University of Naples Federico II
Department of Pharmacy
Doctoral Course in Pharmaceutical Sciences XL Cycle

REGULATION OF THE TRANSSULFURATION PATHWAY IN INFLAMMATORY-BASED DISEASES: THE ROLE OF CANONICAL AND NON-CANONICAL CYCLIC NUCLEOTIDES

TUTOR: Prof.ssa Emma Mitidieri COTUTOR: Prof Giuseppe Cirino

PROPOSED RESEARCH ACTIVITIES:

Hydrogen sulfide (H2S) is a key signaling molecule, endogenously synthesized within the reverse transsulfuration pathway (TSP) by cystathionine-β-synthase (CBS) and cystathionine-γ-lyase (CSE). H2S can trigger multiple signaling pathways and, therefore elicit diverse biological functions1. Among the different mechanisms of action through which H2S exerts its biological activity, cyclic nucleotide signaling has gradually gained attention over the past decade2. H2S directly regulates the function of target proteins by sulfhydration and indirectly by modification of intracellular cyclic nucleotide (cAMP/cGMP) levels. Cyclic nucleotides are important second messengers playing a significant role in signal transduction within the body. More specifically, cAMP and cGMP signaling modulate numerous processes, including cell proliferation, differentiation, inflammatory response, gut peristalsis, smooth muscle relaxation, platelet aggregation, and lipolysis3,4. In physiological conditions, H2S can differentially affect the activity of resting adenylyl cyclase (AC) and activated AC, therefore playing a dual role in cAMP-mediated signaling. Besides, H2S affects soluble guanylyl cyclase (sGC) and phosphodiesterase activity, modulating vascular function. In addition, H2S can trigger the synthesis of cyclic inosine monophosphate (cIMP) a “non-canonical” cyclic nucleotide involved in the contractile mechanism of vasculature5. To date, the contribution of cIMP in inflammatory response remains unknown. Although “canonical” and “non-canonical” cyclic nucleotides are the second messengers driving the control of several biological processes, their interplay with TSP is not well defined.

Based on this evidence, the project aims to:

1) address the role played by the axis TSP/H2S/cyclic nucleotides in healthy vs inflammatory-based diseases;

2) evaluate the role of “non-canonical” cyclic nucleotide cIMP vs the “canonical” cAMP and cGMP in healthy vs inflammatory-based diseases;

3) identify novel potential therapeutic approaches to modulate inflammation.

REFERENCES

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4. Singal A.K, et al. JAMA. 2021;326:165–176.

5. Mitidieri E, et al., Br J Pharmacol. 2021;178(18):3765-3782.