Immunohistochemical expression of stem cell markers CD133 and Oct-4 in cases of endometrial hyperplasia and endometrial carcinoma

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وَاللَّـهُ أَخْـرَجَكُم مِّـن بُطُـونِ أُمَّهَـاتِكُمْ لَـا تَعْلَمُـونَ شَـيْئًا وَجَعَـلَ لَكُـمُ الـسَّمْعَ وَالْأَبْـصَارَ وَالْأَفْئِـدَةَ لَعَلَّكُـمْ تَشْكُرُونَ

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Lists of Abbreviations

ACOG	:	American College of Obstetricians and Gynecologists.
ASCs	:	Adult Stem Cells.
CEH	:	Complex Atypical Hyperplasia.
CLL	:	Chronic Lymphoid Leukemia.
CSC	:	Cancer Stem Cells.
ECDU	:	Early Cancer Detection Unit.
EH	:	Endometrial Hyperplasia.
EHA	:	Simple Atypical Hyperplasia.
EIC	:	Endometrial Intra-epithelial Carcinoma.
EpCAM	:	Epithelial Cell Adhesion Molecule.
ERCs	:	Endometrial regenerative Cells.
ESCs	:	Embryonic Stem Cells.
FIGO	:	International Federation of Gynecology and Obstetrics.
GPC3	:	Glypican 3.
HNPCC	:	Hereditary Nonpolyposis Colorectal Cancer.
HSCs	:	Hematopoietic Stem Cells.
ICM	:	Inner Cell Mass.
IL-4	:	Interlukin-4.
LVSI	:	Lymph vascular Space Invasion.
MMR	:	Mismatch Repair.

MSCs	:	Mesenchymal Stem Cells.
MSI	:	Microsatellite Instability.
PCOS	:	Polycystic Ovarian Syndrome.
RCOG	:	Royal College of Obstetricians and Gynecologists.
RR	:	Relative Risk
SEER	:	Surveillance Epidemiology and End Results program.
SEH	:	Simple Endometrial Hyperplasia without atypia.
SHBG	:	Sex Hormone Binding Globulin.
SSCs	:	Somatic Stem Cells.
TEK	:	Receptor Tyrosine Kinase.
TICs	:	Tumour Initiating Cells.
TNM	:	Tumor, Node, Metastasis.
USPC	:	Uterine Papillary Serous Carcinoma.
WHO	:	World Health Organization.

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INTRODUCTION

Endometrial cancer (EC) is one of the commonest diagnosed gynecological malignancies affecting women in western countries. It accounts for 6% of all cancers in women worldwide **(Hubbard et al, 2009)** and it represents the seventh leading cause of cancer related death in women **(Kyushima et al, 2002).** In Egypt, tumors of the female genital system represent 4.7% of total malignancies. Endometrial cancer is one of the commonest malignancies in Egyptian women. It accounts for 14.72% of female genital tract malignancies **(Mokhtar et al, 2007).**

The risk of endometrial cancer recurrence ranges from 7.7% to 63.3%, depending on the presence or absence of specific prognostic factors **(Sehouli et al, 2008).**

Cancer stem cells (CSC) is one of these prognostic factors which can be defined as a population of undifferentiated tumorigenic cells responsible for tumor initiation, maintenance, and spread leading to failure of cancer treatment **(Pardal et al, 2003).**

For these reasons, novel targeted therapies are currently being developed aiming to achieve greater specificity for a selected population of cancer cells **(Sokbom et al, 2012).**

Several markers have been identified as solid cancer stem cell markers. CD133 is a cholesterol interacting penta-span transmembrane glycoprotein (120 kd) with 3 isoforms—CD133-1, CD133-2 and CD133-3. CD133-1 mRNA was more prominent in fetal brain and adult skeletal muscles. CD133-2, is a cell surface antigen recognized by anti-CD133 monoclonal antibodies that are used for isolation of hematopoietic stem cells. Later, it was found on endothelial, lymphangiogenic and myoangiogenic progenitors **(Shmelkov et al, 2008).** Loss of CD133-2 correlates with gain in a terminal differentiation. Recently, a third variant CD133-3, was found in epididymis and testis **(Fargeas et al, 2003)**.

Although the biological function of CD133 remains unknown, CD133 is recognized as a stem cell marker for normal and cancerous tissue such as bone marrow, brain, kidney, prostate, liver, pancreas, and skin (**Shmelkov et al, 2008).** Indeed, CD133 is found in cancer stem cells from a variety of solid tumors including endometrium **(Schwab et al, 2008),** ovary **(Silva et al, 2011),** brain, prostate, pancreas, melanoma, colorectum, liver and bile duct, and lung **(Kim et al, 2010)**.

On the other hand, the transcription factor Oct-4 (also known as Oct-3 or POU5f1) is a member of the Pit-Oct-Unc (POU) transcription factor family **(Scholer et al, 1990)** that