بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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MONA MAGHRABY

Evaluation of ADAM28 expression in adult Egyptian Acute Myeloid Leukemia patients and its impact on outcome

Thesis

Submitted in Partial Fulfillment of the Requirement of the Master Degree

In

Internal Medicine

By

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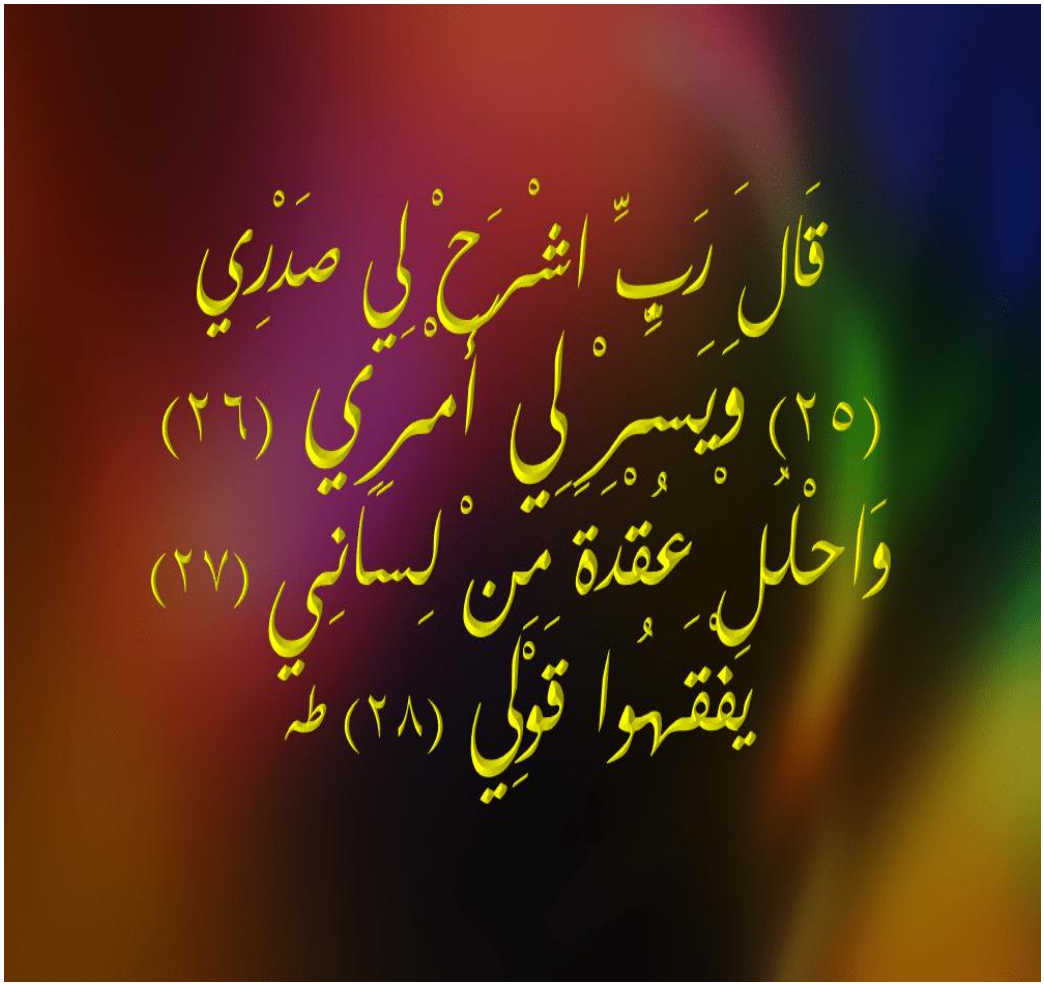

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List of Abbreviations

Abb.	Full term

ADAMDEC1.....*ADAM-like decysin 1*
ADAMs.....*A disintegrin and metalloproteinases*
ADAMTS.....*ADAM and ADAM with thrombospondin motifs*
ALL .....*acute lymphoblastic leukemia*
AML .....*Acute myeloid leukemia*
AP1.....*activator protein 1*
AYA .....*adolescent and young adult*
bFGF.....*basic fibroblast growth factor*
CART.....*chimeric antigen receptor-T*
CBF-AML.....*core binding factors-acute myloid leukemia*
CBFb .....*core binding facto b*
CBFs.....*core binding factors*
CIR .....*Cumulative incidence*
CLL .....*chronic lymphocytic leukemia*
CML .....*chronic myeloid leukemia*
CN-AML.....*Cytogenetically normal acute myeloid leukemia*
CR.....*complete remission*
DNA.....*Deoxyribonucleic acid*
ECM .....*extracellular matrix*
EGF.....*epidermal growth factor*
ELISA.....*Enzyme-linked immunosorbent assay*
FLAG-IDA.....*fludarabine, cytarabine, G-CSF and idarubicin*
FLT3.....*Fms-like tyrosine kinase 3*
FRβ .....*folate receptor family*
GFP.....*green fluorescent protein*
GO .....*Gemtuzumab ozogamicin*
HSCT.....*Hematopoietic stem cell transplant*
IGF-I.....*insulin-like growth factor I*
IL.....*Interleukin*
MAPK.....*mitogen-activated protein kinase*
MDC.....*metalloproteinase disintegrin cysteine-rich*
MDS .....*myelodysplastic syndromes*
MMAE.....*monomethyl auristatin E*
MMPs.....*matrix metalloproteinases*
MMPs.....*matrix metalloproteinases*
MTD .....*maximum tolerated dose*

