Why We Need to Mitigate Radiation Damage:
The 9/11 attacks on the Twin Towers resulted in the deaths of thousands. Since the calamity, fighting terrorism has been a major priority for the United States. The rising global threat of radiological terrorism has caused great concern regarding the protection of Americans and the US. The US Government has asked the NIH to organize research to study the mechanisms of radiation injuries and potential ways to mitigate these effects, as well as to develop protocols for identifying irradiated victims. Our mentor is one of the many researchers who are contributing to the advancement of irradiation protocols and treatments.

High dose radiation to the thorax causes major morbidity. (see Figure 1) The angiotensin-converting enzyme inhibitors, or ACE inhibitors, mitigate the radiation damage to the lungs. A significant effect from radiation damage is delayed pulmonary fibrosis. Without ACE inhibitors, radiation damage causes excessive collagen production in the alveolar walls which disrupts the gas exchange in the lungs, inhibiting respiration. Angiotensin I converts to angiotensin II, which normally binds to receptors on fibroblasts in the lungs to initiate the pathway leading to the production of collagen. The inhibitors disable ACE from converting angiotensin I to angiotensin II, which in turn prevents collagen over-production. (See pathway diagram to right.)

ACE Inhibitors mitigate radiation induced morbidity

The Promise of ACE Inhibitors

- The potential of ACE inhibitors such as lisinopril to mitigate lung damage following high-dose radiation exposure was analyzed. Findings show that ACE inhibitors are capable of reducing morbidity when treatment is given after the radiation dose.
- Our mentor’s study shows that ACE inhibitors have a statistically significant effect in minimizing collagen buildup in lung tissue following irradiation.
- ACE inhibitors show promise as viable treatments for individuals exposed to high doses of radiation by reducing long term damage to the lungs.
- Further studies regarding this topic will benefit victims of nuclear accidents and terrorism. Patients undergoing radiotherapy for cancer can also benefit from this possible treatment.
- We have designed a model of ACE with lisinopril bound in the active site to help understand the molecular mechanism of mitigation.

ACE Inhibitors Reduce Collagen in the Lungs

Figure 4**: These images are Masson’s trichrome stained slides of rat lungs after 7 months of WTI. Figure A shows lungs of rat without irradiation; B: 13 Gy WTI without drug; C: 13 Gy WTI with captoril; D: 13 Gy WTI with enalapril; E: 13 Gy WTI with fosinopril. B shows thickened walls of alveoli where collagen (colored blue) has been deposited.

Figure 5**: A: Four to seven months after 13 Gy whole thoracic irradiation (WTI), newly synthesized collagen in the rats’ lungs were measured. Rats exposed to 13 Gy WTI experienced an increase of collagen in the lung compared to untreated rats. B: Amount of newly synthesized collagen at 7 months post WTI and drug treatment. Rats treated with ACE inhibitors showed less collagen synthesis than WTI rats with no drug. "N" represents sample size.

Lisinopril-ACE Inhibition Pathway

Figure 2**: The diagram to the right shows the pathway leading from Angiotensinogen to Angiotensin I and II, using ACE, and the presence or absence of collagen in the lungs.

ACE Bound to Lisinopril

Figure 3**: Lisinopril, colored yellow, bound to Angiotensin Converting Enzyme (ACE) at its active site composed of Tyr224, His353, Ala354, His383, Glu384, His387, Glu411, Lys511, His513, Tyr520, Arg522, and Tyr523. Active site amino acids are colored CPK. The beta sheets are colored orchid, while the alpha helices are colored midnight blue. The chloride atom at the active site is colored lime, and the zinc atom is colored green. The unconstructed backbone is colored pale goldenrod.

Introduction

- Lungs are very sensitive to radiation: doses of radiation to cancer patients are limited by the damage to the normal lung surrounding a tumor.
- Radiation from a nuclear accident or terrorist event can injure sensitive lung tissue: can we find an effective treatment?
- Research using angiotensin converting enzyme (ACE) inhibitors to mitigate radiation lung injury is ongoing at the Medical College of Wisconsin.
- Our goal was to build a model of ACE to the inhibitor lisinopril, to help determine the molecular mechanism of mitigation of radiation lung injury.