Chapter

Introductory Chapter: Neural Crest Cell-Derived Tumors. An Introduction on Pheocromocytoma, Paraganglyoma and Neuroblastoma

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1. Introduction

In the embryonic period, the nervous system originates from a layer of ectodermal cells which is called neuroectoderm. The neuroectoderm extends along the axis of the body to form the neural plate. The latter, turns inward and surrounds itself of neural folds, which then merge together giving life to the neural tube that will develop all the components of the central nervous system and the spinal cord. Finally, from the posterior portion of the neural tube, specialized cells will separate to form the neural crest. Various differentiated cell types, tissues and organs develop from neural crest cells, the mechanisms for this are not well known. However, these cells are multipotent and their subsequent specialization it could be conditioned by the activity of particular genes and by the microenvironment into which they migrate [1]. Hence, neural crest cells have a multipotent differentiation potential. From these cells originate neurons and glial cells, melanocytes, Schwann cells, parafollicular cells of the thyroid, cells of the adrenal medulla, endothelial cells of large vessels and some components of the connective and skeletal tissue of the head [2] (**Figure 1**). Based on these concepts, the tumors that develop from the cells of the neural crest represent a very varied and heterogeneous group of neoplasms, these can affect different body locations where the neural crest cells-derived are normally present. However, neural crest stem cells are also present in some adult tissues that normally do not originate from the neural crest, such as skin and bone marrow [3]. Heterogeneity of tumors originating from neural crest cells is confirmed by the fact that some of them can arise in both peripheral sites or in the central nervous system, while others are specific to the central nervous system or affect only other peripheral locations. Neural crest cell-derived tumors can be grouped into: tumors of peripheral and cranial nerves, melanocytic tumors, peripheral neuroblastic tumors, embryonal tumors of the central nervous system, paraganglioma group, and other tumors of neural crest origin. Most of these are sporadic, some can be hereditary (hereditary paraganglioma-pheochromocytoma syndrome, von Hippel–Lindau disease, neurofibromatosis, schwannomatosis, and multiple neuroendocrine neoplasia (MEN I). Pheochromocytoma/Paraganglyoma

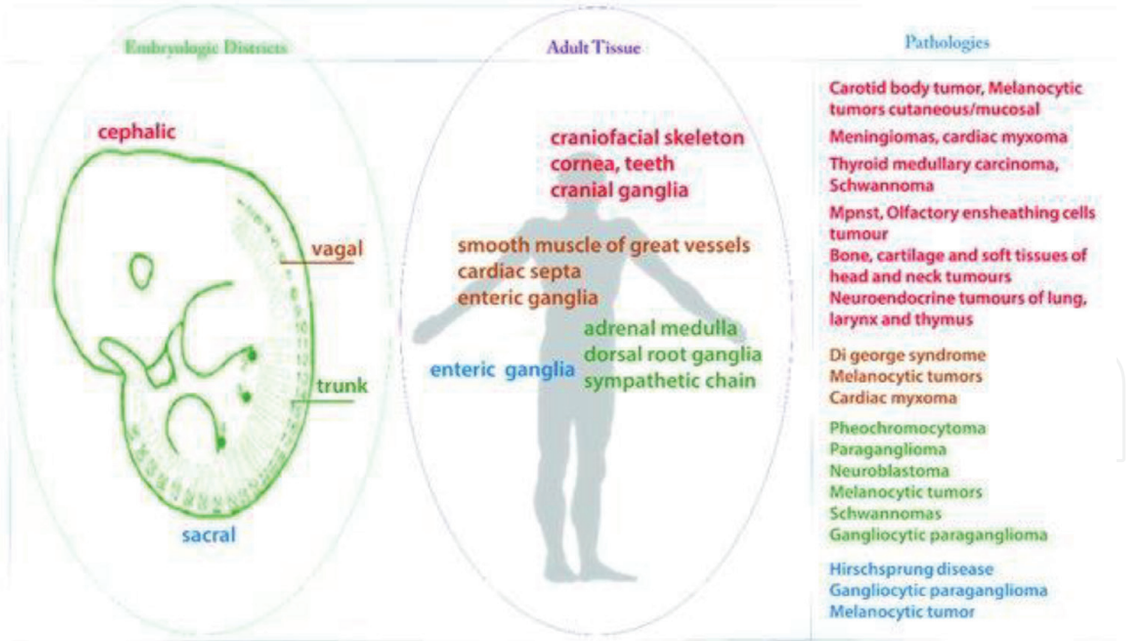

Figure 1.
Segments of neural crest with relative adult tissues and pathologies derivate [2].

and neuroblastoma are the most common neural crest-derived tumors in adults and children, respectively. These neoplasm are both associated with significant morbidity and mortality.