List of Abbreviations (Cont…)

Abb.	Full term

NQO1 .....NAD (P) H: quinone oxidoreductase 1 of relapse
PCR .....Polymerase chain reaction
PKC.....protein kinase C
RAR.....retinoic acid receptor
RECK .....reversion-inducing cysteine-rich protein with Kazal motifs
RFS.....relapse-free survival
RFS.....Relapse-free survival
SEER.....Surveillance, Epidemiology, and End Result
STAT3 .....signal transducer and activator of transcription 3
SVMPs.....snake venom metalloproteinases
TGF.....transforming growth factor
TIMP-3.....tissue inhibitor of metalloproteinases-3
TK.....tyrosine kinase
TKI.....tyrosine kinase inhibitors
TNF- alpha.....tumor necrosis factor- alpha
TRM .....treatment-related mortality
VEGF.....vascular endothelial growth factor
WHO.....World Health Organization

Introduction

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults and is fatal as a result of primary refractoriness, relapse, or treatment-related mortality (**Wouters and Delwel, 2016).** Although the majority of patients with AML enter remission upon induction chemotherapy, the risk of relapse is considerable **(Bower et al., 2016)**. Transplantation regimens can be curative, but it remains challenging to identify high risk patients suitable for early transplantation (**Cornelissen and Blaise, 2016)**.

A disintegrin and metalloproteinases (ADAMs) are a new gene family of proteins with sequence similarity to the reprolysin family of snake venomases that share the metalloproteinase domain with matrix metalloproteinases (MMPs). They are structurally classified into two groups: the membrane-anchored ADAM and ADAM with thrombospondin motifs (ADAMTS) **(Zhang et al., 2016).**

These molecules are involved in various biological events such as cell adhesion, cell fusion, cell migration, membrane protein shedding and proteolysis. Studies on the biochemical characteristics and biological functions of ADAMs are in progress, and accumulated lines of evidence have shown that some ADAMs are expressed in malignant tumors and participate in the pathology of cancers. The activities of ADAMs are regulated by gene expression, intracytoplasmic and pericellular regulation, activation of the zymogens and inhibition of activities by inhibitors (**Dong et al., 2015).**

Many ADAM species, including ADAM8, ADAM9, ADAM10, ADAM12, ADAM15, ADAM17, ADAM19, ADAM28, ADAMTS1,

ADAMTS4 and ADAMTS5, are expressed in human malignant tumors. Many of them are involved in the regulation of growth factor activities and integrin functions, leading to promotion of cell growth and invasion, although the precise mechanisms of these are not clear at the present time **(Reiss and Saftig, 2009).**

ADAM28, a member of the ADAM family, cleaves various substrates including von Willebrand factor. Two isoforms of ADAM28: the membrane associated (ADAM28m) and the secreted (ADAM28s) were identified. Both were overexpressed in solid tumors including breast carcinoma, non-small cell lung cancer, and bladder transitional cell carcinoma **(Hubeau et al., 2020).**

ADAM28 has been shown to relate with tumor proliferation and prognosis However, little is known about expression and potential role of ADAM28 in hematological malignancies. Limited studies suggested that the expression of ADAM28 is up-regulated in acute myeloid leukemia **(Zhang et al., 2019)**. However, the mechanism by which ADAM28 regulates the leukemic cell and the prognostic relevance with AML remain unknown.

Aim of the work

To evaluate ADAM28 expression in newly diagnosed adult Egyptian Acute Myeloid Leukemia patients and to assess its impact on outcome

Review of Literature

Acute Leukemia

Leukemias are a group of life threatening malignant disorders of the blood and bone marrow. In the adolescent and young adult (AYA) population, the acute leukemias are most prevalent, with chronic myeloid leukemia being infrequently seen. Factors associated with more aggressive disease biology tend to increase in frequency with increasing age, whilst tolerability of treatment strategies decreases. There are also challenges regarding the effective delivery of therapy specific to the AYA group, consequences on the unique psychosocial needs of this age group, including compliance **(Baker et al., 2018).**

Epidemiology

Leukemia is the common name for several malignant disorders that present with increased numbers of leucocytes in the blood and/or the bone marrow. The dominantly presenting leukemia cells may be mature such as in chronic lymphocytic leukemia (CLL), or precursor cells of various lineage such as in the acute leukemias, or both precursor and mature cells as in chronic myeloid leukemia (CML) **(Hayakawa et al., 2016).**

Leukemias may present at all ages, from the newborn to the very old, but different forms have very different age distributions, with acute lymphoblastic leukemia (ALL) most common in early childhood and rare in adults, whereas acute myeloid leukemia (AML) is being less common than ALL in children but increasingly common in older adults. CML is very rare in young children, and CLL, the most common form of