DNA Repair systems in Hematological malignancies

Essay

Submitted for the partial fulfillment of
M.Sc.Degree
In

CLINICAL & CHEMICAL PATHOLOGY

By

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2010

بسم الله الرحمن الرحيم

Ackonwledgments

First : all praise to allah

I would like to express my deep gratitude to prof. **Dr.Omaima Gohar** , professor of clinical and chemical pathology for her scientific support and relentless effort to help me through this essay.

I would like to express my gratitude to my supervisor, **Dr. Ghada Mossallam,** whose expertise, understanding, and patience, added considerably to my essay experience. I appreciate her vast knowledge and skill in many areas, and her assistance in writing my essay, which made me wish that some day I can turn up to be like her in any way.

I would also like to thank my family and my mother for the support they provided me through my entire life and in particular, I must acknowledge my Husband , without whose love, encouragement and editing assistance, I would not have finished this essay.

This research would not have been possible without the moral aid of my parents in law and all my friends at National cancer institute I really thank all for their support and love and finally I dedicate this work as a whole for the soul of my father who would have loved to have seen it .

Acknowledgment

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LIST OF ABBREVIATIONS

53BP1: P53 Binding Protein 1
6-4PP:6-4photoproducts
A:adenine
AAF: N-acetoxy-2-acetylaminofluorence
AAG:alkyl adenine DNA glycosylase
ADEPT:Ab directed prodrug therapy
ADP :Adenosine diphosphate
AKAP9: A kinase anchor protein 9
ALL:Acute lymphoblastic leukemia
AML:Acute myeloid leukemia
AP:apurinic or apyrimidinic
APE1:ap endonuclease 1
APEX:arrayed primer extension
ARC :Activator-Recruited Cofactor (Mediator complex)
AT:ataxia telangiectasia
ATF-2: Activating transcription factor-2
ATLD:Ataxia telangiectasia like disorder
ATM: Ataxia–telangiectasia mutated
ATP:Adenosine triphosphate
ATR: Ataxia–telangiectasia mutated related
ATRIP:(**TREX1 (DNase III))** three prime repair exonuclease 1
BAX: BCL2-associated X
BCR/ABL: breakpoint cluster region/ V-abl Abelson murine leukemia viral oncogene homolog 1
BER:base excision repair
BLM:bloom syndrome gene
bp : base pair(s)
BRCA1: Breast-cancer gene 1
BRCA2 (FANCD1): Breast-cancer gene 2
BRIP1: *BRCA1*-interacting protein C-terminal helicase 1
C:cytosine
cAMP : cyclic adenosine 3',5'-monophosphate
CASP8: Caspase 8
CBP: CREB binding protein
Cdc25A:cell division cycle 25 homolog A
CDC25C: cell division cycle 25 homolog C
CDH1: Cadherin-1
CDK: Cyclin-dependent protein kinase
cDNA : DNA complementary to RNA
CHK1: Cell–cycle–checkpoint kinase1
CHK2: Cell–cycle–checkpoint kinase2
CLL:chronic lymphocytic leukemia
CML:Chronic myeloid leukemia
CMMR-D: Constitutional mismatch repair-deficiency syndrome
c-Myc: Cellular DNA-binding proto-oncogene protein encoded by the myc gene
CPD:cyclobutane pyrimidine dimer

CRC: Colorectal cancer
CREB: Cyclic-AMP response element binding protein
CS: Cockayne syndrome
DBP: Adenovirus DNA-binding protein
DCLRE1C (Artemis)
DDR:DNA damage response
DMC1: Disruption of Meiotic Control
DNA: Doexyribonucleic acid
DNA-PK:DNA protein kinase
DNase : deoxyribonuclease
Dntp: deoxyribonucleoside triphosphate
DSB:double strands breaks
dsDNA: double-stranded DNA
EGFP:enhanced green fluorescence protein
ELISA:– enzyme-linked immunosorbent assay
ELISA:enzyme linked immunosorbant assay
EME1 (MMS4L): essential meiotic endonuclease 1 homolog 1 (S. pombe)
EME2: essential meiotic endonuclease 2
ENase (or R·) : restriction endonuclease
ERCC1: Excision Repair Cross Complementing1
ERCC2, 3:TFIIH Helicases (Excision Repair Cross Complementing), also known as XPD and XPB (Xeroderma Pigmentosum), respectively
EXO1 (HEX1):exonuclease I
FANCD2: Fanconi anemia, complementation group D2
FCP1 :TFIIF-associated CTD phosphatase
FEN1 (DNase IV): flap structure-specific endonuclease 1
FISH:fluorescent insitu hybridization
G – guanine
G22P1 (Ku70): XRCC6
Gap 0 G0
Gap 1 G1
Gap 2 G2
GDEPT:gene directed prodrug therapy
GEN1: Gen homolog 1, endonuclease (Drosophila)
GGR: Global genome repair
GST: Glutathion S-transferase
GTF: General Transcription Factors
H1,2A, ..5 Histone (1, 2A, 2B, 3, 4, 5)
HAT: Histone acetyl transferase
HDAC: Histone deacetylase
HIV :Human Immunodeficiency Virus
HMT: Histone methyltransferase
HNPCC:Hereditary nonpolyposis colon cancer
HP1: Heterochromatin Protein 1
HR: homologous recombination
HR23B: RAD23 homolog B (S. cerevisiae)
ICL: Interstrands crosslinks

