Title:
Role of the myelomonocytic lineage in Noonan syndrome-associated clinical traits

Keywords: genetic diseases, macrophage, senescence, inflammation

Summary

The general aim of the thesis project is to better understand the pathophysiology of Noonan syndrome (NS), a relatively frequent (1/2000 live births) genetic disorder associating cranio-facial features, cardiopathies, short stature and learning disability. Beside these congenital involvements, patients with NS also display a wide range of clinical traits that are reminiscent of early ageing, the pathophysiology of which is misunderstood: bone defects (*e.g.* decreased bone mass), muscle weakness, predisposition to myeloproliferative disorders (*e.g.* juvenile myelomonocytic leukaemia, JMML) and metabolic imbalance (*e.g*. insulin resistance).

Interestingly, other and we obtained striking evidences that many of NS impairments are related to the dysfunction of cells from the myelomonocytic lineage: myeloid precursors in JMML, osteoclast in bone defects, monocytes/macrophages in insulin resistance.

As a result, our project now aims 1) to understand the cellular and molecular mechanisms that confer on these cells their pathophysiological potential with a particular focus on the pro-senescent potential of RAS/MAPK hyperactivation, 2) to assess the relative contribution of myelomonocytic cells to the development of the different traits of the disease, and 3) to translate the obtained observations to the clinics. For this, we will favour a **translational, comprehensive approach** taking advantage of our expertise on the pathophysiology of NS, a wide range of approaches to specifically alter myeloid cells in pre-clinical models (knock in mouse and zebrafish) and evaluate the consequences on major postnatal / evolutive symptoms of the disease and a large and well-documented cohort of patients associated to a full biological collection and results from ongoing clinical trials.

We expect to demonstrate that a dysfunction of cells from the myeloid lineage, in line with increased senescence, participates to multiple traits of NS, thereby highlighting a founding pathophysiological mechanism which could pave the way for the development of “many birds/one stone” therapeutic strategies. Beyond rare diseases, these results could help better understanding monocyte/macrophage biology and provide new insights into frequent pathologies involving myelomonocytic cells.

Context

Although rare diseases affect by definition few individuals (less than 1 person per 2 000), there are about 6 000 to 7 000 different rare diseases with a combined prevalence of 1/20, concerning 3 million patients in France and 30 million patients in Europe. Rare diseases are severe, often chronic and progressive, diseases. For many rare diseases, signs may be observed at birth or in childhood. To date, there is no cure for most rare diseases, the only available option for patients being symptomatic treatment. Thus, rare diseases represent a major stake for public health in order to identify the molecular bases of the diseases, as a first step to propose appropriate

treatment and medical care that can improve the quality of life of those affected and extend their life expectancy.

Moreover, rare genetic diseases often share common symptoms with more frequent chronic diseases (*e.g.* cardiovascular, metabolic, endocrine diseases, and cancers), which are by far the leading causes of death and disability in the world. In the framework of our study, understanding link between myelomonocytic cell dysfunctions and different involvements of NS can have wider fallouts to identify pathophysiological mechanisms of more common disorders. Beyond the field of rare diseases, this project could also provide the steppingstone for the development of new therapeutics against, chronic metabolic disorders, growth retardation and pathological bone loss, haematological and cardiovascular defects**.**

References

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Background and skills required

The candidate must be highly motivated, persevering, committed and passionated for research. Curiosity and creativity are key skills, as well as ability for teamworking and building of scientific interactions on state-of-the-art technologies.

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