The Molecular Pathology of Some Pediatric Renal Tumors

An essay study

Submitted for partial fulfillment of master degree in pathology

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2014

بسم الله الرحمن الرحيم

{سبحانك لا علم لنا الا ما علمتنا انك انت العزيز الحكيم}

صدق الله العظيم

سورة البقرة الآية (٣٢)

Acknowledgement

All thanks are due purely to Allah, whose blessings make possible all good deeds. He has guided us to this and without Him we would not be guided.

My thanks also go to Prof. Dr. ***Samir Alhariry,*** *Professor of Pathology, Faculty of medicine, Al-Azhar University, for his support and assistance.*

I would like to thank my supervisor, Prof. Dr. ***Abd El_Hamid Ahmed Wafik****, Professor of Pathology, Faculty of medicine, Al-Azhar University, who was supportive and helpful in this work.*

*My deepest appreciation and thanks go to my supervisor, Prof.Dr.****Nasser Anwar****, Professor of Pathology, Faculty of medicine, Al-Azhar University, who guided me in each step of this work despite of his responsibilities.*

*I would like also to thank, Dr.****Sayed Tealeb****, Lecturer of Pathology, Faculty of medicine, Al-Azhar University, who gave me valuable advices and suggestions for this work.*

I would like also to thank all my professors and colleagues at the pathology department, faculty of medicine, Al-Azhar University, for their help and encouragement.

My special thanks go to my family, specially my parents and my wife, for their care and support during my work in this essay.

CONTENTS

Table of Contents

List of figures

List of tables

Abbreviations

ALK: Anaplastic lymphoma kinase.

APAF1: Apoptotic protease-activating factor 1.

ASPL: (also known as) ***ASPSCR1:*** alveolar soft part sarcoma chromosome region, candidate 1.

APO1: Accumulation of photosystem one 1.

ASPS: Alveolar soft part sarcoma.

***ATM*:** Ataxia telangiectasia mutated.

BAD: BCL2-antagonist of cell death.

BAK: BCL-2 killer.

BAX: BCL-2 associated X protein.

Bcl-xl: Bcl-XL protein [Xenopus laevis].

Bcl-2: B cell lymphoma 2.

BER: Base excision repair.

BH3: BCL-2 homology 3.

BID: BH3 interacting-domain death agonist.

BIR: Baculovirus IAP repeat protein domain.

***BRCA1*:** Breast cancer gene1.

***BRCA2*:** Breast cancer gene2.

BWS: Beckwith–Wiedemann syndrome.

CCSK: Clear cell sarcoma of kidney.

CD: Cluster of differentiation.

CDKs: Cyclin-dependent kinases.

CDKIs: CDK inhibitors.

CDKN1C: Cyclin-dependent kinase inhibitor 1C gene.

CIP1: CDK inhibitory protein-1.

***CLTC*:** Clathrin heavy chain 1.

CNS: Central nervous system.

CTNNB1: Catenin (cadherin-associated protein), beta 1.

c-Sis: Simian sarcoma viral oncogene homolog.

DDS: Denys-Drash syndrome.

DNA: Deoxy ribonucleic acid.

DR5: Death-inducing receptor 5.

DSBs: Double-strand breaks.

DSRCT: Desmoplastic small-round-cell tumor.

EMA: Epithelial membrane antigen.

ER: Endoplasmic reticulum.

ERK: Extracellular signal-regulated kinases.

ES/PNET: Ewing sarcoma and primitive neuroectodermal tumor.

***ETV6*:** E-twenty six translocation variant 6.

FADD: FAS-associated death domain protein.

***FAM 22*:** Family with sequence similarity 22.

FAS: Cell surface receptor protein of the TNF receptor family.

FRN: Fetal Rhabdomyomatous Nephroblastoma.

FWT1: Familial Wilms tumor 1 gene.

FWT2: Familial Wilms tumor 2 gene.

GADD45: Growth arrest and DNA damage 45.

GDP: Guanosine diphosphate.

GFAP: Glial fibrillary acidic protein.

GTP: Guanosine triphosphate.

GU: Genitourinary.

G1: Gap 1 phase of cell cycle.

HMB-45: Human Melanoma Black-45.

hMLH1: human mutL homolog 1.

hMSH1: human mutS homolog 1.

hMSH2: human mutS homolog 2.

***hSNF5*:** (also known as) **SMARCB1:** SW1/SNF related, matrix associated, actin dependent regulator of chromatin B1.

H19: (also known as) **ASM:** Adult Skeletal Muscle gene.

IAP: Inhibitor of apoptosis.

IC1: Imprinting center 1.

IFS: Infantile fibrosarcoma.

IGF2: Insulin-like growth factor 2 gene.

IHC: Immunohistochemistry.

ILNR: Intralobar nephrogenic rests.

IMS: Intermembrane space.

INI1: Integrase interactor 1.

Kb: Kilobase.

KILLER: (also known as) **TNFRSF10B**: Tumor necrosis factor receptor superfamily.

