shown that chromogranin interacts with ATP through the adenine base of the nucleotide [23]. The IP3Rs are calcium release channels in the secretory granules. It was shown that chromogranins A and B bind to the IP3R and modulates its activity at low pH values [27], increasing the open probability of the channels 8- to 16-fold and the mean open time 9- to 42-fold [28,29]. At physiological pH, CHGA fails to bind the receptor while CHGB still can bind and modulates it activity [27-29], suggesting critical roles played by chromogranins in both storage and flux of the intragranular calcium through the IP3R/Ca^{2+} channels [30]. The binding of calcium to the chromogranins was reported by many studies based on the presence of high contents of the negatively charged amino acids but direct evidence that how chromogranins are involved in the storage of the high amount of the calcium. The interaction of the chromogranins (CHGA & CHGB) was based on the pull down assay but the interaction was very week [31] and also we are not able to repeat these results in our laboratory. So it might possible that chromogranins did not interact directly to the IP3Rs or interactions were transient so almost impossible to form the complex once they are purified from the cells. Thought chromogranins modulates IP3Rs channels which were reported by multiple studies.

After exocytosis i.e. after release from the secretory granules, chromogranins further employed in an important physiological function. Large amounts of the chromogranins are released in the blood stream. The secreted chromogranins serve as the source of the many bioactive peptides, including catestatin, vasostatin, pancreastatin, and secretoneurin, that circulate in the bloodstream [32-40]. Among a variety of functions that are attributed to these peptides, catestatin and vasostatin are known to control the release of catecholamines [32,33] and blood vessel dilation [34,36], respectively, whereas pancreastatin and secretoneurin are known to reduce glucose metabolism [38] and to potentiate angiogenesis [36,37], respectively. Recently, Alexendra, et al. [42] reported the association of chromogranin A with gut microbiome. According to their data chromogranin A was exclusively associated with 61 microbial species whose abundance was ~ 53% of the microbials present in the gut microbiome. As usual this study also lacks the molecular mechanism underlying the association of the CHGA with gut microbiome.

The granin proteins reviewed here share many structural and biochemical features. Most of the members contribute to very diverse functions within the regulated secretory pathway of endocrine and neuronal cells. Chromogranin-derived peptides provide autocrine, paracrine, and endocrine signals, with a range of bioactivities. Characterization of KO mouse models in preclinical studies and human genetic analyses suggests important functional roles and specific disease associations of granin peptides. Relatively abundant and selective expression of these secreted proteins in the nervous system and in endocrine and neuroendocrine tissues has led to their increased utility as biomarkers of disease and therapeutic efficacy. The main challenges moving forward will be to identify the molecular mechanisms underlying different cellular functions of the chromogranins. First step towards understanding the molecular mechanism of the granins is to elucidate their structure under different conditions as in the presence of the Calcium, at low pH values, in the presence of the lipids or in association with membrane and in complex with different proposed interacting proteins (IP3Rs and CPE).

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