2. Sympatho-adrenal lineage neoplasms

Neural crest cell-derived of the truncal area after a ventral migration reach the vertebral parasympathetic ganglia of the trunk and the chromaffin cells secreting catecholamines of the adrenal medulla and paraganglia [4, 5]. Tumors arising from the cell line involving the sympathetic ganglia can have variable aggressiveness, they can develop from neuroblastomas to ganglioneuromas. Pheochromocytomas and paragangliomas are tumors that develop from neural crest cells that have migrated into the adrenal medulla and paraganglia, they can occur sporadically or within familial syndromes.

2.1 Neuroblastoma

Neuroblastoma is the most frequent extracranial malignancy in children, accounting for 8–10% of pediatric malignancy and with a mortality of 15%. About 38% of primary tumors are located in the adrenal medulla and 1–2% of newly diagnosed neuroblastomas are related to the family history of the disease [6]. At diagnosis, 50% of patients present with lymph node, liver, cortical bone and bone marrow metastases. Due to the presence of an expanding mass, compression of nearby vascular and neuronal structures may occur. The disease can also manifest itself with paraneoplastic syndromes including opsoclonus-myoclonus and intractable watery diarrhea, due to autoimmune cerebellar destruction or production of vasoactive intestinal peptide, respectively [6]. The prognosis is varied, ranging from spontaneous regressions of the disease, neuroblastoma can change into more differentiated ganglioneuromas or have a clearly aggressive course with poor survival [7]. Tumor regression is an unknown process, but may be due to expression of the nerve growth factor (NGF) receptor TrkA, which promotes differentiation in

the presence of NGF and apoptosis in its absence, as described below. Familial type of neuroblastoma is quite rare, it is associated with mutated PHOX2B. Its sporadic form is also frequently associated with the mutated PHOX2B, but the most significant lesion is MYCN amplification. The molecular and genetic characteristics of neuroblastoma are complex and are responsible for the clinical course and prognosis of the disease. The presence of MYCN amplification, chromosomal abnormalities, DNA ploidy, degree of stromal differentiation, tumor stage, and patient age all impacting outcome [8, 9]. This tumor characterized by a remarkable plasticity and by its wide spectrum of presentation remains a stimulating and fascinating subject for both doctors and researchers who deal with it in a specialized way.

2.2 Pheocromocytoma and paraganglioma

Pheochromocytoma and paraganglioma (PPGL) have a prevalence in autopsy studies of 0.05%, which indicates that during the life of many people it is not diagnosed [10, 11]. Amar in 2005 reports an average delay in diagnosis of about 3 years [12]. Their prevalence varies from 0.2% to 0.6% in hypertensive patients to less than 0.05% in the general population, with an annual incidence of about 5 cases per million per year. Two recent retrospective series reported that two thirds were discovered as incidentalomas [13, 14]. PPGL are tumors originating from tissues arising from the neural crest respectively in the paraxial autonomic ganglia or in the chromaffin cells of the adrenal medulla, these tumors are highly vascularized. PPGL arise from tissues derived from the neural crest, respectively in the paraxial autonomic ganglia or in the chromaffin cells of the adrenal medulla. Pheochromocytoma and truncal paraganglioma arising from the sympatho-adrenal lineage cells secrete cathecholamines and are highly vascularized. Clinical symptoms can be characterized by tachycardia, hypertension, and a high risk for stroke [15]. In contrast, paragangliomas arising from the parasympathic ganglia are generally nonsecretory and are most commonly found in the head and neck [16, 17], these tumors present as a mass and cause symptoms from compression of adjacent vascular or neuronal structures. In 35% of cases, PPGLs are caused by autosomal dominant germ-line mutations in the succinate dehydrogenase genes or they are found in multitumor syndromes such as neurofibromatosis type 1and MEN2A/2B [18, 19]. Compared to sporadic cases, patients with hereditary forms are younger, with a higher incidence of metastases and a more aggressive disease [20]. Familial syndromes are associated with loss-of-function mutations in the SDH mitochondrial enzyme complex II genes, including the four subunits of SDH and SDHAF2, which flavinates SDHA [21].

