ORAL COMMUNICATIONS

RESILIENCE ASSOCIATED WITH DEFECTS IN VITAMIN B12 METABOLISM: BALANCING BETWEEN HOMEOSTASIS AND DISEASE

E. Selita[1], E. Tomaselli[2], G. Di Matteo[3], L. Mannina[3], M. Rossi[2|4], D. Passeri[2|4], L. Angeloni[2|4], M. Fidaleo[1|4]

[1]Dept of Biology and Biotechnology, Charles Darwin, University of Rome Sapienza, Italy; [2]Dept of Basic and Applied Sciences for Engineering, Sapienza University of Rome, Italy; [3]Dept of Chemistry and Technology of Drugs, Sapienza University of Rome, Italy; [4]Research Centre for Nanotechnology for Engineering of Sapienza (CNIS), Sapienza University of Rome, Italy

CblC deficiency is an inborn error of intracellular Vitamin B12 (B12) metabolism caused by loss-of-function mutations in the MMACHC gene leading to metabolic decompensation, including homocysteine (Hcy) accumulation [1,2]. Cognitive impairment and variable disease onset among patients with identical mutations[1,3] motivates investigation of Hcy effects in a neural-like model and supports the concept of metabolic resilience, whereby cells maintain function despite biochemical defects [4].

SH-SY5Y neuroblastoma cells were cultured in B12-deprived media, differentiated into a neural-like phenotype, then exposed to increasing Hcy concentrations and recovered in unsupplemented or B12-supplemented conditions. This approach defined cytotoxic Hcy levels and explored changes in metabolomics, oxidative stress and protein and DNA methylation.

Hcy induced dose-dependent cytotoxicity, with significant effects at higher doses, while B12 partially rescued viability. ^{1}H-NMR metabolomics identified key alterations. Exploratory analyses revealed compartment-specific methylation changes on a proteic level and treatment-specific DNA methylation changes.

These findings support the concept of a metabolic tipping point, where Hcy-induced stress reveals limited resilience. Overall, this study highlights the interplay between metabolic imbalance, protein and epigenetic modulation in neural dysfunction.

References

1. Lerner-Ellis JP, Tirone JC, Pawelek PD, Qiang L, Chuai H, Duan Y, et al. Identification of the human MMAB gene (cblB complementation group) and characterization of mutations in patients with vitamin B12-responsive methylmalonic aciduria. Nat Genet. 2006 Oct;38(10):1166-72.
2. Mascarenhas R, Li Z, Gherasim C, Ruetz M, Banerjee R. The human B12 trafficking protein CblC processes nitrocobalamin. J Biol Chem. 2020 Jul 28;295(28):9630-9640.
3. Chen Z, Prince E, Kang Y, Zhou K, Li W, Hu J, et al. Deep learning for rare disease: a scoping review. Orphanet J Rare Dis. 2022 Jun 28;17(1):438.
4. McKenna HT, O'Brien KA, Fernandez BO, Minnion M, Tod A, McNally BD, West JA, Filipe H, Lau L, Murray AJ, Stevens JL. Divergent trajectories of cellular bioenergetics, intermediary metabolism and redox state in sepsis. Redox Biol. 2021 Jun;41:101907.