SPRING 2023

Biochemistry and Molecular Biology Brown Bag Series

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Graduate Teaching Student

"Characterization of adduct-containing DNA release from cisplatin-treated cells"

Tuesday, March 21, 2023

11:00 AM

Location 135 Oelman Hall

Lab: Mike Kemp, Ph.D.

Boonshoft School of Medicine
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https://science-math.wright.edu/biochemistry-and-molecular-biology

Abstract

On a daily basis, the human body is exposed to various genotoxins. Chemotherapeutic agents are one of them. Cisplatin is one of the most efficient and widely used chemotherapeutic agents for a variety of cancer types. The platinum atoms in cisplatin bind covalently to the N7 position of purines, leading to the formation of intra- and inter-strand crosslinks, which are referred to as DNA adducts. These DNA adducts are potentially mutagenic and lethal to cells if not removed by the nucleotide excision repair machinery. When the damage is too extensive, cells undergo apoptosis to generate large adduct-containing DNA fragments in a caspase-dependent manner. The final fate of these adduct-containing DNA fragments is not yet known. However, we have recently detected damaged DNA in association with extracellular vesicles (EVs), which have an important role in intercellular communication, diverse organ distribution patterns, and a distinct role in transferring disease states. Upon treating cancerous and non-cancerous cells with cisplatin and then performing differential centrifugation of culture medium, we have found cisplatin adduct-containing DNA to be enriched in smaller extracellular vesicle (SEV) fractions. Furthermore, we have found that the loading of these cisplatin DNA adducts into SEVs can be reduced by caspase-3 inhibitor treatment. Because the content of SEVs can be transferred to other cells, transfer of damaged DNA via SEVs to bystander cells may activate the DNA damage response in recipient cells throughout the body to contribute to the systemic effects of cisplatin chemotherapy regimens. Further research in this direction can help us understand the role of SEVs containing cisplatin-DNA adducts in the toxicity caused by cisplatin treatment in the kidney and brain and developing a targeted drug delivery system to limit the side effects of cisplatin regimen.