Humans are protected from the harsh space radiation environment by the Earth’s magnetic field, which deflects high-energy radiation charged particles. These charged particles are ionized and are known to induce carcinogenesis in almost all parts of the body. Astronauts have an increased risk for cancer, mainly due to the space radiation environment and its harmful effects. Based on the current information and lack of knowledge about high-energy radiation, it is important to research possible effects and pathways affected by high-energy radiation exposure. The transcription factor Nuclear Factor-kappaB (NF-κB) is activated in cancer cells. NF-κB regulates numerous genes including cytokines, chemokines, adhesion molecules, and acute phase proteins through its activation of genes responsible for innate immunity, inflammation, and cell survival. With the knowledge that radiation is a known carcinogen, and astronauts are exposed to high-energy radiation, NF-κB is a good target to study the effects of high-energy radiation induced carcinogenesis. In this study, we demonstrated that high-energy radiation induced the activation of MMP-9 and COX-2 in mice, through activation of NFκB. Effective countermeasures against radiation-induced deleterious effects, through the suppression of the NF-κB pathway, will be examined in future studies.