IL:interleukins
In vitro:term used to describe effects in biological material outside the living animal
In vivo :term used to describe effects in living animals
IRIF:IR-induced immunofluorescent foci
IRIonizing radiation
ISWI :Class of chromatin remodeling complexes, (named after a drosophila ATP hydrolysing protein called Imitation SWItch)
kb : kilobase(s) or 1000 bp
kDa: kilodalton(s)
KID :Kinase-inducible activation domain of CREB
LFS: Li-Fraumeni syndrome
LIG4:ligase 4
LP-BER: long patch base excision repair
LM-PCR:ligation mediated PCR
M: mitosis
MAD2L2 (REV7):MAD2 mitotic arrest deficient-like 2 (yeast)
MAF:Minor allelefrequency
MALDI-TOF: Matrix Assisted Laser Desorption Ionization Time-of-Flight
MBD4: methyl-CpG binding domain protein 4
MDC1: Mediator of DNA damage checkpoint protein 1
MDM2:murine double minute GENE
MDR1:Multi drug resistance gene1
MDS:myelodysplastic syndrome
MLH1: MutL homolog 1
MLH3: MutL homolog 3
MLL:mixed lineage leukemia gene
MMR: mismatch repair
Mre11: meiotic recombination 11
mRNA :messenger RNA
MS: Mass Spectrometry
MSH2: MutS homolog 2
MSH3: MutS homolog 3
MSH4-:MutS homolog 4
MSH5: MutS homolog 5
MSH6: MutS homolog 6
MSI: microsatellite instability
mt : mitochondria(l)
MTase (or M ·): DNA methyltransferase
MUS81; MUS81 endonuclease homolog (S. cerevisiae
MW: Molecular weight
MYH: MutY homolog
NAD : nicotinamide-adenine dinucleotide
NADH its reduced form
NBS1: Nijmegen breakage syndrome 1
NBS1:Nibrin
NEIL1,2,3
NER: nucleotide excision repair

NF:B Nuclear Factor B
NFQ:non fluorescent quencher
NF-Y: Nuclear Factor Y, a trimeric CCAAT-binding factor
NHEJ: Non-homologous end-joining
nt :nucleotide(s)
NTCP:normal tissue complication probability
NTH1: nth endonuclease III-like 1 (E. coli)
OOG1: oogenesin 1
ORF : open reading frame
ori :origin(s) of DNA replication
p : plasmid
p, P:– promoter
p21, Cip1:cyclin-dependent kinase inhibitor 1A
P53: protein 53 or tumor protein 53),
PA : polyacrylamide
PAGE: PA-gel electrophoresis
PALB2: Partner and localizer of BRCA2
PARP1: Poly–adenosine diphosphate–ribose polymerase 1
PCNA: proliferating cell nuclear antigen
PCR: Polymerase Chain Reaction
PEG : poly(ethylene glycol)
PLDR:potential lethal damage repair
PMS1: Postmeiotic segregation 1
PMS2: Postmeiotic segregation 2
PMS2L3: postmeiotic segregation increased 2-like 3
PMS2L4 (PMS6): postmeiotic segregation increased 2-like 4 pseudogene
POLB,D,E,G,H,I,K,M,N,Q:polymerase B,D,E,G,H,I,K,L,M,N,Q
POLD1: polymerase (DNA directed), delta 1, catalytic subunit
PRKDC: protein kinase, DNA-activated, catalytic polypeptide
PRSS1: Protease serine 1
PTEN: Phosphatase and tensin homologue
QPCR:quantitative PCR
RAD50 :RAD50 homolog (RecA homolog, E. coli) (S. cerevisiae)
RAD51: RAD51 homolog (RecA homolog, E. coli) (S. cerevisiae)
RAD51C RAD51 homolog (RecA homolog, E. coli) (S. cerevisiae)
RAD51L1 (RAD51B) RAD51 homolog (RecA homolog, E. coli) (S. cerevisiae)
RAD51L3 (RAD51D) RAD51 homolog (RecA homolog, E. coli) (S. cerevisiae)
RAD52 RAD52 homolog (RecA homolog, E. coli) (S. cerevisiae)
RAD54B RAD54 homolog (RecA homolog, E. coli) (S. cerevisiae)
RAD54L RAD54 homolog (RecA homolog, E. coli) (S. cerevisiae)
RAP30, RAP74 :RNA Polymerase-associated proteins, also known as TFIIFb and TFIIFa
RAR, RXR:Retinoic Acid Receptor, Retinoid X Receptor
RBBP8 (CTIP): retinoblastoma binding protein 8
RDS:radioresistant DNA synthesis
REV1L (REV1): REV1-like (yeast).
REV3L (POLZ): REV3-like, catalytic subunit of DNA polymerase zeta (yeast)
RFC:Replicating factor c

