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**Elucidation of Signal Transduction Pathways Involved in Molecular Subtypes of Endometrial Cancer**

1Siti Syazani Suhaimi, 1Nurul-Syakima Ab Mutalib, 2Khor Sheau Sean, 1Saiful Effendi Syafruddin, 1Nadiah Abu, 3Reena Rahayu Md Zain, 4Ahmad Zailani Hatta Mohd Dali, 1Rahman Jamal\*

*1UKM Medical Molecular Biology Institute (UMBI), Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; 2Thermo Fisher Scientific, Taman Perindustrian Axis, Shah Alam, Selangor, Malaysia; 3Department of Pathology; 4Department of Obstetrics and Gynaecology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia*

**ABSTRACT**

A comprehensive view of the mutation spectrum in oestrogen receptor positive (ER positive) and oestrogen receptor negative (ER negative) endometrial endometrioid cancer (EEC) has not been extensively reported. The aim of this study is to characterize somatic alterations in ER positive and ER negative EEC as well as to functionally validate their involvement in oestrogen related EEC carcinogenesis. Next generation targeted sequencing of 409 cancer-related genes was performed on the DNA of ER positive and ER negative EEC using Ion Ampliseq™ Comprehensive Cancer Panel on the Ion Torrent PGM. The sequencing results were analysed using Torrent Suite, annotated using ANNOVAR and validated using Sanger sequencing. Focusing on genes involved in endometrial cancer, PTEN is the most frequently altered gene in ER positive subtype (64%, n=11) while PI3KCA and ARID1A are the most frequently altered genes in ER negative group (50%, n=8). Further analysis on genes related to the oestrogen receptor signalling pathway revealed alterations in ERBB3 (36%, n=11), GNAS (27%, n=11) and WHSC1 (27%, n=11) in the ER positive subtype. We further investigated the impact of WHSC1 mutations using in vitro analyses. Mutations in SET domain (R1126H) and PHD domain (L1268P) caused significant increases in cell viability, proliferation, migration and survival, consistent with a gain of function mutation in the endometrial cancer cell line, EEC-1. Mutant L1268P potentially enhanced oestrogen receptor pathway activation and reduction in oestrogen receptor expression in the EEC-1 cells sensitised to Fulvestrant treatment. Using the next generation sequencing approach, we have identified the mutational spectra in ER positive and ER negative subtype of endometrioid endometrial cancer, in our local patients that may lead to understanding of the biological mechanisms for endometrial cancer and ultimately result in improvements in prevention, early detection and treatment.