General Summary

Endometrial cancer is the most frequently diagnosed malignancy of the female genital tract. According to the National Cancer Institute (NCI), endometrial cancer is the most common type of gynecological cancer. In the United States, approximately 43,470 cases are diagnosed and about 7,950 women die from the disease each year. Normal endometrial function requires a balance of progesterone and estrogen effects. A bias towards estrogen action and away from progesterone action underlies endometrial adenocarcinoma, the fourth most common cancer in women. Determining the molecular mechanisms by which the steroid hormones control uterine physiology is critical to understanding the etiology and pathology of these diseases. Disruption of the steroidal control of uterine proliferation leads to the pathology found in endometrial cancer. Molecular mediators of this cellular communication have not been determined. Identification of the mediators of progesterone inhibition of estrogen-stimulated proliferation is critical to the development of treatments for these diseases. We have identified Mitogen Inducible Gene 6, Mig-6, (also known as Errfi1, RALT or gene 33) as an essential mediator of Progesterone Receptor (PR) action in the uterus. Ablation of Mig-6 in the murine uterus leads to the development of endometrial hyperplasia at 5 months of age and endometrial cancer upon unopposed estrogen exposure. Furthermore, we have identified a decrease in Mig-6 expression in endometrial cancer. The basis of this proposal is that Mig-6 acts as a tumor suppressor in endometrial cancer to modulate endometrial cell proliferation and apoptosis regulated by estrogen signaling. The goal of this proposal is to investigate the role of Mig-6 in the tumorigenesis of endometrial cancer and will be accomplished by achieving the following specific aims. First, the tumor suppressor role of Mig-6 in the regulation of estrogen signaling and the tumorigenesis of endometrial cancer will be investigated. Second, the interaction between Mig-6 and the PTEN/PI3K/Akt signaling pathway in the regulation of the tumorigenesis of endometrial cancer will be dissected. Finally, the molecular mechanism by which Mig-6 regulates apoptosis will be investigated. The data derived from these mouse models will facilitate clinically relevant experiments. This study will also provide a model system to investigate the genetic and molecular events involved in the transition from normal to hyperplastic/neoplastic endometrium. This analysis may identify potential diagnostic and therapeutic targets for the treatment of endometrial cancer allowing for the development of future therapeutic tools to attenuate the expression of genes that are harmful to uterine function.