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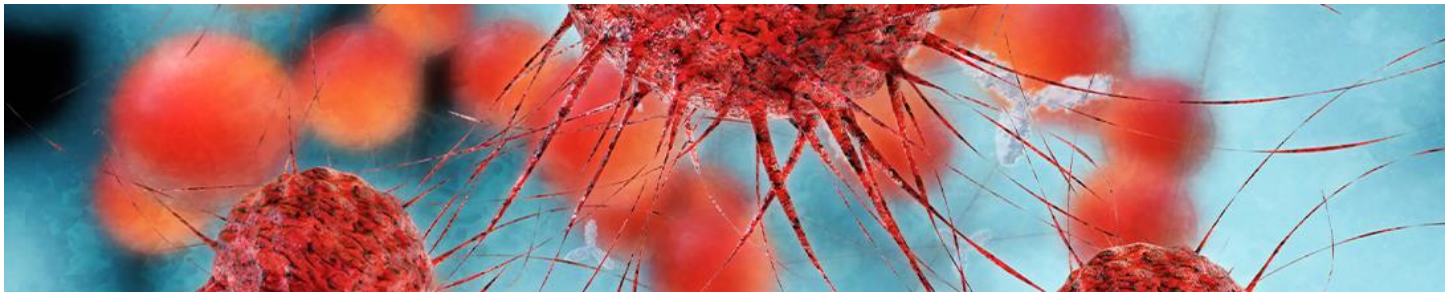
Controlling the Cell Stress Response to Improve Cancer Immunotherapy

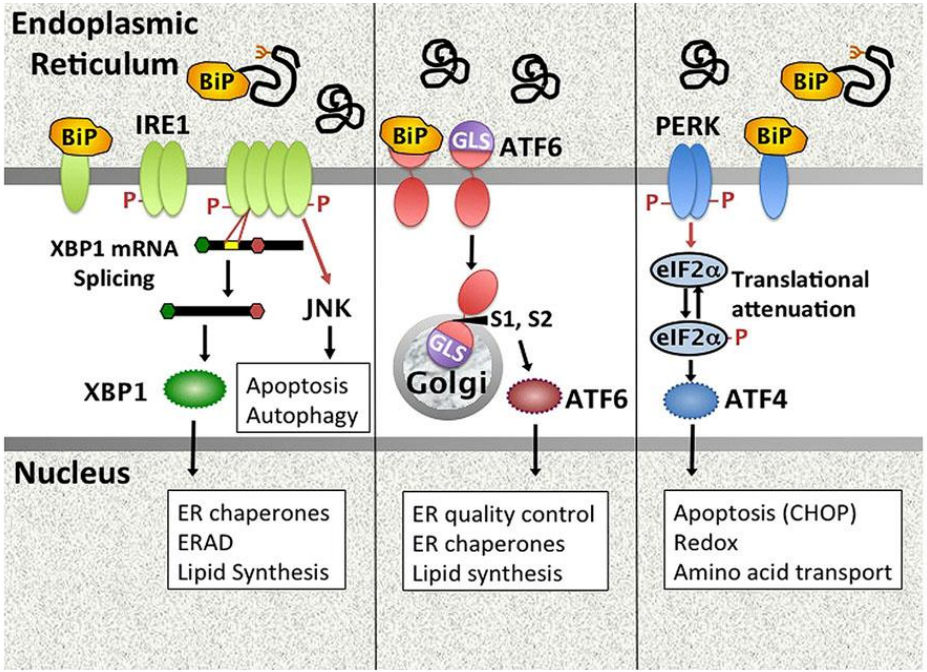
Jessica E Thaxton, PhD, MsCR
Assistant Professor
Departments of Orthopedics & Microbiology & Immunology
NCI Calabresi Clinical Oncology Scholar, Hollings Cancer Center
Medical University of South Carolina



