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"The Role of Neutrophil YAP in Cardiac Ischemia/Reperfusion Inflammation and Injury"

By

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Thursday, June 19th, 2025
Medical Science Building, B619
10:00 A.M.

Join Zoom presentation
https://rutgers.zoom.us/j/93911373767?pwd=QALG4q49hgXuLP4AkwDE3VjagUBrLa.1
Meeting ID: 939 1137 3767
Password: 333224

ABSTRACT

Cardiovascular disease, including myocardial infarction (MI), is the leading cause of death worldwide. Reperfusion (i.e. percutaneous intervention) is currently the gold standard treatment of MI patients; however, it paradoxically contributes to injury by inciting inflammatory responses that promote infarct expansion. Neutrophils are the first inflammatory cells recruited to the heart after MI and their numbers have been shown to positively correlate to infarct size in both humans and mice. However, neutrophil depletion resulted in defective cardiac repair after infarction in rodents, suggesting neutrophils play an important role in cardiac repair after MI. Therefore, elucidating the mechanisms regulating neutrophil inflammatory and reparative functions during reperfusion may identify novel therapeutic targets for MI. Previous investigations by our lab and others have identified Yes-Associated Protein (YAP) as a transcriptional co-activator that regulates polarization in macrophages after heart injury, however whether YAP regulates neutrophil function in any context, including reperfused MI (I/R), remains unknown. We hypothesize that YAP is important for neutrophil pro-inflammatory effector functions in the I/R heart. Neutrophils isolated from the bone marrow, blood and hearts of WT mice subjected to cardiac I/R revealed rapid *YAP* upregulation. We generated neutrophil-specific YAP KO mice (YAP $^{F/F}$: MRP8-^{cre}) and controls (YAP $^{F/F}$) and subjected them to cardiac I/R. YAP KO mice exhibited decreased infarct size, neutrophil infiltration and increased CD206 surface expression acutely as well as preserved cardiac function after stable scar formation. scRNA-seq revealed that cardiac neutrophils from YAP KO mice demonstrated suppressed inflammatory genes during I/R, supported by qPCR validation of inflammatory gene suppression, chemotaxis and NETosis in YAP KO ex vivo neutrophils when compared to WT. Similar results were obtained using pharmacological inhibition of YAP in WT neutrophils. Mechanistically, YAP positively regulated *JAK2* expression, a well-established inflammatory signal transducer in neutrophils. Taken together, these data suggest that YAP facilitates inflammatory neutrophil functions during I/R injury in the heart and that suppression of neutrophil YAP promotes a reparative phenotype, thereby affording cardiac protection. As the injury due to reperfusion currently has no effective treatment, the results of this work could advance the field toward improved therapeutic options for MI patients.