3. Future perspectives

The neural crest is an example of a unique and transient developmental structure, endowed with plasticity, proliferative capacity, migratory capacity, and remarkable self-limitation. Its biological and behavioral similarity of the malignant metastatic cell has led to make comparisons between them and to develop the idea that mutual cancer development programs for invasion and proliferation can be exploited [22] (**Figure 2**). In neuroblastoma, clinical maturation from aggressive "precursor-like" lesions to well-differentiated ganglioneuromas speaks to the plasticity of the NC and the normal developmental limitation of pluripotency. Based on these theories and shares regarding the development of the neural crest and cancer, we can understand the importance of studying these growth mechanisms and how fundamental these implications are for the treatment of malignancy. Cancer is

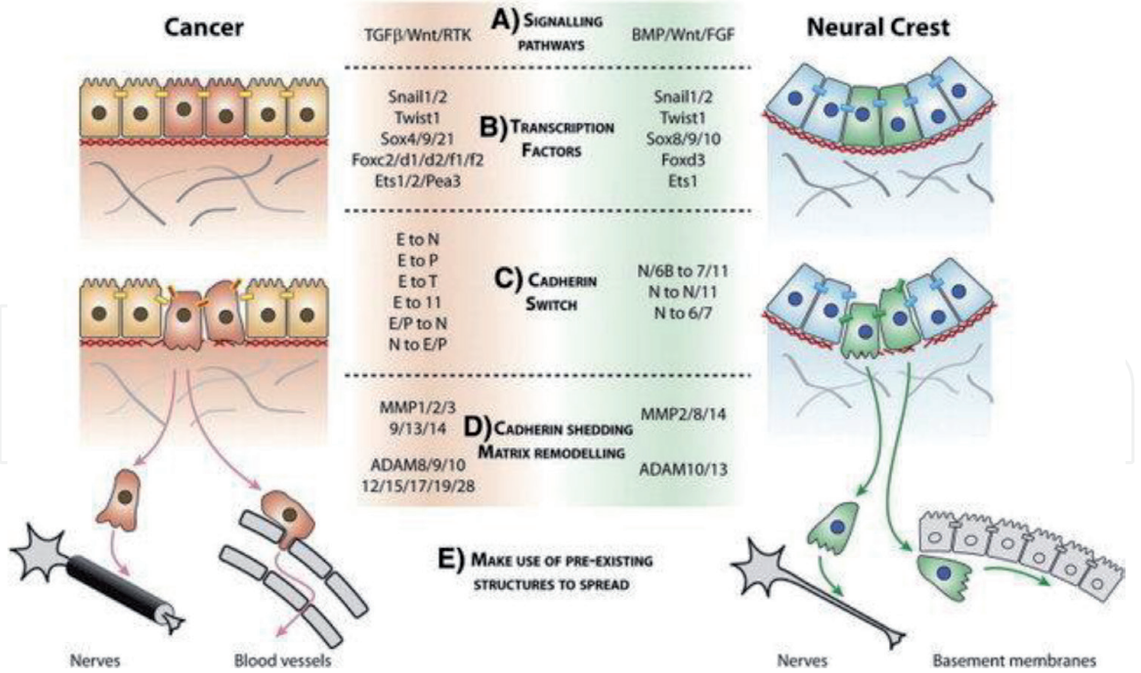

Figure 2.
Cancer metastasis and neural crest cell migration exhibit striking similarities [22].

usually treated surgically, but also in a multidisciplinary way with chemotherapy and radiotherapy. Each of these disciplines has led to many improvements in the survival of these patients but also to an increase in morbidity. Designing targeted therapies is a priority in order to achieve more effective treatment with less collateral damage. Azmi [23] in 2013 and Muller [24] in 2014 tested the therapeutic potential of Snail and c-Myc inhibitory molecules, respectively. Also Chua [25] in 2012 carried out a study aimed at identifying inhibitors of epithelial – mesenchymal transition in order to inhibit cell invasiveness and metastasis. The future direction should point to a complete identification of these factors which are very important for both neural crest development and tumor growth and metastasis, including cell survival, proliferation, motility, invasiveness, and differentiation. Only a more complete understanding of molecular similarities, we will then be poised to develop targeted therapies aimed at modulating those processes that are critical to tumor growth and metastasis. Testing potential new anti-cancer drugs is also an important future step, but is often slow, expensive, and limited to cultured cancer cells or artificial tumor models. NC development study can certainly represent a fundamental topic through which to develop new strategies and new drugs for cancer therapy.

In this book we want to offer the reader some elements of epidemiology, genetics and treatment of pheochromocytoma, paraganglioma and neuroblastoma. Our work does not reach definitive conclusions but aims to provide elements of knowledge regarding non-common neoplasms that have a unique denominator: they are Neural crest cell-derived tumors.

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