ER Stress Response Pathways

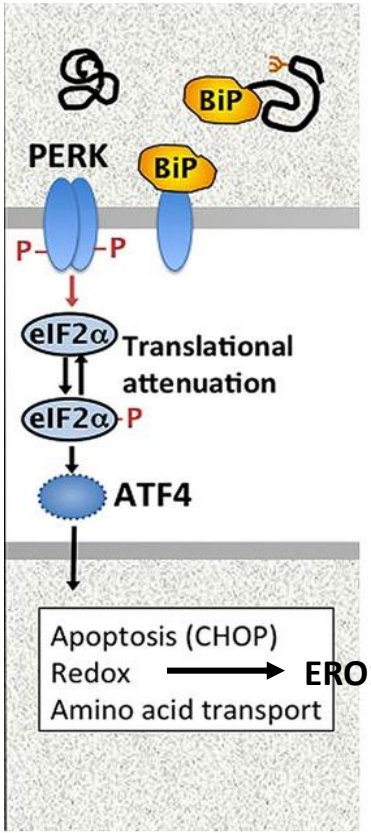
The ER is a signaling hub with the capability to define cell bioenergetic program and metabolic fate

The ER integrates external stressors with intracellular signaling cascades through sensing a burden of unfolded/misfolded proteins



Front. Microbiol., 16 May 201 .

The PERK Stress Response: Acute & Chronic/ Terminal Arms



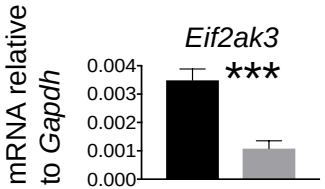
Acute: Momentary attenuation of protein synthesis
Restoration of proteostasis

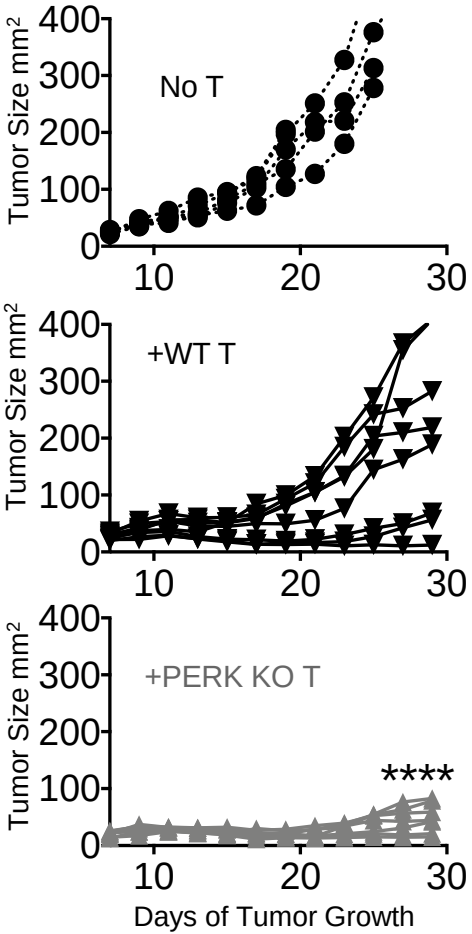
Chronic, Terminal Unfolded Protein Response:
Cell Death

