Abstract 1036

A Biochemical Investigation on the Structural Integrity of Bovine Serum Albumin During Exposure to Plastic Particles

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Keywords: Nanoplastics, Microplastics, Bovine Serum Albumin, Circular Dichroism Spectroscopy

Plastic pollution is a growing global health problem that has broad research implications. This project explored the effects of microplastics (MPs, 5mm – 1μm) and nanoplastics (NPs, 999nm – 1nm) on the overall molecular structure of bovine serum albumin (BSA), a transporter of fatty acids and common in vitro protein stabilizer. As plastic breaks down in nature due to a multitude of mechanical and chemical forces, it can become small enough to pass through the blood-brain barrier and interact with blood-borne proteins. Within this study, BSA serves as a model for determining the potential extent of this interaction, which was measured using circular dichroism (CD) spectroscopy, microscopy, and preliminary protein docking computational calculations. CD spectra revealed that BSA underwent significant global structural changes after exposure to polypropylene (PP) MPs and NPs at 20℃. CD data obtained during thermal denaturation assays revealed that while the melting temperature (Tm) of BSA decreases from 61℃ to 60℃ after exposure to plastic particles, the thermodynamics of unfolding were notably different which again indicated notable structural changes. Secondary structural analysis of BSA from CD spectra revealed that before exposure to MPs and NPs, BSA was shown to have 55.5% alpha helices, 17.4% beta sheets, 11.9% beta turns, and 15.2% random coiling. After exposure to MPs and NPs, those values changed to 57.9%, 13.6%, 15%, and 13.5% respectively. Comparing those values to docking data revealed that the potential binding pockets for PP altered the secondary and tertiary structures as well. The proposed binding affinities for PP in BSA revealed that it binds strongly enough to the protein for its natural efficiency to be impeded due to decreased availability to transport.

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Theme: Advances in Natural Product Biochemistry and Biotechnology

Abstract 1044

Mitomycins Interstrand crosslinks with opposite stereochemical configuration differently impact cellular repair pathways

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Keywords: Mitomycin, Interstrand crosslinks, DNA addducts, Stereochemical configuration, p53

Our study objectives are to identify critical cellular pathways triggered by the presence of DNA interstrand crosslinks (ICLs) produced by mitomycins and to identify how the structure of mitomycins ICLs determines the cellular signaling in the absence of a functioning p53. This study includes mitomycin C (MC), an anti-cancer drug currently used in the clinics and decarbamoyl mitomycin C (DMC), a derivative of mitomycin C (MC) lacking a carbamoyl group. These compounds form highly cytotoxic interstrand crosslinks (ICLs) that share common structural features. MC forms the α-ICL (trans) with DNA and DMC, the β-ICL (cis). Representative conformations of the two ICLs indicate that the level of DNA perturbation induced by each ICL increases in the order α<β with the α-ICL inducing minimal DNA perturbation. Previous research has also shown that both drugs differ in their cytotoxicity and p53 signaling. Since ICLs are the lesions primarily responsible for the cytotoxicity of mitomycins, this indicates that the two ICLs trigger very diverse biochemical cellular mechanisms, mediated by specific mutations present in cancer cells, a hallmark of modern cancer therapy. We generated site-specific ICL adducts (i.e. duplex oligonucleotides containing a single interstrand crosslink at a specific site) formed by mitomycins and transfected them into two cell lines with different p53 status: WT p53 MCF-7 and mutant p53 K562 cell lines. We used a PanCancer expression array to identify similarities and differences between the changes in gene expression induced by the two ICLs . The array included 770 targets involved in tumorigenesis related pathways as well as targets related to immune response and tumor microenvironment. Finally, we conducted bioinformatics analysis using IPA on the main pathways related to cell cycle control, cell proliferation and DNA damage response. Our results show that exposure to the β and α-ICL causes changes in gene expression encoding proteins involved in integrity of cells and tissues as well as others responsible for the maintenance of genome stability and cellular response to DNA damage. The expression of several DNA repair genes was differently impacted by each ICL: the α-ICL uniquely impacted the level of gene expression encoding proteins in the Fanconi Anemia (FA) pathway whereas the β-ICL impacted the level of gene expression encoding proteins in the MMR, NHEJ and MMEJ pathways. Using bioinformatics