Therapeutic approaches to Ondine's Syndrome

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Congenital Central Hypobentilation Syndrome (CCHS, MIM 209880), also known as Ondine's Curse, is a very rare neonatal neurocristopathy, a definition implying a pathogenesis sustained by defective migration and/or differentiation of neural crest derivatives: as CCHS is characterized by abnormal ventilatory response to hypoxia and hypercapnia, owing to failure of autonomic respiratory control, affected children show an adequate ventilation while are awake but hypoventilate during sleep. In particular disordered ventilatory control may range in severity from relatively mild hypoventilation during quite sleep with adequate ventilation during wakefulness to complete apnoea during sleep and severe hypoventilation during wakefulness (Weese-Mayer et al, 2009). Lack of diagnosis, mis-diagnosis or inadequate treatment can be responsible for either fatal consequences or very severe neurological damages, due to apnoea episodes and cerebral hypoxia. Frameshift mutations (5%) and polyalanine triplet expansions (95%) have been detected in the coding region of the paired-like homeobox gene PHOX2B in about 90% of CCHS patients (Amiel et al., 2003). Autosomal dominant transmission with reduced penetrance has been demonstrated in CCHS families. A correlation between length of the expanded tracts and both severity of the respiratory phenotype and age at onset has been reported. On the other hand, the number and severity of CCHS associated symptoms, including HSCR and neuroblasrtoma, seem especially to correlate with frameshift mutations.
PHOX2B is a homeodomain transcription factor whose expression is restricted to neurons that regulate the cardiovascular, respiratory and digestive organs, forming the sensory and motor arms of the visceral reflex circuits.
Consistently with PHOX2B expression distribution, all autonomic ganglia fail to form properly in Phox2B Knock-out (KO) mice, as do the three cranial sensory ganglia, that are part of the autonomic reflex circuits, and all of the central and peripheral neurons that express noradrenergic traits. Thus, PHOX2B is considered one of the master genes whose expression is required for the development of those neural structures that participate in the formation of autonomic visceral circuits (Brunet and Pattyn, 2002).
Very little is known about the genes regulated by PHOX2B. According to our current knowledge, two classes of genes might be tentatively identified as PHOX2B target genes: regulatory genes and effector genes. Effector genes encode proteins that enable neurons to perform their autonomic functions. This is the case of tyrosine hydroxylase (TH) and Dopamine-Beta-Hydroxylase (DBH), two genes encoding enzymes involved in the cathecolamine biosynthesis. Regulatory genes encode transcription factors that control downstream processes involved in the survival and differentiation of specific neural structures. Very recently it has been fortuitously observed that two females patients (20/25 and 20/26 genotype), using a progestin drug, desogestrel, for contraceptive purposes, dramatically ameliorated the clinical symptoms of CCHS, showing chemosensitivity recovery. However the molecular mechanism of this unexpected pharmacological effect is completely unknown.
Our work focussed on the following topics:

- Identification of PHOX2B target genes by genome-wide ChIP as possible drug targets to improve symptoms
- Characterization of the molecular mechanisms underlying desogestrel effects
- Generation of iPS from CCHS patients as new cellular tools to test drugs

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