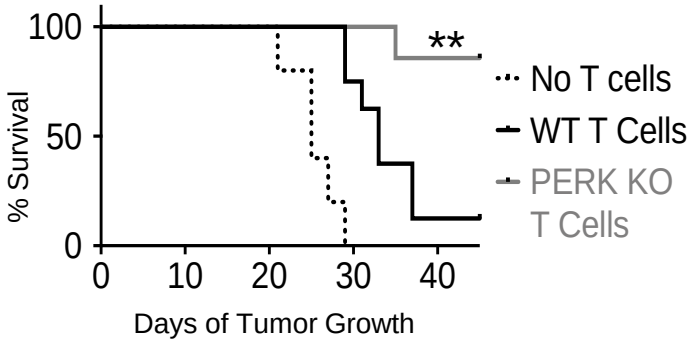
Front. Microbiol., 16 May 2014

PERK Hinders T cell anti-tumor immunity

OT-1xLckcrexPERK$^{f/f}$

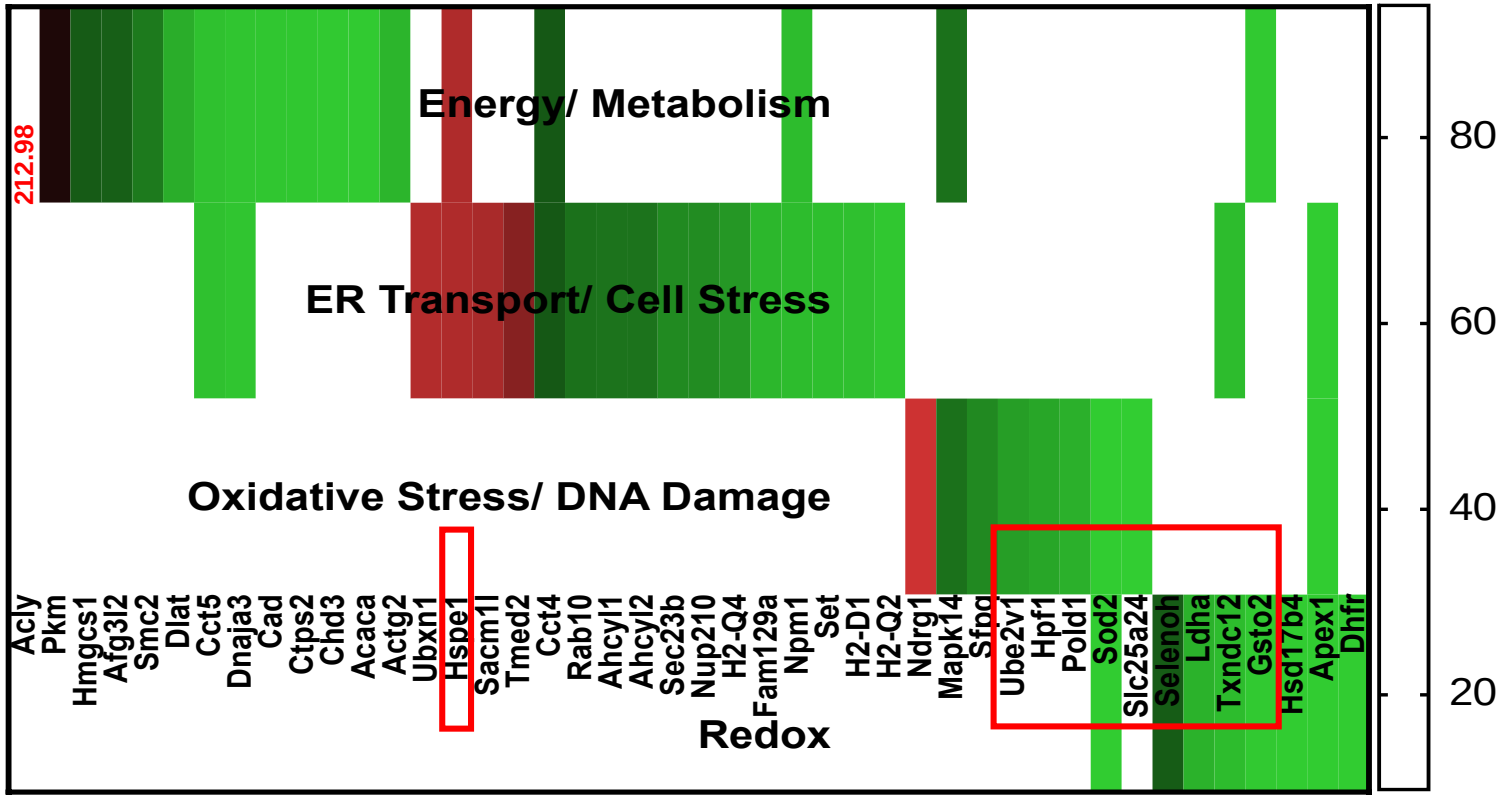






In Press, Cancer Immunology Research

PERK Drives a T cell Proteomic Signature of Cell Damage & Oxidative Stress Indicative of Chronic UPR



