A NMR APPROACH TO IDENTIFY THE DIFFERENCES AMONG ANGIOPENIN AND SOME OF ITS MUTANTS INVOLVED IN ALS

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Human angiogenin (ANG) is a so called "pancreatic-type" ribonuclease (RNase 5) present in plasma and other biological fluids, such as cerebrospinal and amniotic fluids, or tumor microenvironments\textsuperscript{1-3}.

WT ANG is able to cleave tRNA\textsuperscript{Ala}, producing a G-quadruplex fragment that promotes the formation of stress granules and inhibits protein synthesis, assisting motor neuron survival\textsuperscript{4, 5}. This activity is altered in many ANG mutants found in patients affected by Amyotrophic Lateral Sclerosis (ALS)\textsuperscript{6, 7}. In this study, we selected three ANG mutants (H13A, C39W, R121C) involved in ALS, with the aim of determining their effect on protein structure and dynamics, using NMR spectroscopy. By following the specific RNA cleavage reaction with NMR spectroscopy, it is also possible to reveal if the mentioned mutations compromise ANG activity against tRNA\textsuperscript{Ala} substrate.

Moreover, since ribonuclease A (RNase A) and other "pancreatic-type" ribonucleases are able to form oligomers through three-dimensional domain swapping (3D-DS)\textsuperscript{8, 9}, it is interesting to study the oligomerization propensity of WT ANG and its mutants. It was in fact demonstrated that aggregated mutants of other proteins cause proteostasis impairment in the motor neurons of patients with ALS\textsuperscript{10}.

1. R. Shapiro, D. J. Strydom, K. A. Olson KA, B. L. Voolse, Biochemistry, 1987, 26, 5141–5145.

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