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Toxin-based targeted therapeutics for the treatment of solid tumors

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The toxicity of conventional chemotherapeutic drugs owing to non-specific activity, as well as the development of multidrug resistance, support the need to find new treatments, according to the distinctiveness of the molecular profile of tumor cells and tumor environment. In the last decades, the use of targeted toxins has shown promising results in pilot preclinical and clinical studies, due to their ability to cope with cancer cells heterogeneity and off-target activity. In the current study, we have developed a chimera consisting of the plant toxin saporin (SAP) fused to the amino-terminal fragment (ATF) of human urokinase-type plasminogen activator (uPA), the latter previously demonstrated to specifically deliver payloads to uPA receptor (uPAR) overexpressing cells. ATF-SAP was produced in the *P. pastoris* yeast optimized as host for production of toxic SAP chimeras. The cytotoxicity of ATF-SAP, evaluated *in vitro* on different human solid and hematological tumor cell lines and compared to SAP alone, was found to correlate with the expression of the target antigen. Notably, we show that ATF-SAP activity is proportionally confined to uPAR-expressing malignant cells and that its cytotoxicity is unambiguously due to the activity of saporin, as a catalytically inactive mutant (ATF-SAP KQ) failed to exert any effect. The present data suggest that the employment of ATF-SAP can be considered a suitable toxin-based anti-cancer therapeutic option. The assessment of ATF-SAP activity on uPAR overexpressing patient-derived samples and on human tumor xenograft mouse models derived thereof will provide key informations for its future development as anticancer agent.

Biography

Stefania Zuppone has completed her studies in Biology from University of Salento, Italy. She is attending a PhD studentship in Experimental and Translational Medicine at University of Insubria. She is conducting her research at San Raffaele Scientific Institute in Milan, Italy, working on the development of targeted toxins for the treatment of solid tumors.

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