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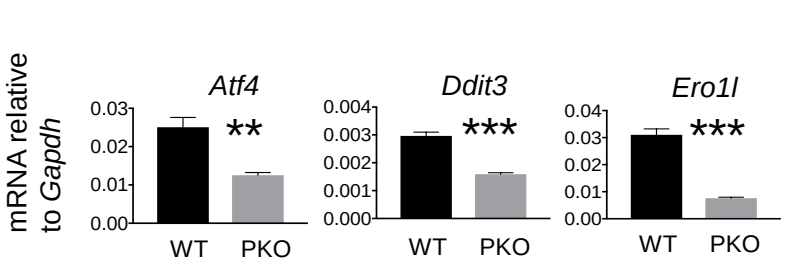
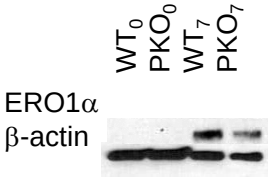
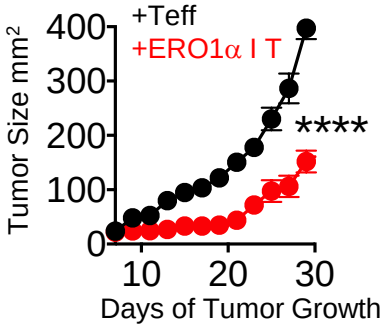
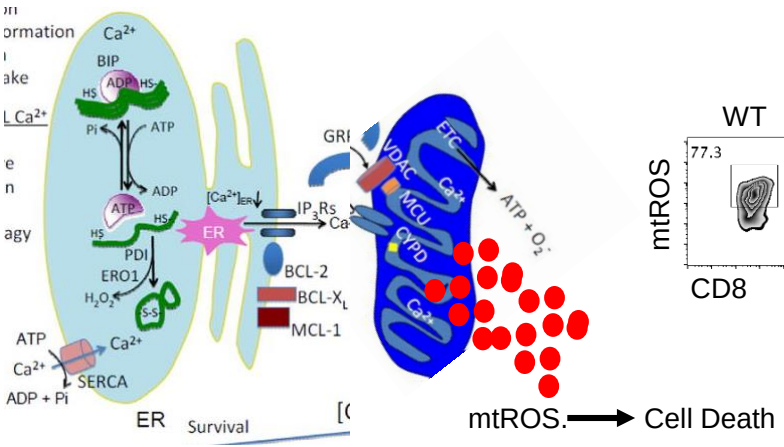
The PERK axis drives mitochondrial oxidative stress in CD8 T cells

