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Granins and their derived peptides in normal and tumoral chromaffin tissue: Implications for the diagnosis and prognosis of pheochromocytoma

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ABSTRACT

Pheochromocytomas are rare catecholamine-secreting tumors that arise from chromaffin tissue within the adrenal medulla and extra-adrenal sites. Typical clinical manifestations are sustained or paroxysmal hypertension, severe headaches, palpitations and sweating resulting from hormone excess. However, their presentation is highly variable and can mimic many other diseases. The diagnosis of pheochromocytomas depends mainly upon the demonstration of catecholamine excess by 24-h urinary catecholamines and metanephrines or plasma metanephrines. Occurrence of malignant pheochromocytomas can only be asserted by imaging of metastatic lesions, which are associated with a poor survival rate. The characterization of tissue, circulating or genetic markers is therefore crucial for the management of these tumors. Proteins of the granin family and their derived peptides are present in dense-core secretory vesicles and secreted into the bloodstream, making them useful markers for the identification of neuroendocrine cells and neoplasms. In this context, we will focus here on reviewing the distribution and characterization of granins and their processing products in normal and tumoral chromaffin cells, and their clinical usefulness for the diagnosis and prognosis of pheochromocytomas. It appears that, except SgIII, all members of the granin family *i.e.* CgA, CgB, SgII, SgIV–SgVII and proSAAS, and most of their derived peptides are present in adrenomedullary chromaffin cells and in pheochromocytes. Moreover, besides the routinely used CgA test assays, other assays have been developed to measure concentrations of tissue and/or circulating granins or their derived peptides in order to detect the occurrence of pheochromocytomas. In most cases, elevated levels of these entities were found, in correlation with tumor occurrence, while rarely discriminating between benign and malignant neoplasms. Nevertheless, measurement of the levels of granins and derived peptides improves the diagnostic sensitivity and may therefore provide a complementary tool for the management of pheochromocytomas. However, the existing data need to be substantiated in larger groups of patients, particularly in the case of malignant disease.

Contents

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1. Introduction

The granin proteins are widely distributed in secretory granules of endocrine, neuroendocrine and nerve cells [1–3], and have also been described in other secreting cells like exocrine cells, cardiomyocytes or immune system cells [4–6]. At present, the granin family can loosely be divided into two groups, the chromogranins (Cg) and the secretogranins (Sg), distinguishable by the presence of a disulfide-bonded loop at the N-terminus of Cg but not in Sg proteins [7,8]. They constitute a family of acidic glycoproteins whose major members are chromogranin A (CgA), which was first isolated from chromaffin cells of the adrenal medulla [9]; chromogranin B (CgB, previously also called secretogranin I), initially characterized in a rat pheochromocytoma cell line [10]; and secretogranin II (SgII, previously also called chromogranin C), which was originally described in the anterior pituitary [11]. The granin family has further expanded to include other members such as secretogranin III (SgIII or 1B1075) [12], secretogranin IV (SgIV or HISL-19) [13], secretogranin V (SgV or 7B2) [14], secretogranin VI (SgVI or NESP55) [15], secretogranin VII (SgVII or VGF) [8,16] and proSAAS [17].

Granins are characterized by a high proportion of acidic amino acids (aspartic and glutamic acids) that confers the acidic nature of these proteins. This property enables them to play a role in the formation of secretory vesicles and sequestration of hormones in neuroendocrine cells [18–20]. In addition, granins encompass in their sequence numerous pairs of basic amino acids which are potential cleavage sites for prohormone convertases and which may give rise to bioactive peptides through post-translational proteolytic processing. Indeed, numerous studies have shown that peptides derived from granin maturation occur in various tissues and exhibit autocrine, paracrine, or endocrine activities [21,22]. The ubiquitous distribution of granins in endocrine and neuroendocrine tissues from which they are secreted into the bloodstream, makes granins useful markers of normal and tumoral neuroendocrine cells. In fact, multiple studies have documented the clinical value of detecting granins and their derived peptides in tissues and measuring their circulating levels [7]. In particular, measurement of CgA levels in plasma can be used to diagnose or monitor the progression of neuroendocrine tumors [23]. The highest accuracy has been observed in tumors characterized by an intense secretory activity, although the specificity and sensitivity remain high also in non-functioning tumors [24].

Among neuroendocrine tumors, pheochromocytomas are rare catecholamine-producing neoplasms primarily (80–85%) arising from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia (Fig. 1). Tumors from extra-adrenal location are referred to as paragangliomas. Most of pheochromocytomas occur sporadically but approximately 25% result from germline mutations in 6 genes identified to date. Mutations of the VHL tumor suppressor gene predispose to the development of von Hippel–Lindau (VHL) syndrome, those of NF1 gene to von Recklinghausen's syndrome, and those of the RET proto-oncogene to multiple endocrine neoplasia (MEN) type 2A and 2B [25]. More recently, mutations identified in genes encoding succinate dehydrogenase (SDH) subunits B, C and D have been shown to predispose to familial paraganglioma syndromes [26]. Clinical presentation of pheochromocytoma can vary greatly, with similar signs and symptoms produced by many other clinical conditions. Most but not all the clinical manifestations of pheochromocytoma are due to the indirect actions of secreted catecholamines. Hypertension, tachycardia, pallor, headache and feeling of panic or anxiety, usually dominate the clinical presentation. Metabolic effects include hyperglycemia, lactic acidosis and weight loss. Less common signs and symptoms are nausea, fever and flushing [27]. Despite the increasing availability of molecular diagnostic and prognostic markers, it remains impossible to predict the development of malignant disease, based on histological findings in a resected tumor. Only the presence of metastases of tumoral chromaffin tissue establishes a definite diagnosis of malignant pheochromocytoma [27,28]. It should be noted that the incidence of pheochromocytomas is only 2–8 cases per 1,000,000 subjects and that malignant pheochromocytomas only represent about 10% of all pheochromocytomas.

In this review, we have explored the literature concerning the occurrence of granins in normal and tumoral chromaffin cells, and the

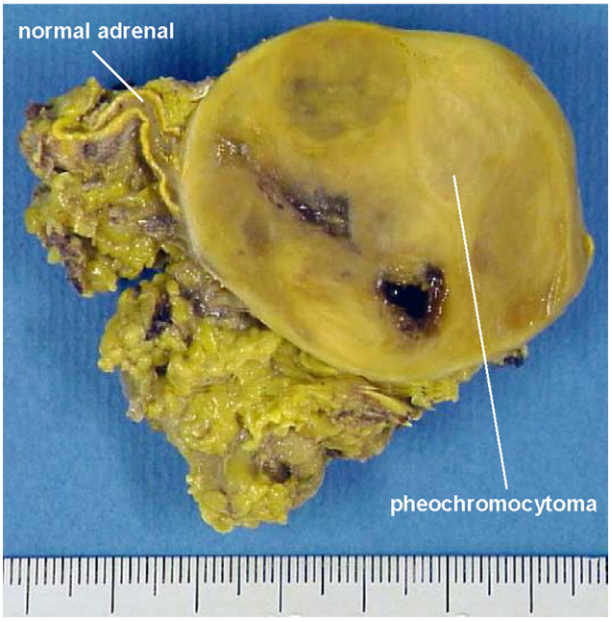

Fig. 1. Macroscopic photography of a pheochromocytoma.