STEM CELL EVALUATION BY ALDH1A1 EXPRESSION IN OVARIAN EPITHELIAL TUMORS

Thesis

Submitted for partial fulfillment of the Master degree in pathology

By

Maha Emad El-dein Muhammad Hussein

M.B.B.Ch,

Cairo University

Supervisors

Prof. Dr. Ahmed Mahmoud Abd El- Aziz

Professor of Pathology

Faculty of Medicine

CairoUniversity

Prof.Dr. Hala Naguib Hosni

Professor of Pathology

Faculty of Medicine

Cairo University

Dr. Rasha Ahmed Khairy

Lecturer of Pathology

Faculty of Medicine

Cairo University

Faculty of Medicine

Cairo University

2016

ACKNOWLEDGEMENT

First and foremost always feel indebted to the mighty of ALLAH the most kind and the most merciful.

I express my deepest gratitude to ***Prof. Dr. Ahmed Abd El- Aziz****, Professor of pathology, Pathology Department, Faculty of Medicine, Cairo University, for giving me the advantage of working under his supervision. He saved no time and effort in helping me.*

There are no words to express my sincere gratitude and deepest appreciation to ***Prof. Dr. Hala Naguib Hosni****, Professor of Pathology, Faculty of Medicine, Cairo University, for her constant support, continuous encouragement, priceless suggestions and her constructive comments that allowed me to accomplish this work.*

My profound gratitude goes to ***Dr. Rasha Ahmed Khairy****, Lecturer of Pathology, Faculty of Medicine, Cairo University, for her meticulous scientific supervision, guidance, great help and her creative support throughout this work.*

I'd like to express my great appreciation to all staff members of the Pathology department for their support and encouragement and also my colleagues who helped me with their effort and advice.

Finally, I would like to thank my family for their patience, love, motivation and support throughout this work.

Maha Emad El- Dein Muhammad

ABSTRACT

Background: Increasing evidence has proposed that tumors contain tumors initiating cells or cancer stem cells (CSCs) that are responsible for its progression and relapse. Aldehyde dehydrogenase 1A1 (ALDH1A1) has recently been identified as a marker for cancer stem cells in some human malignancies including ovarian epithelial cancer.

Aim of Work: The assessment of immuno-histochemical expression of ALDH1A1 in epithelial ovarian tumors, tracking stem cells during ovarian cancer development and its correlation with the clinic-pathological features of such tumors.

Methods: This study consisted of 42 cases of ovarian epithelial tumors, classified as 14 cases of benign cystadenomas, 14 cases of borderline tumors and 14 cases of carcinomas. Immuno-histochemical reactions were carried out by using ALDH1A1 monoclonal antibody. Cases were classified into two groups, low ALDH1 expression and high ALDH1 expression.

Results: Immuno-histochemical staining of ALDH1A1 displayed a heterogeneous expression pattern, with differences in the distribution and intensity of positivity. High ALDH1 expression was detected in 26 cases (62%) out of the forty-two studied cases of ovarian tumors. The positivity of ALDH1 was significantly higher in the malignant tumors (86%) than in benign and borderline tumors (50%) (***p*** value = 0.025). There was a significant correlation between ALDH1expression score and the tumor grade (***p*** value = 0.05) where the highest expression of ALDH1 was detected among high grade tumors; grades II & III (100%). More expression of ALDH1A1 was noticed in cases with advanced stage but without statistically significant relation (***P*** = 0.42). Highest ALDH1A1 expression was noticed in cases of serous type tumors (71%) and endometrioid type tumors (100%), although it doesn't reach statistical significance.

Conclusion: ALDH1A1 expression was significantly higher in malignant than benign and borderline tumors and showed significant correlation to prognostically poor parameters in malignant tumors, and thus can be a prognostic indicator in malignant ovarian tumors and a target for further therapy.

Key Words: Cancer stem cells**,** ALDH1A1**,** ovarian epithelial tumors.

CONTENTS

LIST OF ABBREVIATIONS

AACR : American Association for Cancer Research Workshop

ABC : Avidin biotin complex

A-catenin : Alpha- catenin

AI : Auto-implant

ALDH : Aldehyde dehydrogenase

ALDH1 : Class 1 of the ALDH family

ALDH1A1 : Aldehyde dehydrogenase isoform 1A1

APC : Adenomatous polyposis coli gene

APST : Atypical proliferative serous tumor

ASC : Adipose derived stem cells

ASCs : Human adipose derived stem cells

BM : Bone marrow

BPH : Benign prostatic hyperplasia

BRCA1 : Breast Cancer 1

BRCA2 : Breast Cancer 2

CD 133 : Cell membrane differentiation antigen 133

CD 34 : Cell membrane differentiation antigen 34

CD 44 : Cell membrane differentiation antigen 44

CICs : Cancer initiating cells

CSCs : Cancer stem cells

CTNNB : Catenin beta

EOC : Epithelial ovarian carcinoma

ESS : Edessy stem cell score

FC : Flow cytometry

FIGO : International Federation of Gynecology and Obstetrics

GOG : Gynecologic Oncology Group

GSCs : Germ line stem cells

H&E : Hematoxylin and Eosin

IHC : Immunohistochemistry

I-MBOT : Mucinous Borderline Ovarian Tumors of Intestinal Type

KRAS : Kirsten rat sarcoma viral oncogene homolog

LMP : Low malignant potential

LOH : Loss of heterozygosity

MBOTs : Mucinous borderline ovarian tumors

MBTs : Mucinous borderline tumors

N.C.I : National Cancer Institute

Oct 4 : Octamer-binding transcription factor 4

OSCs : Ovarian stem cells

OSE : Ovarian surface epithelium

P53 : Protein 53

PIK3CA : Phosphoinositide 3-kinase catalytic subunit alpha

PP : Pseudomyxoma Peritonei

PTEN : Phosphatase and tensin homolog

SBOT-MP : Serous borderline ovarian tumors, micropapillary patterns

SBOTs : Serous Borderline Ovarian Tumors

SBTs : Serous borderline tumors

SCs : Stem cells

SD : Standard deviation

SLMNs : Sarcoma-like mural nodules

SP : Side population

SPSS : Statistical package for social science

STIC : Serous Tubal Intraepithelial Carcinoma

WB : Western blot

WHO : World Health Organization

LIST OF FIGURES

LIST OF TABLES

LIST OF GRAPHS

INTRODUCTION