Chemical Research in Toxicology

Spotlight

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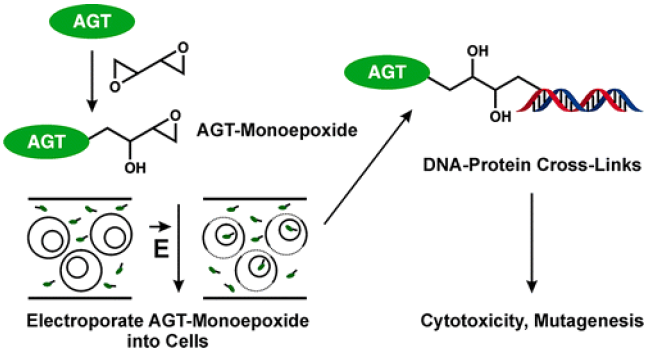
BIOMIMETIC NANOSPONGE ABSORBS PORE-FORMING TOXINS

Scorpion stings, snake bites, and bacterial infections are all extremely unpleasant and are all sources of exposure to pore-forming toxins (PFTs), which are proteins that perforate cells, thus altering cellular permeability. Produced in venom as well as in pathogenic bacteria, PFTs (of which there are over 80 indentified families) have diverse structures and targets, and may be detoxified by a plethora of treatments including antisera, monoclonal antibodies, and small-molecule inhibitors. Each of these treatments is specific for its target PFT, meaning that the identity of the PFT-producing species must be known in order for the appropriate antidote to be selected.

For cases in which time is short and evidence for PFT verification is scant, it would be desirable to have a universal antidote on hand for beginning immediate treatment. To this end, Liangfang Zhang and co-workers developed a biomimetic nanosponge for absorbing PFTs ((2013) *Nat. Nanotechnol.*, *8*, 336). Consisting of natural red blood cell (RBC) bilayers wrapped around biodegradable poly(lacto-co-glycolic acid) (PLGA) cores, these nanoparticles were found to absorb staphylococcal alpha-hemolysin (α-toxin), streptococcal streptolysin-O, and bee-venom derived mellitin, thus preventing hemolysis of mouse RBCs exposed to these PFTs. Ultimately, a single injected dose of nanosponge reduced the mortality of mice treated with a lethal dose of α-toxin by almost one-half, without causing any apparent tissue damage at the site of nanosponge accumulation in the liver. The authors note that the broad-applicability of the nanosponges gives them extremely attractive therapeutic potential. **Heidi A. Dahlmann**

CYTOTOXICITY AND MUTAGENICITY OF DNA–PROTEIN CROSS-LINKS VERIFIED



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Chemotherapeutic agents such as nitrogen mustards and platinum compounds as well as industrial contaminants such as formaldehyde and butadiene are notorious for being mutagenic and carcinogenic. These compounds (or their bioactivated derivatives), as bis-electrophiles, are capable of forming both DNA–DNA cross-links and DNA–protein cross-links (DPCs). While the mutagenicity and cytotoxicity of DNA–DNA cross-links have been thoroughly established in a variety of studies, the biological effects of their DPC counterparts were poorly understood because DPCs are difficult to generate in cells without producing DNA–DNA cross-links simultaneously.

To overcome this problem, a group of researchers led by Colin Campbell and Natalia Tretyakova developed a functionalized reactive protein that could be introduced into cells to selectively form DPCs ((2013) *Biochemistry*, *52*, 3171–3181). They treated recombinant alkylguanine transferase (AGT), a protein known to localize in nuclei, with diepoxybutane, the bioactivated derivative of butadiene, to create AGT proteins with appended reactive epoxide moieties. The labeled proteins formed DPCs when incubated with DNA in vitro and after being introduced into mammalian cells via electroporation. Moreover, recombinant wild-type AGT probes were both mutagenic and cytotoxic, while probes constructed with mutant AGT that does not accumulate in the nucleus caused fewer DPCs and had lower cytotoxicity. The authors note that now that the cytotoxicity of DPCs has been verified, further studies on the role of DNA repair in mediating DPC damage are being pursued. **Heidi A. Dahlmann**

