Titre de thèse: *Regulation of Sortilin expression: impact on tumorigenicity.*

Financement : région

Nom de l'équipe et du directeur : EA 3842 - Homéostasie Cellulaire et Pathologies – Pr Marie-Odile JAUBERTEAU

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Key words :
Sortilin, micro-RNA, polymorphism, epigenetic regulation, oncogenesis

Required Competences :
Master 2
Skills: Molecular and cellular biology; cell cultures, transcriptomic and proteomic analyses, primary culture, experimental models (mice).

Topics, state of the art:

Sortilin or NTSR3 (neurotensin (NT) receptor-3), is a type 1 membrane protein belonging to Vps10 (Vacuolar Protein Sorting) family. This protein initially characterized in neurons [1] is widely expressed in normal tissues. Whereas its major cellular localization is intracellular in the trans-Golgi network (TGN), 10% of sortilin is expressed at the cytoplasmic membrane. At the cell surface, sortilin is the coreceptor for other neurotrophin receptors such as tropomyosin-related kinase receptors (Trk) and P75 NTR, a death domain receptor. Thereby, sortilin activates cell proliferation and migration or induces apoptosis, upon either mature or immature neurotrophins binding. Indeed, sortilin is associated with several pathologies including neurodegenerative and metabolic diseases, and cancers [2].

The Vps 10 domain of sortilin, localized in TGN, selects growth factors allowing their secretion. This cytoplasmic part of sortilin is recognized by retromers proteins and Rab GTPases controlling the traffic of growth factors and tyrosine kinase receptors toward cell membrane [3]. Recently, we characterized the function of sortilin in the transfer and release of exosomes and in the assembly of two RTK receptors [4].

According that the ligands of sortilin (both neurotensin and neurotrophins) are known to be associated with several cancers [5, 6, 7], the objective of the team is to determine sortilin expression in several cancer cells and tumors to define its relationship with the oncogenesis and patients 'prognostic.

In lung cancers (non-small cell carcinoma), we evidenced that sortilin expression was decreased with high pathologic grades. Therefore, *in silico*, analyses support the different expression levels of sortilin according to tumor type. Therefore, the goal of this study is to address its function in different types of cancer, especially in the regulation of sortilin expression and its functions in cancer cell controls.

Domains :

Oncology, cell biology, molecular biology.

Objectives:

1) Analyze of sortilin expression in several cancer models and its interactome.
2) Characterization of molecular mechanisms regulation the sortilin expression.
3) Identification of protein complexes regulating sortilin functions
4) Correlations of sortilin with clinical data of patients and their outcome.

Methods:

1) Bioinformatic analyzes of public data banks to identify cancer cell lines depending on sortilin expression levels
2) Molecular studies: genomic, ARN and protein analyzes of cancer cells and tumors
3) Chromosomic and epigenetic analyzes.

Expected results:

1) Determination of mechanisms regulating sortilin expression
2) Correlation of this expression with types and subtypes of cancer
3) Perspective: search for modeling factors controlling this expression in vitro

References:

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