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Title of the thesis: "Assessment of the role of PARKIN gene and its associated molecular mechanism in cervical cancer**"**

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Abstract

Cancer is a complex disease characterized by tumor or malignant growth which results from an uncontrolled proliferation and division of abnormal cells in a part of a body thereby invasion and metastasis of nearby healthy tissues. Hallmarks of cancer states that the normal cells transformed into neoplastic state by continuous acquisition of abnormal traits. The genesis of the tumor could be understood by the alterations that the tumor growth are sustained proliferation, insensitivity to growth suppressor, inducing angiogenesis, resisting cell death, modify cellular metabolism, replicative immortality, evade immunological destruction and tissue invasion and metastasis. Recent advancement in the field of cancer biology explains that the active set of genes involved in the controlling of normal cell behavior. Moreover the constant research is enabled to reach out that the fundamental role played by TSG and oncogene as they take up mostly critical component of cell control like cell cycle and apoptosis.

Cervical cancer is a malignant tumor that occur in region of cervix. It arises in female when normal squamous epithelial cells in the cervix region transformed into developing precancerous lesions and invade to nearby area and form invasive tumor. It also arises due to the genetic or epigenetic alterations or by environmental factors affecting lower reproductive tract of women. The cells of the cervix gradually change into pre-cancerous cells which later results into cancer. It usually takes several years to change pre-cancerous cells into cancerous cells. The disease is preventable if it is detected at early stage of lesion by proper screening methods. But it develops mainly due to the lack of awareness, low socioeconomic, poor genital hygiene, smoking, etc. Massive research has significantly validated that eighty five percent of cervical cancer is caused by HPV (Human papilloma virus). According to Globocan 2018, estimated new cancer case in female worldwide are 86,22,539, out of which 5,69,847 are of cervix uteri. United States of America has shown better scenario of reduction of cervical cancer cases in 2018 with 13,240 cases of incidence and 4,170 cases of mortality. Genetic instability in cervical cancer is commonly associated with loss of heterozygosity or gain of function of tumor suppressor genes/oncogenes.

PARK2 gene was first identified in a Japanese family of patients having hereditary Parkinson's disease (PD) the most frequent form of familial Parkinson disease maps to FRA6E (6q25-q27) the third most active fragile site in the human genome. Loss of expression of *PARK2* have been demonstrated in different types of cancer. At the cellular level, *PARK2* participate in some various cellular activities by its ubiquitination of target protein. *PARK2* has been recommended to regulate the crucial oncogenic molecular target and signaling network in cancer. However, functional impact and explicit mechanism on how *PARK2* deactivation causes cervical cancer has not been established till now.

The molecular mechanisms involve its suppression remains elusive. In this study, we have analyzed molecular mechanisms and functional role of *PARK2* in cervical cancer. It was found that *PARK2* inhibit the proliferation and growth of cervical cancer. We observed that targeted inhibition of *PARK2* induces clonogenic and migratory potential of cervical cancer cells. However, ectopic expression of *PARK2* arrests cell cycle in the G1 phase, inhibits clonogenic potential and metastatic phenotypes of cervical cancer cells. Targeted knockdown of *PARK2* increases both pStat3 and Stat3 levels, inhibited p53, and modulated the expression of cell cycle regulatory proteins (cyclin D1, cyclin E, and CDK2, CDK4, CDK6, p21, p27). Moreover, the progressive loss of *PARK2* in a cervical tissue arrays collected from 100 patients with various ethnic populations was accessed. These results suggest that *PARK2* act as a tumor suppressor in cervical cancer. Over expression of it can inhibit growth and metastasis of cervical tumors possibly *via* suppression of oncogenic Stat3 signaling pathway and cell cycle regulatory proteins.

Our results indicate the tumor suppressive role of *PARK2* in cervical cancer which is evident from cell growth inhibition, apoptosis induction, and reduction in the metastatic potential of cervical cancer cells after overexpressing *PARK2*. Present study elucidates the molecular mechanisms that loss of *PARK2* activates Stat3 signaling pathway and induces the cell cycle regulatory proteins (cyclin D1 and cyclin E), cyclin-dependent kinases (CDK2, CDK4, CDK6), and decreases the expression of p21, p27 and tumor suppressor p53. We also observed a progressive loss of *PARK2* expression in cervical tumor tissues of various ethnic populations. Our findings enlighten the *PARK2* as an emerging genetic molecule having numerous functional role in regulation of various signaling molecules during the cervical cancer progression. Also, the study opens the window to exploit the *PARK2* by gene therapy to develop the pharmacological agents for treatment of human cervical cancer.