POSTER

ALTERED NEUROTRANSMISSION AND METABOLISM IN A GFAP R239C ZEBRAFISH MODEL OF ALEXANDER DISEASE

S. Candiani[1|2], M. Bozzo[1], V. Bazzurro[1], D. Bellitto[3], A. Tripi[1], S. Ferrando[1], G. Rosa[1], T. Bacchetti[3]

[1]Dept. of Biology, University of Genova, Italy; [2]RCCS Azienda Ospedaliera Metropolitana, Genova, Italy; [3]UO Proteomica e Spettrometria di Massa, IRCCS Ospedale Policlinico San Martino, Genova, Italy

Alexander's disease (AxD) is a rare neurodegenerative disorder of astrocytes caused by mutations in the GFAP gene, leading to the formation of protein aggregates (Rosenthal fibers) and severe neurological dysfunction, including myelin disruption. This study focuses on the R239C mutation, using zebrafish as a model organism in which the human mutation was genetically introduced [1,2]. The aim was to investigate glutamate and GABA release and uptake using isolated synaptosomal and gliosomal preparations. The results show an alteration in glutamate and GABA neurotransmission, suggesting a potential role of this mechanism in the pathogenesis of the disease.To better understand disease progression, we studied neurodegeneration by using isotropic fractionator combined with NeuN and DAPI staining to quantify neuronal and glial cell populations. These analyses aimed to determine whether zebrafish carrying the mutation exhibit alterations in the number of neurons and glial cells compared to controls. Furthermore, using a transgenic line for mpeg, neuroinflammation was assessed by comparing microglial cell numbers between control and R239C mutant lines. Our analyses show that the mutation leads to a progressive increase in neuroinflammation during development, followed by neuronal cell death and impaired neurotransmission, with the most pronounced effects observed in adulthood. These cellular alterations are also reflected at the metabolic level, as evidenced by changes in the production of specific lipids involved in myelin formation and in the sulfur metabolism. Our study clearly demonstrates the usefulness of the zebrafish model for better understanding the pathogenesis of AxD and highlights its potential for future drug screening studies.

Acknowledgements: We gratefully acknowledge the Italian Alexander Syndrome Association "Più Unici che Rari".

References

1. Bellitto D et al. Redox Biol 2025; 81:103544.
2. Candiani S, et al. Genes (Basel) 2020; 11(12):1490.