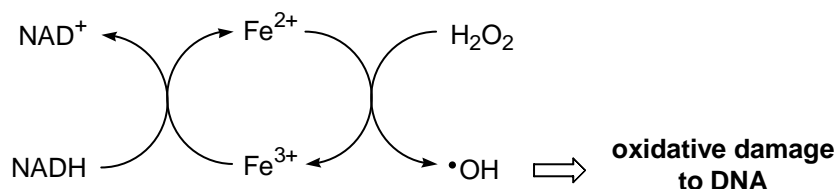


Understanding Antioxidant Inhibition of DNA Damage: The Role of Metal Coordination

Dr. Julia Brumaghim

Dr. Brumaghim's research focuses on metal-mediated DNA damage and how antioxidants prevent this damage. Research projects combine areas of synthetic coordination chemistry, biochemistry, and toxicology. Because of the diversity of research areas, students have an opportunity to develop skills in both synthetic inorganic chemistry as well as biochemistry of nucleic acids and DNA damage.

Reactive oxygen species, especially the hydroxyl radical ($\bullet\text{OH}$), are a major cause of damage to DNA, lipid membranes, and proteins in biological systems. Fe^{2+} and Cu^+ catalyze the formation of $\bullet\text{OH}$ from H_2O_2 . Cellular reductants such as NADH make the cycle catalytic by reducing the metal ions back to their oxidized forms. Oxidative damage to DNA can result in cancer, and this is thought to be one reason metals such as nickel, chromium, and cobalt are carcinogenic. Metal-generated hydroxyl radical damage is also responsible for tissue damage in cancer, Alzheimer's and Parkinson's diseases, arteriosclerosis, heart attack, and stroke. In many cases, this damage can be prevented or ameliorated by antioxidants.



Generation of $\bullet\text{OH}$ radical by iron.

Sulfur, selenium and polyphenolic antioxidants have been well-studied for their radical scavenging abilities and have been shown in clinical trials to prevent cancer and cardiovascular diseases. We are examining the ability of these antioxidant compounds to inhibit DNA damage, and have determined that metal coordination is required for their antioxidant behavior. In addition, we have determined that sulfur and selenium antioxidants are most effective at preventing copper-mediated damage, whereas polyphenolic antioxidants are most effective at preventing iron-mediated damage. Currently, we are correlating chemical and physical properties of these antioxidants with their DNA damage inhibition to elucidate the chemical features that contribute to antioxidant activity.

Summer projects for undergraduates will involve synthesis and characterization of metal selenolate (RSe^-) and thiolate (RS^-) model complexes as well as testing the ability of known antioxidants to prevent DNA damage. In the course of their research projects, students will learn air-sensitive synthetic techniques, DNA gel electrophoresis, cyclic voltammetry, and kinetics.