Apoptotic cell's dying wish is to be replaced

It has been estimated that out of ~37.2 trillion cells in an adult human, 50-70 billion cells die each day through the highly regulated programmed cell death, known as apoptosis. Thus, new cells must be generated to account for cell loss in order to maintain tissue integrity and restore homeostasis. Not surprisingly, apoptosis – in addition to its role in cell death – has also been implicated in the process of compensatory proliferation signaling (CPS) whereby dying cells stimulate proliferation in neighboring cells to account for their own demise. However, the exact mode of communication between apoptotic cells and the neighboring cells responsible for mediating CPS remained largely unknown for over two decades. A major research focus in our laboratory has been to study the mechanisms by which ExoT- an exotoxin produced by *Pseudomonas aeruginosa* pathogenic bacterium - induces apoptosis in target epithelial cells. During these studies, we serendipitously discovered the communication signal that underlie CPS.

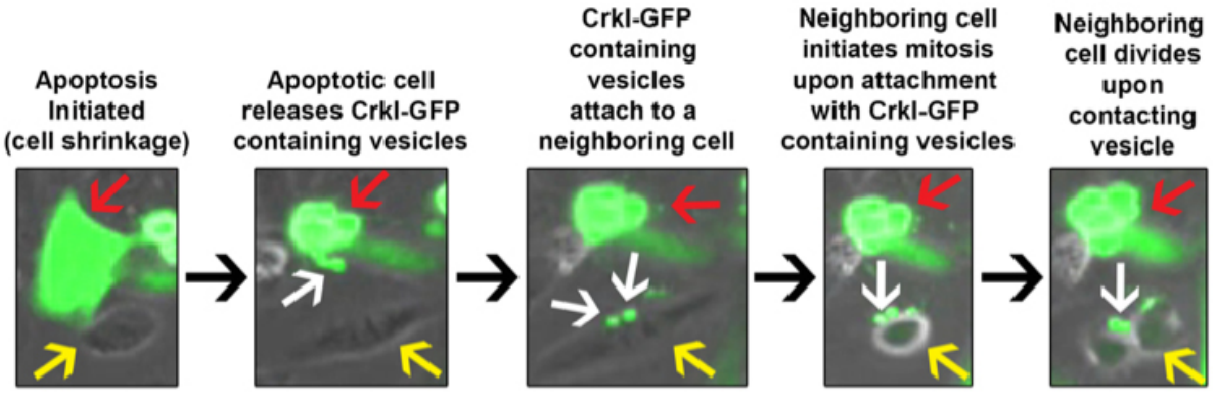

Fig. 1. Red arrow points to apoptotic cells; White arrow points to ACPSV; Yellow points to neighboring bystander cell.

In a recent publication, (Gupta, et, al, 2017, Dev. Cell), we provided the first visual evidence for CPS and demonstrated that a fraction of apoptotic cells release specialized CrkI-containing microvesicles, prior to their death, which stimulate compensatory proliferation in neighboring cells upon contact (Fig. 1 shows selected movie frames of an apoptotic cell producing three CrkI-containing vesicles, as identified by green color, which stimulate proliferation (mitosis) in a neighboring cell upon contact). We purified these microvesicles and called them "ACPSVs" for Apoptotic Compensatory Proliferation Signaling Vesicles. ACPSVs were distinct from exosomes and apoptotic bodies (other important extracellular vesicles) - based on their physical and functional properties (size, surface texture, sedimentation rate, proteomics content, and the ability to promote compensatory proliferation in neighboring cells). We further demonstrated that vesicle biogenesis requires CrkI adaptor protein in apoptotic cells and ASPSV-induced CPS is dependent

on c-Jun N-terminal kinase (JNK) activity in neighboring cells.

ACPSV production and CPS occurred in both primary and cancerous cell lines, under apoptotic conditions, as well as in vivo indicating that CPS is a conserved cellular process. Using an animal model of kidney disease (glomerulonephritis), we demonstrated that apoptotic kidney cells also produce ACPSVs with the ability to stimulate compensatory proliferation in other kidney cells. Of note, we also detected low level ACPSVs in normal kidney glomeruli, which most likely reflect the natural low level cellular turnover occurring in kidney. Intriguingly, cells undergoing necrotic cell death did not have the ability to produce ACPSVs and failed to stimulate compensatory proliferation in other cells, suggesting that CPS may be limited to apoptotic programmed cell death.

Apoptotic CPS could have important ramifications in health and disease. Our animal data suggest that CPS may have an important regenerative/reparative role in kidney where cell loss due to apoptosis has been reported and the need for CPS is obvious. Cancer is an example of a disease state where CPS could play a detrimental role. As majority of current cancer drugs destroy tumor cells by apoptosis, CPS could limit their effectiveness, contributing to the disappointing outcomes associated with existing therapeutic agents against cancer. Importantly, we reported that blocking CrkI function can interfere with vesicle production and CPS in apoptotic cells. This finding is important as it indicates that apoptotic programmed cell death and CPS are distinct processes which can be uncoupled from each other. It also indicates that targeting components of CPS may be able to enhance the effectiveness of current cancer therapeutics. More research is needed to unravel the phenomenon of CPS and its role in health and disease.

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Publication

Apoptosis and Compensatory Proliferation Signaling Are Coupled by CrkI-Containing Microvesicles.
Gupta KH, Goldufsky JW, Wood SJ, Tardi NJ, Moorthy GS, Gilbert DZ, Zayas JP, Hahm E, Altintas MM, Reiser J, Shafikhani SH
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