RFLP: restriction-fragment length polymorphism
RIA:radio immune assay
RNA: Ribonucleic acid
RNAPII:RNA Polymerase II
RNase : ribonuclease
ROS:Reactive oxygen species
RPA: Replication protein a
RPB1,2:12 RNA Polymerase II subunit 1-12
rRNA :ribosomal RNA
S: Synthesis
SAP130: spliceosome-associated protein 130
SCF (Skp1/Cullin/F-box protein)-
SDS: sodium dodecyl sulfate
SHFM1 (DSS1): split hand/foot malformation (ectrodactyly) type 1
SiRNA:small inhibitory RNA
SMC1: Structural maintenance of chromosome protein 1
SMCC :SRB/MED-containing cofactor complex
SMUG: single-strand-selective monofunctional uracil-DNA glycosylase 1
SP1: Cellular transcription factor
SP-BER: Short patch base excision repair
SPO11: SPO11 meiotic protein covalently bound to DSB homolog (S. cerevisiae)
Ss: single strand(ed)
SSB:-Single strand breaks
SSCP:single strand conformational polymorphism
SsDNA: single-stranded DNA
SWI/SNF: Class of chromatin remodeling complexes, (named after the mating type SWItching and Sucrose Non Fermenting yeast genes)
T :thymidine
t, T :terminator of transcription
TAD :Transcription Activation Domain
TAFII:TBP associated factor
TCP:tumour control probability
TCR:Transcription coupled repair
TDG: Thymine DNA glycosylase
TFIIA, B,: Transcription factor II (A, B, D, E, F, H)
TK : thymidine kinase
TLS: translesion DNAsynthesis
TP53: Tumor protein p53
TREX1 (DNase III): three prime repair exonuclease 1
TREX2: three prime repair exonuclease 2
Trna: transfer RNA
TTD: trichothiodystrophy
u : unit(s)
U :URACIL
UDS: unscheduled DNA synthesis
UNG: uracil-DNA glycosylase
URF :unidentified open reading frame

UTR: unstranslated region(s)
UV(A,B,C): ultraviolet (A,B,C)
UV: ultraviolet
UV-DDB: UV-damaged DNA binding protein
WRN:Werner syndrome gene
wt : wild type
XLF:XRCC4 like factor
XP(C,D,B,G,A,F): xeroderma pigmentosum (C,D,B,G,F)
XP: xeroderma pigmentosum
XRCC1,2,3,4: X-ray repair complementing defective repair in Chinese hamster cells1,2,3,4
XRCC5 (Ku80) X-ray repair complementing defective repair in Chinese hamster cells5
XRT:radiotherapy

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Introduction

In human cells, both normal metabolic activities and environmental factors such as UV light and radiation can cause DNA damage, resulting in as many as 1 million individual molecular lesions per cell per day. DNA repair refers to a collection of processes by which a cell identifies and corrects damage to the DNA molecules that encode its genome ***(Lodish, 2004.).***

Many of these lesions that cause structural damage to the DNA molecule can alter or eliminate the cell's ability to transcribe the gene that the affected DNA encodes. Other lesions induce potentially harmful mutations in the cell's genome, which affect the survival of its daughter cells after it undergoes mitosis ***(Maynard, 2009)***. Consequently, the DNA repair process is constantly active as it responds to damage in the DNA structure.

Depending on the type of damage inflicted on the DNA's double helical structure, a variety of repair strategies have evolved to restore lost information (***Watson, 2004***). Recent evidence suggests that alterations in protiens participating in the DNA repair systems may result in cellular senscence, cell death and neoplastic transformation ***(Papaefthymiou, 2008)***. DNA damages in frequently dividing cells, because they give rise to mutations, are a prominent cause of cancer ***(Browner, 2004).***

Inherited mutations that affect DNA repair genes are strongly associated with high cancer risks in humans. Hereditary nonpolyposis colorectal cancer (HNPCC) is strongly associated with specific mutations in the DNA mismatch repair pathway ***(Meyer, 2009).*** BRCA1 and BRCA2, two famous mutations conferring a hugely increased risk of breast cancer on carriers, are