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Title of presentation: **Ribosomes as sensors of exposure to free radicals, radiation and toxic metabolites**

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Abstract

The ribotoxic stress response (RSR) denotes a signaling pathway in which the MAP3 kinase ZAKa senses ribosomal stalling and/or collision to activate the MAP kinases p38 and JNK. These kinases in turn mediate metabolic regulation, programmed cell death and inflammation, just to mention a few. The evolutionary conservation of the response is well-appreciated and some insight into the molecular underpinnings have been gleaned. However, we know preciously little about the physiological and pathological conditions that are associated with ribotoxic stress signaling in vivo. Our recent work with ZAK-/- mice highlights ribosomes as exquisitely sensitive sensors of a range of stress conditions, and the RSR as an effector pathway for stress adaptation at a tissue-wide and/or organismal level. I will discuss our unpublished work highlighting the role of RSR signaling in metabolic adaptation to amino acid starvation and ROS-generating diets. I will also describe the emerging role of the RSR in skin reactions to UV-irradiation (sun exposure), where ZAKa, p38 and JNK orchestrate early pyroptosis, apoptosis and immune cell infiltration. Finally, I will discuss the role of the RSR in the clinically relevant reaction to paracetamol overdose which is associated with depletion of hepatocyte glutathione content, oncotic necrosis and fulminant liver failure. I will show how the paracetamol metabolite “NAPQI” is a potent ribotoxic stress inducer on account of its reaction with ribosomal and messenger RNA. In this context, the RSR mediates early and protective apoptotic cell death that soon gives way to uncontrolled and JNK-independent necrosis. In sum, our work highlights free radicals, UV radiation and toxic metabolites as physiologically and/or pathologically relevant ribotoxic stress agents.