New approaches to the molecular pathogenesis of CCHS: implications for therapeutic strategies

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Congenital Central Hypoventilation Syndrome (CCHS, MIM 209880), is a very rare neonatal neurological disorder characterized by a broad variety of symptoms of autonomic nervous system dysfunction including inadequate control of breathing.

In humans, heterozygous mutations, including frameshift mutations (5%) and polyalanine triplet expansions from 4 to 13 additional residues (95%), have been detected in the coding region of the paired-like homeobox gene PHOX2B in about 90% of CCHS patients. A correlation between length of the expanded tracts and both severity of the respiratory phenotype and age at onset has been reported. CCHS is a lifelong disorder, and no pharmacological respiratory stimulants have turned out to be effective. Patients need ventilatory supports such as tracheotomy, nasal mask, or diaphragm pacing by phrenic nerve stimulation.

PHOX2B plays a crucial role in autonomic nervous system development; it regulates the transcription of *RET*, *ALK* and *PHOX2B* itself by an autoregulatory mechanism of its own promoter. In vitro, polyA expansions alter the transcriptional regulation of PHOX2B target genes such as *DBH*, *PHOX2A* and *PHOX2B* in a promoter-specific manner; as in CCHS patients, different PHOX2B mutations may affect different target genes, this highlighted the importance of identifying PHOX2B target genes in order to get new insights into the molecular pathogenesis of the disease. ChIP-Seq experiments, from IMR32 neuroblastoma cells, allowed us to identify promising candidate target genes that we are validating by biochemical and functional approaches.

Very recently it has been fortuitously observed that two females patients, using the progestin Desogestrel, for contraceptive purposes, dramatically ameliorated the clinical symptoms of CCHS, showing chemosensitivity recovery. However, the molecular mechanism of this pharmacological effect is completely unknown. Our recent data showed that Desogestrel enhanced the expression of some relevant PHOX2B target genes in a promoter specific manner, by acting on the activity of the wild type as well as mutant protein.