Estrogens and Malignant Mesothelioma

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Abstract

Malignant mesothelioma (MM) is a highly aggressive cancer with only 10% of patients surviving after five years. The disease is caused by occupational and environmental exposure to asbestos. A higher prevalence of MM is seen in women due to environmental exposure than in men. Why women are more at risk of developing MM following environmental exposures to asbestos is unknown. 17β-estradiol (E2) is the most potent estrogenic hormone in women and it mediates its effects by binding to its nuclear receptors, estrogen receptor alpha (ERα) and beta (ERβ), and to its membrane-bound receptor GPR30. Inverse correlations between the levels of E2 (in human MM samples) and mesothelioma cancer patient survival post diagnosis suggested decreased E2 levels inhibited mesothelioma cancer growth. Likewise, the aromatase inhibitor exemestane was found to inhibit the growth of MM cells. Nevertheless, treatment with E2 showed inhibition of MM cell proliferation via ERβ. These contradictory observations urge further study to explain the roles of estrogen in MM cells. Our hypothesis is that malignant mesothelioma cells make their own estrogens, which bind and activate both ERα and ERβ, and modulate MM cell growth. We aim to determine whether MM cells conduct denovo synthesis of estrone (E1) and E2 and investigate the roles of ERα and ERβ on mesothelioma cancer cell growth. Estrogen biosynthesis will be measured by stable isotope dilution liquid chromatography mass spectrometry (LC-MS/MS) and cell proliferation assays will be combined with pharmacologic and genetic tools to dissect the roles of ERα and ERβ. This study will elucidate the roles of estrogens and their receptors in MM, and will determine whether inhibition of E2 synthesis or the use of adjuvant hormonal therapy has a role in the treatment of MM in women. Our studies may provide a mechanistic underpinning as to why women are susceptible to mesothelioma following environmental exposure to asbestos.