Proposal for the 2020 Imagine International PhD program

Laboratory: Molecular and physiopathological bases of osteochondrodysplasia
Head of laboratory: Valérie Cormier-Daire
Project and student supervisor: Name and given name (HDR Y/N)
Number of HDR in the lab: 2
Field of research: skeletal dysplasia, ossification process
Number and names of PhD students currently in the lab in 2020: 1st y, 2nd Y, 3rd y, 4th Y
Alessandra Guasto 3rd Y
Solène Vo Quang-Constantini 2nd Y
Number and names of PhD students under the Imagine program:
0
Project Title: deciphering proteoglycan impairment in skeletal dysplasia with multiple dislocations and development of new therapeutic approach

Project description (Max 2 pages including abstract and publications)

Skeletal dysplasia with multiple dislocations are severe disorders characterized by dislocations of hips, knees, elbows and fingers, scoliosis, short stature and a variable combination of cleft palate, teeth anomalies, heart defects, intellectual deficiency and obesity. More than 6 recessive disorders, including Desbuquois dysplasia and Larsen of Reunion island syndrome have been described so far.

In 2009, we identified mutations in *CANT1* which encodes a UDP soluble nucleotidase in Desbuquois dysplasia type 1. We then identified mutations in Xylosyltransferase gene (Xylt1) in Desbuquois dysplasia type 2. XYLT1 participates in the biosynthesis initiation of proteoglycans (PG) glycosaminoglycan (GAG) chains by transferring a xylose to specific Serine residues of the core protein. This steps is then followed by the addition of 2 galactoses and one glucuronic acid via the action of the galactosyltransferase I and II and the glucoronosyltransferase I to form the common linker region. Mutations in the genes coding for all those three enzymes lead to skeletal dysplasia with multiple dislocations, as we shown for example for *B4GALT7,* encoding the Galactosyltransferase I, in Larsen of Reunion island syndrome. Furthermore, mutations in genes coding for enzymes implicated in GAG chains elongation, such as CHST3 or CHSY1, have also been identified in patients with this type of skeletal dysplasia.

In all cases, we observed in patient fibroblasts PG synthesis impairment, supporting a common physiopathological basis in skeletal dysplasia with multiple dislocations.

More recently, we identified, in patients presenting with a skeletal dysplasia with multiple dislocations associated with an amelogenesis imperfecta (congenital tooth enamel defect), homozygous mutations in *SLC10A7* encoding a transporter of unknown substrate from the SLC family implicated in cytosolic calcium homeostasis. To further understand the function of SLC10A7 and to clarify the impact of the GAG biosynthesis impairment on the endochondral ossification process, we developed a *Slc10a7*-deficient mouse model that mimics the human phenotype.

In both patient cells and mouse tissues, we demonstrated a specific impairment in Heparan sulfate (HS) PG biosynthesis. Furthermore, our first analyses on *Slc10a7*-deficient mouse model growth plates suggest an impairment of chondrocyte differentiation and maturation processes responsible for an advanced ossification.

The first aim of the project is understand the specific consequences of a GAG biosynthesis defect on endochondral ossification processes and to further characterize the chondrocyte maturation impairment observed in the *Slc10a7*-deficient mouse model *in vitro* and *in vivo*.

In parallel, we demonstrated that *SLC10A7* deficiency was associated with an intracellular calcium accumulation in patient cells. As it is known that variation of divalent ions (such as calcium) concentration in the Golgi might affect the PG biosynthesis, we hypothesized that the altered intracellular calcium homeostasis in SLCA10A7 deficient cells was responsible for the HS biosynthesis observed. Based on that, we were able to restore the HS biosynthesis defect in patient cells by treating them with manganese, used to reduce calcium concentration in the Golgi.

The second aim of the project is to test this new therapeutic approach on the *Slc10a7*-deficient mouse model.

Lab members

5 researchers (INSERM or Paris Descartes University), 5 graduate students, 4 Postdoc, 3 technical staff
4 MD from the reference center for skeletal dysplasia also involved in clinical trials
Lab members involved in the project : Celine HUBER, IR INSERM; Johanne DUBAIL, PostDoc

Major Publications

. 1) Genevieve D, et al. Thromboxane synthase mutations in an increased bone density disorder (Ghosal syndrome). ***Nat Genet. 2008, 40: 284-286***

2) Le Goff C, et al. *ADAMTSL2* mutations in geleophysic dysplasia reveal a role for ADAMTS-like proteins in the regulation of TGFβ bioavailability. ***Nat Genet 2008, 49: 1119-1123***

3) Dagoneau N, et al. DYNC2H1 mutations cause asphyxiating thoracic dystrophy and short rib-polydactyly syndrome, type III. ***Am J Hum Genet. 2009, 84:706-711***

4) Huber C, et al. Identification of CANT1 Mutations in Desbuquois Dysplasia. ***Am J Hum Genet. 2009, 85:706-10***

5) Michot C, et al. Exome Sequencing Identifies PDE4D Mutations as Another Cause of Acrodysostosis. ***Am J Hum Genet. 2012, 90:740-745***

6) Le Goff C, et al. Mutations at a single codon in Mad homology 2 domain of SMAD4 cause Myhre syndrome. ***Nat Genet. 2012, 44:85-8***

7) Huber C, et al. WDR34 Mutations that Cause Short-Rib Polydactyly Syndrome Type III/Severe Asphyxiating Thoracic Dysplasia Reveal a Role for the NF-kB Pathway in Cilia. ***Am J Hum Genet 2013, 93: 926-931***

8) Bui C, et al. XYLT1 Mutations in Desbuquois Dysplasia Type 2. ***Am J Hum Genet. 2014, 94: 405-414***

9) Le Goff C, et al. Heterozygous Mutations in MAP3K7, Encoding TGF-β-Activated Kinase 1, Cause Cardiospondylocarpofacial Syndrome. ***Am J Hum Genet. 2016, 99:407-13.***

10) McInerney-Leo AM, et al. Mutations in LTBP3 cause acromicric dysplasia and geleophysic dysplasia***; J Med Genet*** 2016 53:457-64.

11) Dubail J, et al. SLC10A7 mutations cause a skeletal dysplasia with amelogenesis imperfecta mediated by GAG biosynthesis defects. *Nat Commun. 2018, 9(1):3087*