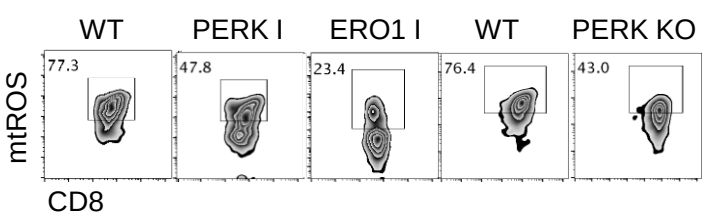


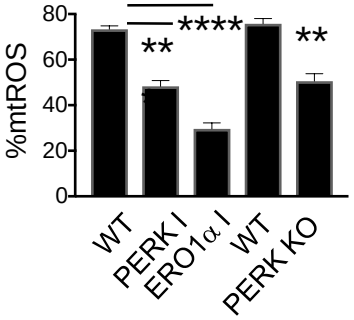






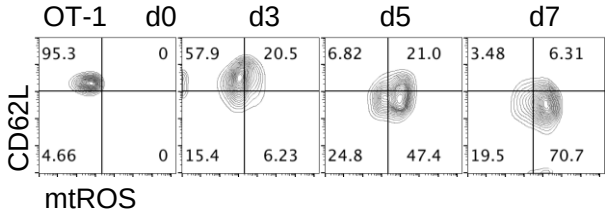
mtROS → Cell Death

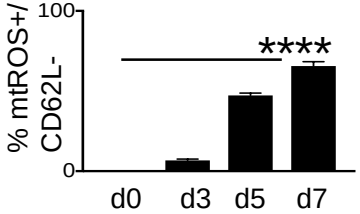


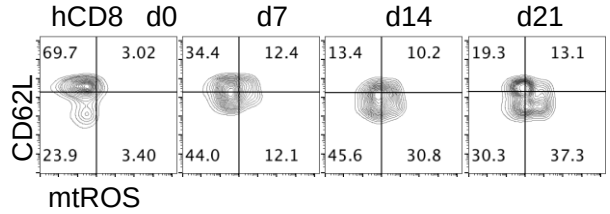


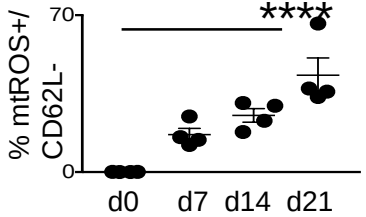
Kaufman et al, Bioc Biophys Acta, 2014

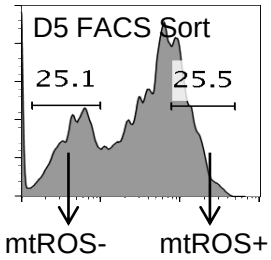
Mitochondrial oxidative stress is associated with CD8 T cell aging and death

