



Consiglio Nazionale
delle Ricerche



ISTITUTO PER L'ENDOCRINOLOGIA
E L'ONCOLOGIA SPERIMENTALE
"G. SALVATORE"
2nd UNIT

Seminar

Friday, 20th October 2023, 14:00h
CEST

Emilia Pedone

IBB-CNR

**Molecular studies toward the
comprehension of the role of the
polyalanine expansion in the
aggregation of PHOX2B: a significant
contribution by NMR structural
characterization**

Host: Giovanna Grimaldi (g.grimaldi@ieos.cnr.it)

Conference Room, CNR, P. Castellino Campus



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Abstract: The detection in about 90% of patients with congenital central hypoventilation syndrome (CCHS) of poly-alanine triplet expansions in the coding region of the transcription factor PHOX2B makes this protein an intriguing target for understanding the onset of the syndrome and for designing a new therapeutic approach. Consistent with its role as a transcriptional regulator, it is reasonable to think that transcriptional dysregulation may represent an important mechanism of CCHS pathogenesis. Therefore, our study primarily focused on the biochemical characterisation of PHOX2B variants containing the correct C-terminal tract (20 alanine), one of the most frequent poly-alanine expansions (+7 alanine) and a variant lacking the complete alanine tract (0 alanine). Comparison of the different variants by means of a multidisciplinary approach revealed the aggregation propensity of the PHOX2B variant containing the poly-alanine expansion (+7 alanines) especially in the presence of DNA. Furthermore, and unexpectedly, fibril formation was only revealed for the pathological variant, suggesting a plausible role of such fibrils in the onset of CCHS. Secondly, as structural information on PHOX2B is an important goal to obtain clues to elucidate the onset of the alanine expansion-related syndrome and also to define a viable therapy, we focused on the structural characterisation by NMR spectroscopy of the homeodomain (HD) of PHOX2B and the HD + C-terminus PHOX2B protein both alone and in the presence of the target DNA. The structural model obtained of the PHOX2B-DNA interaction opens up an interesting scenario aimed at elucidating the basis of the onset of CCHS. With the same methodology also the +7 Ala variant was analysed, showing different conformational properties in solution and a strong propensity to aggregate. Overall, therefore, this study paves the way for the future rational design of therapeutic drugs, suggesting as a possible therapeutic route the use of specific anti-aggregating molecules capable of preventing the aggregation of the variant and possibly restoring the DNA-binding activity of PHOX2B.

Biography:

Emilia Pedone is a Senior researcher and Group Leader at Institute Biostructures and Bioimaging of C.N.R. She received her PhD from the University of Naples "Federico II" in Biochemistry and Molecular Biology in 1999. Until 2000 she worked at the Department of Organic and Biological Chemistry (UNINA) focusing on the study of proteins involved in the peroxides detoxification or in oxidative folding and redox homeostasis isolated from thermophilic microorganisms. In 2000, she became a researcher at the CNR, where she set up a research group whose main interest is the study of structure-function relationships related to different human protein targets and protein-protein interactions involved in the onset of various pathologies. She has participated in several national and international scientific projects and is currently PI of both a grant from the Italian CCHS foundation and an international agreement with a US biotech. She is involved in several editorial activities for high-impact journals and she is author of about 120 scientific publications on international peer-reviewed journals.