MOLECULAR MECHANISM OF 3-NITROBENZANTHRONE MUTAGENESIS ELUCIDATED

Diesel exhaust fumes and airborne particles are well-known to negatively impact human health, in part due to the presence of mutagenic polycyclic aromatic hydrocarbons (PAHs). Among nitrated PAHs, 3-nitrobenzanthrone (3-NBA) is one of the worst. Strongly mutagenic, 3-NBA is considered to be an environmental risk factor contributing to human lung cancer incidence in urban areas. Like many PAHs, 3-NBA is metabolized into reactive electrophiles that bind to DNA, with three major adducts forming at the 8- and N^2-positions of deoxyguanosine (to generate dG-C8-*N*-ABA and dG-N^2-C2-ABA) and the N^6-position of deoxyadenosine (to generate dA-N^6-C2-ABA). Recently, the occurrence, persistence, and repair of these adducts in 3-NBA-treated cells, as well as their translesion synthesis, have been investigated by Takashi Yagi and co-workers ((2013) *Mutat. Res.*, *753*, 93–100).

The researchers found that following a 24-h treatment with 3-NBA, human hepatoma HepG2 cells contained dG-N^2-C2-ABA and dG-C8-*N*-ABA as the major lesions, followed by dA-N^6-C2-ABA. The apparent rates of formation paralleled the persistence of the adducts in the cells following a 24-h repair period, after which 86% of the dG-N^2-C2-ABA, 52% of the dG-C8-*N*-ABA, and 38% of the dA-N^6-C2-ABA lesions remained. Cell-based translesion synthesis (TLS) assays showed that dG-C8-*N*-ABA not only did block TLS most strongly but also was the most mutagenic of the three adducts studied, inducing primarily G to A transtions. Collectively, these results complement existing data implicating 3-NBA in carcinogenesis. **Heidi A. Dahlmann**

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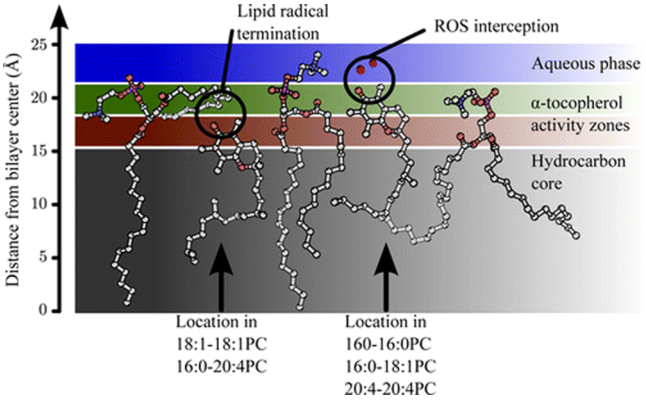
TOCOPHEROL ANTIOXIDANT ACTIVITY IN MODEL MEMBRANES: NEW FUEL FOR VITAMIN E DEBATE



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The tocopherol and tocotrienol molecules that are collectively known as "Vitamin E" are well known to be antioxidants in solution. Whether or not this activity applies in the cellular environment is still up for debate. Roles in cell signaling, apoptosis, protein activity, and gene regulation have all been cited as alternative functions for Vitamin E in biological systems, while low abundances in vivo and a lack of observable antioxidant health benefits following Vitamin E supplementation comprise the evidence against its status as a biologically relevant antioxidant. No matter the role, the importance of Vitamin E is undeniable, although only one of its constituents, α-tocopherol (αToc), is retained in the human body under regulation by α-tocopheol transport protein, the only identified Vitamin E receptor.

To help clarify what αToc might be doing in a cell membrane, researchers led by Thad A. Harroun investigated how the molecule's location in model membranes and orientation impact its antioxidant properties ((2013) *J. Am. Chem. Soc., 135*, 7523−7533). By performing neutron diffraction, NMR, and UV spectroscopy experiments, the team determined that αToc-mediated reduction of both reactive oxygen species (generated by Fenton chemistry) and lipid radicals (generated by thermolysis of 2,2′-azobis(2,4-dimethylvaleronitrile)) occurred at the hydrophilic−hydrophobic interface of the membrane in which αToc was embedded. Overall, their data support the model that αToc does not prevent radical formation in the cytosol but rather terminates lipid peroxide chain reactions and reduces the concentration of radicals diffusing into the bilayer.
Heidi A. Dahlmann

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