KTS: Lysine, threonine, and serine.

LOH: loss of heterozygosity.

LOI: Loss of imprinting.

MAPK: Mitogen activated protein kinase.

MCL1: Myeloid cell leukemia sequence 1.

MDM2: Mouse double minute 2.

MEK: Alternative name to mitogen activated protein kinase.

MET: Mesenchymal-epithelial transition factor gene.

MMR: Mismatch repair.

MOMP: Mitochondrial outer membrane permeabilization.

MRTK: Malignant rhabdoid tumor of kidney.

MRTKs: Malignant rhabdoid tumor of kidneys.

MutH: Mutator H.

MutL: Mutator L.

MutS: Mutator S.

***MYC*:** Myelocytomatosis viral oncogene homolog.

NER: Nucleotide excision repair.

NONO: Non-POU domain-containing octamer-binding.

NOXA: NADPH oxidase activator.

NSE: Neuron-specific enolase.

***NTRK3*:** Neurotrophic tyrosine kinase, receptor, type 3.

OMI: (also known as) **HtrA2:** HtrA serine peptidase 2.

Pax-2: Paired box 2.

***Pax6*:** Paired box 6.

PDGF: Platelet derived growth factor.

PDGF-R: Platelet derived growth factor receptor.

PIGs: P53-inducible genes.

PNET: Primitive neuroectodermal tumor.

PRCC: Papillary renal cell carcinoma gene.

***PSF*:** (also known as) ***IGFBP7*:** insulin-like growth factor binding protein7

PUMA: P53 up-regulated modulator of apoptosis.

P21: Protein 21.

RAD51: RecA homolog repair protein.

RAF: v-raf-1 murine leukemia viral oncogene.

RAS: Rat Sarcoma.
RCC: Renal cell carcinoma.
ROS: Reactive oxygen species.

SMA: Smooth muscle actin.

SMAC: Second mitochondria-derived activator of caspace.

SMARCB1: SW1/SNF related, matrix associated, actin dependent regulator of chromatin B1.

tBID: Truncated BID.

TEL: (also known as) **ETV6:** E-twenty six translocation variant 6.

TFEB: Transcription factor EB.

***TFE3*:** Transcription factor binding to IGHM enhancer 3.

TGF-beta: Transforming growth factor beta.

TNF: Tumor necrosis factor.

TP53: Tumor protein 53.

UPD: Uniparental disomy.

UV: Ultra-violet.

***WAF1*:** Wild-type activating fragment-1.

WAGR: Wilms tumor, aniridia, genitourinary anomalies, and mental retardation.

WT: Wilms tumour.

WTs: Wilms tumours.

WTX: Wilms Tumor Gene on X chromosome.

WT1: Wilms tumour1 gene.

WT2: Wilms tumour2 gene.

XIAP: X-linked inhibitor of apoptosis protein.

XPA: Xeroderma pigmentosum complementation group A.

XPB: Xeroderma pigmentosum complementation group B.

XPC: Xeroderma pigmentosum complementation group C.

YWHAE: Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon.

Introduction

Renal tumors are the fifth most common tumors in children, of which Wilms tumor (WT) is the most frequently occurring. Pediatric renal tumors present special challenges for surgical pathologists. Their histologic diversity makes a potential for clinically significant diagnostic errors. Tumor-specific treatment approaches depend on accurate diagnosis and staging ***(Mills et al., 2010).***

In early infancy (up to the age of 3 months); the predominant renal tumor is mesoblastic nephroma while during the rest of childhood, Wilms tumor accounts for about 95% of all primary renal tumors and this percentage starts to decrease above the age of 10 years. Renal cell carcinomas accounts for one third of all cases above the age of 10 years. Clear cell sarcoma of kidney (CCSK) and malignant rhabdoid tumor of kidney (MRTK) each comprises about 2-3% of all childhood renal tumors but they have different age distributions. MRTKs are diagnosed in the first year of life whereas CCSK has a similar age distribution to Wilms tumor, with a median age at diagnosis of 3-4 years ***(Jones and Vujanic, 2010).***

In the last decade traditional diagnostic approaches were supplemented with a significant number of reliable molecular diagnostic tools, detecting tumor type-specific genetic alterations. In addition, the successful application of some of these techniques to formalin-fixed paraffin-embedded tissue made it possible to subject a broader range of clinical material to molecular analysis. Thus, molecular genetics has already become an integral part of the work-up in some tumors ***(Antonescu, 2006).***

Much progress has been made in understanding the molecular basis of the various renal tumours of childhood in the last decade. However, to date, the impact on clinical practice has been limited mainly to improved diagnostic classification. There is a continued need for translational research to identify better biomarkers that predict response to therapy and long term outcomes. Understanding the biological pathways that underlie high' and low' risk tumour behavior and how these relate to histological subtypes will be a key to the introduction of targeted therapies, that should improve efficacy and reduce toxicity of current treatments ***(Jones and Vujanic, 2010).***