University of Massachusetts Medical School

GRADUATE SCHOOL OF BIOMEDICAL SCIENCES
CANCER BIOLOGY

Ph.D. THESIS DEFENSE

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ROLE OF TISSUE MICROENVIRONMENT IN RECRUITING MACROPHAGES DURING APOPTOSIS-INDUCED PROLIFERATION

Apoptosis-induced compensatory proliferation (AiP) is a mechanism that maintains tissue homeostasis after stress-induced cell death. During AiP, apoptotic cells induce proliferation of the neighboring surviving cells to compensate for tissue loss. AiP is important for wound healing and tissue regeneration in several model organisms. Additionally, AiP is an important feature of tumorigenesis and tumor relapse as it contributes to tumor repopulation following radiation or chemotherapy. Using an overgrowth tumor model ("undead tissue") in *Drosophila melanogaster*, we determined that the initiator caspase Dronc promotes generation of extracellular Reactive Oxygen Species (ROS), which drive activation of the stress kinase JNK and downstream mitogens to promote AiP. We also observed increased numbers of *Drosophila* macrophages, termed hemocytes, which are attracted to undead tissue. However, the specific mechanisms by which macrophages are recruited to undead tissue are still unclear.

Here, we report that the tissue microenvironment of the overgrown undead tissue directs macrophage recruitment during AiP. We demonstrate that ROS, JNK, and the matrix metalloproteinase Mmp2 are important for recruiting macrophages. Mechanistically, undead tissue-produced ROS and active JNK damage the basement membrane (BM) surrounding the undead tissue, by upregulating the expression and activity of Mmp2. The damaged BM then recruits macrophages to the undead tissue. Taken together, we propose a model in which the ROS-JNK-Mmp2 signaling axis damages the BM of undead tissue, resulting in changes in the tissue microenvironment that recruit macrophages to the area of damage to promote AiP and overgrowth.

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