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Apoptotic compensatory proliferation signaling and its implication in tumor biology and cancer therapy

Apoptosis, in addition to its role in programmed cell death (PCD), has also been implicated in triggering Compensatory Proliferation Signaling (CPS)-whereby dying cells induce proliferation in neighboring cells as a means to restore homeostasis. To date, the molecular components, the nature of signaling, and the underlying mechanism of CPS remain largely unknown. Recently, we demonstrated that *Pseudomonas aeruginosa* Exotoxin T (ExoT) induces potent apoptosis in a variety of highly metastatic and resistant tumor cells *in vitro* and in vivo. We demonstrated that ExoT induces two distinct forms of apoptosis. Through its GTPase Activating Protein (GAP) domain activity, it induces caspase-9-dependent intrinsic apoptosis, while through its ADP-ribosyl transferase (ADPRT) domain, it disrupts integrin survival, causing anoikis apoptosis. During these studies, we have discovered that a fraction of apoptotic cells generates and release CrkI-containing microvesicles, *in vitro* and *in vivo*, which are capable of inducing compensatory proliferation in neighboring cancer cells upon contact by activating JNK. For the first time, we provide visual evidence of CPS and show by live video microscopy how CrkI-containing microvesicles are generated and how they induce proliferation in other cancer cells upon contact. Our scanning electron microscopic (SEM) and differential interference contrast (DIC) imaging, as well as our proteomics and biochemical data, indicate that ACPSVs are distinct from apoptotic bodies and exosomes. We further provide evidence that inactivating CrkI by ExoT or by mutagenesis blocks vesicle formation and inhibits CPS in apoptotic cells, thus uncoupling CPS from apoptosis. We show that these vesicles are also present in various tumors resected from human cancer patients. Given that majority of existing cancer cytotoxic therapeutics destroy tumor cells by apoptosis, CPS could significantly limit their effectiveness, contributing to the disappointing outcomes associated with therapeutic agents against cancer. Understanding the mechanism of CPS could lead to the development of novel targeted therapies that improve the effectiveness of current cancer therapies by inhibiting CPS.

Biography

Sasha Shafikhani is an Associate Professor in the Department of Medicine, Division of Hematology, Oncology, and Cell therapy at Rush University Medical Center. His group is interested in understanding how the presence of tumor and infection lead to a state of immune-confusion affecting both anti-tumor and anti-bacterial immune defenses. His group is also interested in developing bacterial toxins as effective anti-cancer therapeutics. His group is also interested in innate immune dysregulation that renders diabetic wounds vulnerable to infection.

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