## Progetti innovativi per le malattie rare

# *Role of tumour microenvironment in malignant pheochromocytoma/paraganglioma growth and spread: identification of new pharmacological targets*

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**Abstract**

Pheochromocytomas and Paragangliomas (PPGL) are rare neuroendocrine tumours arising from neural crest derived cells, and they carry the highest degree of hereditability among human neoplasms. Indeed, up to 40% of all cases are caused by germline mutations, and another 30-40% are due to somatic mutations in one of the 20 susceptibility genes identified so far. Approximately 40% of the patients develop metastatic disease, with a poor prognosis, and a 5-year overall survival of about 40%. Germline variants in genes encoding subunits of the succinate dehydrogenase (SDHA-D) are the most important risk factors for PPGL, explaining around two-thirds of all hereditary cases, and SDHB mutations are considered molecular metastatic risk markers.

Tumour tissue analysis has demonstrated that SDH impairment induces deep changes in cell metabolism and functions, and the inhibition of SDH enzymatic activity is responsible for an accumulation of succinate. Moreover, an increasing body of evidence shows not only that the concentration of cytosolic succinate increases in different types of cancer, in addition to PPGL, but that succinate also acts in a paracrine way by binding to its specific cell-surface G-protein-coupled receptor (SUCNR1), and this interaction plays a critical role in cancer spread.

In the past decades, cancer research has mainly focused on cancer cells, and the role of tumour microenvironment in promoting cancer growth and spread has only recently been considered. Tumours are very complex masses comprising not only cancer cells, but also non-malignant stromal cells such as endothelial cells, fibroblasts, immune cells and an insoluble extracellular matrix (ECM), forming the so-called tumour microenvironment. The interplay between cancer cells and tumour microenvironment implies also ECM remodelling. Thus, it is not surprising that recent studies have shown that cancer-associated fibroblasts (CAFs) contribute to tumour progression not only fuelling cancer cells, but also as key components in remodelling the ECM.

Overall, the present research proposal aims at identifying new therapeutic targets for malignant PPGL, and at better understanding the processes that lead to metastatization.

The project is based on different coordinated experiments, and primary PPGL tumours tissues and fibroblast cultures already present in our human biological Repository will be used (permission obtained by the Local Ethical Committee, Prot. n° 2011/0020149).

In particular we will investigate:

1. The expression of SUCNR1 in primary PPGL tumours tissues obtained at surgery, exploring the possible correlation of SUCNR1 expression levels with the gene mutations and tumour behaviour.

2. The role of CAFs in ECM remodelling. We will analyse whether CAFs might be differently activated by *SDHB* mutated tumour cells, or more in general malignant cancer cells, compared with benign tumour cells. CAFs associated with malignant cells could secrete different ECM molecules and lead to a more favourable substrate for tumour invasion.

Although our research project is specifically design for PPGL, it is our opinion that the possible identified targets can lead to the development of new drugs aimed at interfering in the crosstalk among the different cell types within the tumour mass, and that they can be most likely applied for different types of cancers.