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Computational modeling of ATM signaling: a predictive framework for drug repurposing in ataxia-telangiectasia

Aurora Eliana Merulla, Valentina Di Salvatore, Giorgia Serena Gullotta, Avisa Maleki, Giulia Russo, Filippo Caraci, Agata Copani & Francesco Pappalardo

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Abstract

Ataxia-Telangiectasia (A-T) is a rare genetic disorder caused by ATM mutations, leading to impaired DNA repair, oxidative stress, and neurodegeneration. We developed a computational model of ATM-mediated signaling using ordinary differential equations in COPASI, capturing key processes including DNA damage sensing, cell cycle regulation, autophagy, and oxidative stress response. The model simulates physiological, ATM-deficient, and drug-treated conditions to explore repurposing strategies. We evaluated the effects of spermidine, omaveloxolone,

and HDAC4 inhibition, revealing mechanisms by which these compounds modulate dysfunctional signaling. Sensitivity and stability analyses confirmed the model's robustness, while enrichment analysis validated involvement of key pathways. Our results highlight the synergistic potential of combining autophagy activation and epigenetic modulation to partially restore homeostasis in ATM-deficient cells. This work introduces a generalizable modeling framework for simulating disease-specific signaling dysfunction and identifying therapeutic interventions, illustrating the value of computational systems biology in rare disease drug repurposing.

Data availability

The model is available in a GitHub repository, visiting the following URL: https://github.com/francescopappalardo/ATM-ATR-DDR-DrugRepositioning-Model.

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Author information

These authors contributed equally: Aurora Eliana Merulla, Valentina Di Salvatore, Giorgia Serena Gullotta.

Authors and Affiliations

Department of Physics and Astronomy, University of Catania, Catania, Italy
Aurora Eliana Merulla

Department of Drug and Health Sciences, University of Catania, Catania, Italy
Valentina Di Salvatore, Avisa Maleki, Giulia Russo, Filippo Caraci, Agata Copani & Francesco Pappalardo

Oasi Research Institute-IRCCS, Unit of Neuropharmacology and Translational Neurosciences, Troina, Italy
Giorgia Serena Gullotta & Filippo Caraci

Oasi Research Institute-IRCCS, Unit of Bioinformatics and Statistics, Troina, Italy

Giulia Russo

Contributions

A.E.M. and G.S.G. performed the experiments, carried out the formal analyses, and wrote the draft of the manuscript. V.D.S. performed the experiments and statistical analysis and contributed to both the original draft and its revision. A.M. conducted formal analysis and contributed to writing the original draft. G.R. curated the data and contributed to writing and revising the manuscript. F.C. and A.C. revised the manuscript and provided critical input. F.P. conceived the study, developed the main conceptual framework, and supervised the methodology. All authors have read and approved the final version of the manuscript.

Corresponding author

Correspondence to Francesco Pappalardo.

Ethics declarations

Competing interests

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