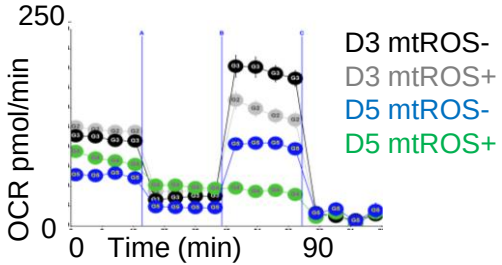


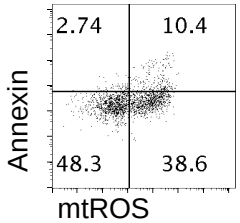


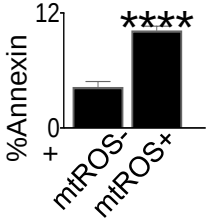




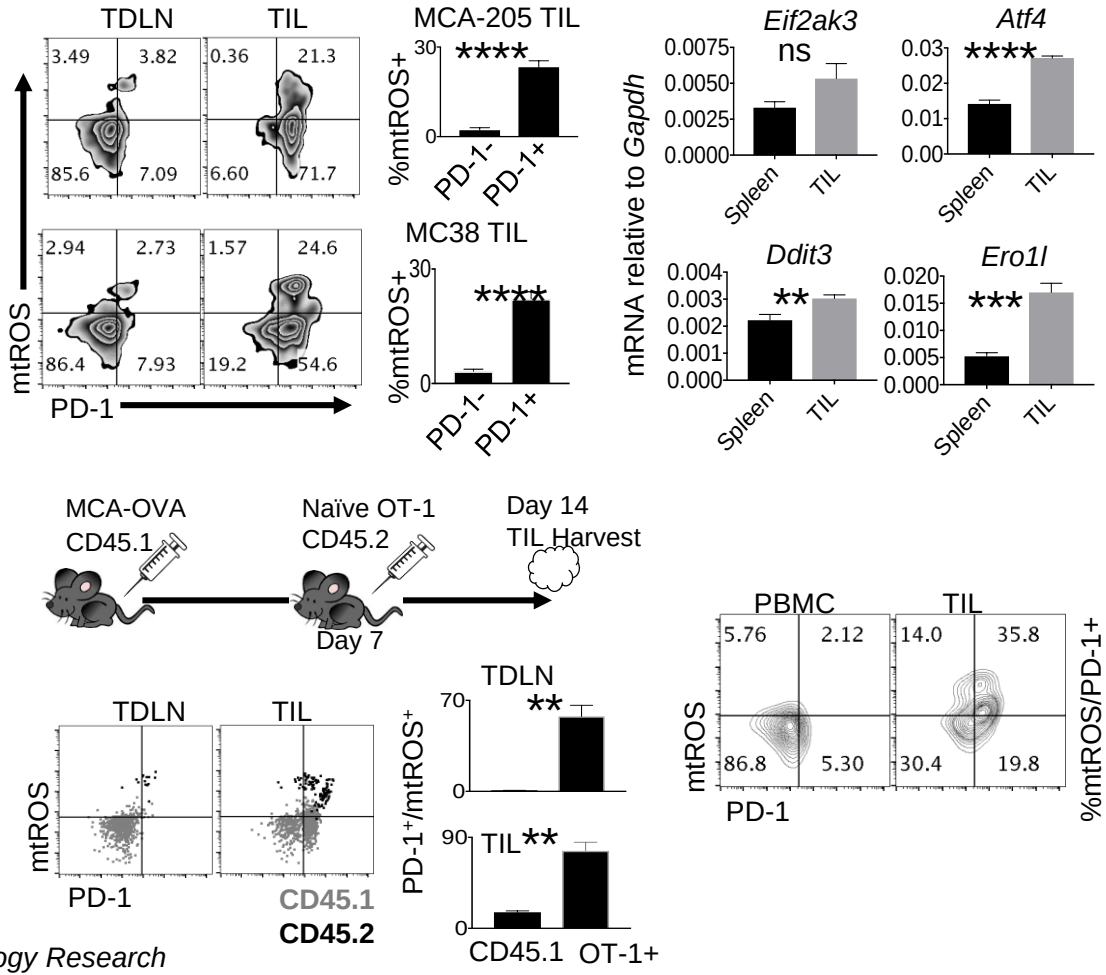








PD-1+ CD8 TILs experience mitochondrial oxidative stress



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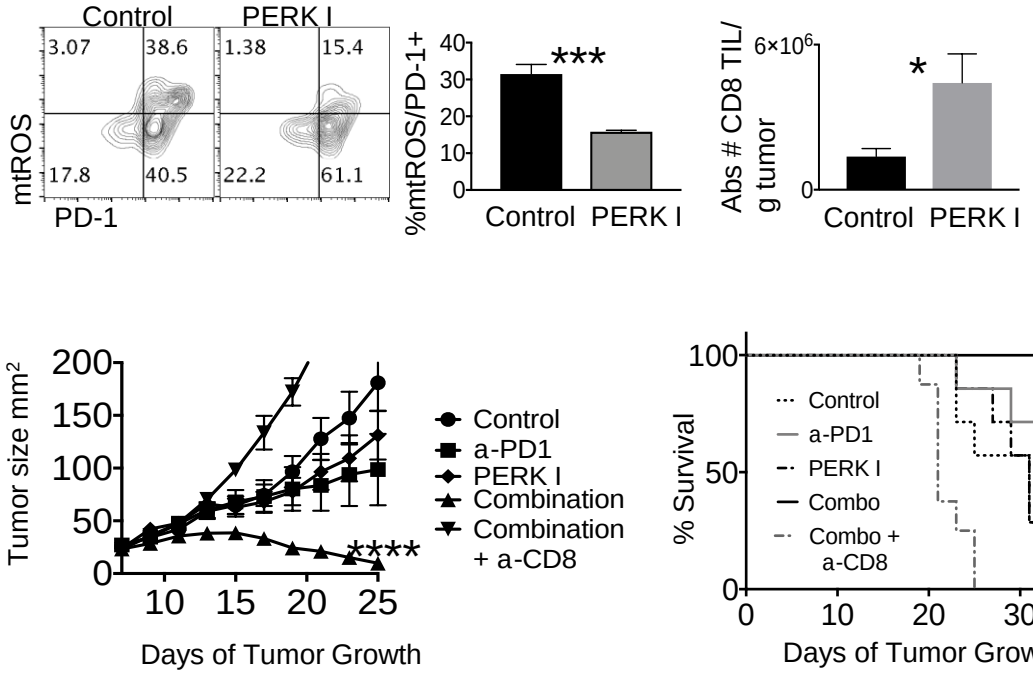
PERK inhibition repairs mitochondrial oxidative stress and augments α-PD-1 therapy



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Summary

1. *PERK impairs T cell anti-tumor immunity*

2. *The terminal UPR is activated in T effector cells and is associated with oxidative stress and cell death*

3. *PD-1+ CD8 TILs exhibit mitochondrial oxidative stress that is relieved by PERK inhibition that augments α-PD-1 therapy*

Acknowledgments

Thaxton Lab
Katie Hurst
Kiley Lawrence
Matthew Essman
Molly Sekar
Zeke Walton, MD
Lee Leddy, MD, MsCR

Collaborators & Mentorship
Zihai Li, MD, PhD
Michael Lilly, MD.
Gustavo Leone, PhD.
Chrystal Paulos, PhD
GlaxoSmithKline, Jeffrey Axten, PhD

The authors declare no conflicts of interest
Pertaining to this work.

Funding

https://immuno.wixsite.com/thaxtonlab