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THE DIVERSE ROLES OF MUCOSAL-ASSOCIATED INVARIANT T LYMPHOCYTES IN HEMATOLOGICAL MALIGNANCIES

Ali A Ahmed[1*], Omnia Hassan El-Badawy[2], Mohamed A El-Mokhtar[2,3], Omer A Ahmed[4] Marwa A Sabet [5], Asmaa M. Zahran [6], Salwa Seif Eldin [2]

[1]*Microbiology and Immunology Department, Faculty of Pharmacy, Assiut University, Assiut, Egypt*
[2]*Medical Microbiology and Immunology Department, Faculty of Medicine, Assiut University, Assiut, Egypt*
[3]*Gilbert & Rose-Marie Chagoury School of Medicine, Lebanese American University, Byblos, Lebanon*
[4]*Department of Pharmacy, Al-Mansha Central Hospital, Sohag Health Directorate, Sohag, Egypt*
[5]*Department of Microbiology and Immunology, Faculty of Pharmacy, Sphinx University, New-Assiut, Egypt*
[6]*Department of Clinical Pathology, South Egypt cancer Institute, Assiut University, Assiut 71515, Egypt*

The majority of studies on Novel Mucosal-associated invariant T (MAIT) cells have focused on their involvement in solid tumours; however, the role and significance of MAIT cells in hematological malignancies are not well understood and have not been thoroughly investigated. MAIT cells is a population of αβ T cells that recognize non-peptide antigens presented by the non-polymorphic MR1 molecule. They are characterized by the expression of Vα7.2 together with high expression of the CD161. MAIT cells have been linked to a variety of tumours including, solid tumours such as hepatocellular carcinoma, colorectal, lung and kidney cancers and their frequencies in the tumour sites appeared to correlate with prognosis. MAIT cells were also studied in hematological malignancies such as multiple myeloma and leukaemia. In this review we will outline our current understanding of the relationship between MAIT cells and hematological malignancies, which will underline the possibility of targeting this subset for modern immunotherapy development

Keywords: *MAIT cells, Acute myeloid leukemia (AML), Vα7.2, IFN, GrB and Immunotherapy*

INTRODUCTION

Hematological malignancies are a broad category of illnesses that need intensive and severe therapy, such as Hodgkin vs non-Hodgkin lymphoma and lymphoid versus myeloid leukemia. Many patients with hematological cancer, especially those with lymphoma and myeloma, have psychological anguish and a poor quality of life throughout their disease trajectory. With the use of more tolerable medications, such as monoclonal antibodies or immuno-modulatory drugs, in the early treatment of multiple myeloma and an increase in older patients undergoing hematopoietic stem cell transplantation for myelodysplastic syndrome or acute myeloid leukemia, treatment options for these malignancies have improved recently [1-3].

Mucosal-associated invariant T (MAIT) cells represent a T cell subset, distinguished chiefly among the double negative (DN) ($CD8^-$ and $CD4^-$) subgroup of T cells. These distinctive T cells are existing in elevated quantities within human blood and mucosae. These cells could be detected via the

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*Corresponding author: Ali A Ahmed, E-mail: aliabdelhafiz@pharm.aun.edu.eg

expression of invariant T cell receptor Vα7.2−Jα33 (TCR) along with elevated levels of surface CD161; which have been demonstrated to offer reliable markers for MAIT cell detection in a variety of settings [4].

In the field of immuno-oncology, Fozza, La Nasa and Caocci [5] demonstrated that IFNγ and other immune-regulatory mediators can be released by T cells in the event of sharing the microenvironment with AML cells, which may play a part in AML coherence of Pro/anti-angiogenic (the growth of new blood vessels) chemokine release, cell proliferation, and control apoptosis. Furthermore, IFNγ appears to affect the growth of several non-leukemia cells in the microenvironment. Conversely, Chopra and Bohlander [6] reported that certain subsets of AML cells ($CD64^+$ AML cells) exhibited apoptosis via GrB cell specific cytotoxicity. However, $CD64^-$ AML cells were uninfluenced.

MAIT cells might have a potential future in malignancy immunotherapy just as drugs and/or endogenous ligands could regulate their function, making them interesting targets from a therapeutic perspective [7]. However, there is a notable need for more knowledge to understand the role of MAIT cells in the pathophysiology of hematological malignancies. In this review, we will go over what is currently known about the function of MAIT cell subsets and their significance for anti-cancer immunity.

Mucosal-associated invariant T (MAIT) cells

Mucosal-associated invariant T (MAIT) cells constitute a type of αβ thymocyte found in humans which exhibit natural immunity-like characteristics and are evolutionarily conserved. They are mainly present in the double-negative subset and constitute a noteworthy quantity of T lymphocytes in the peripheral blood (PB) and liver. Although their exact function is uncertain, they can be found in various locations throughout the body. MAIT cells possess conserved T cell receptor repertoires and prompt the sequence-specific DNA-binding factor Promyelocytic Leukemia Zinc Finger (PLZF), that is accountable in favor of their nonspecific immunity similar functionality [8]. These cells can produce cytokines in reply to inflammation and do not require thymocyte receptor stimulation. MAIT cell activation can be initiated by inflammatory cytokines and can be modulated by other aspects. Whenever active, MAIT cells are able to produce immunomodulatory cytokines. They respond to a conserved antigen shared among different microorganisms [9]. MAIT cell stimulation is reliant on the TCR and the molecule related to major histocompatibility complex class one. (MR1). These molecules are abundantly demonstrated in all kinds of cells and is conserved across species, indicating their important role in immunity. Soluble microbial compound has been identified as the activating ligand for MAIT cells, later recognized as riboflavin (vitamin B2). These specific molecules are specifically present in yeasts and bacteria that synthesize riboflavin, and they grant a wide range of antimicrobial reactivity to MAIT cells. They traverse the entire organism and govern the maturation process of MAIT cells within the thymus [10]. Within 2014, an investigation demonstrated that the robust activating molecule in the process of producing riboflavin was a compound "that does not require an enzyme" derived from 5-amino-6-d-ribitylaminouracil (5-A-RU). The discovery of vitamin B2/B9 as ligands for MR1 greatly aided in the advancement of MR1 tetramer development in both humans and mice. These instruments have greatly improved our knowledge of the biology of MAIT cells, especially in the context of tissues and developmental processes. One of the primary observations made when utilizing the MR1 tetramer in human subjects was the absence of a solitary constant TCR expression in MAIT cells. MAIT, on the other hand, exhibits limited TCRs that include Vα7.2−Jα12, Jα20, or Jα33. Ultimately, MAIT cell, are distinguished from other T lymphocytes by two primary features first: they exhibit the presence of a partial invariant Vα7.2 TCR. Second: their activation is facilitated by microbial vitamin B antigens, which are presented by MR one [11]. This activation enables T cells to carry out both type one and type seventeen effector functions. Third, demonstrate inherent characteristics that resemble those of natural immunity, which are controlled by the expression of PLZF [11]. These characteristics include the capacity to be activated by cytokines, regardless of TCR. It has been determined that a soluble microbial molecule, more precisely an unstable metabolite of vitamin B2, is the ligand that

causes the activation of MAIT cells. These compounds are unique to bacteria and yeasts, which produce riboflavin and provide MAIT cells with antibacterial reactivity. The compound involved in the biosynthesis pathway of riboflavin was subsequently recognized as a nonenzymatic product derived from 5-A-RU [12].

Biology of MAIT cells

Frequency and Localization

Human MAIT cells are located in the bloodstream, making up a noteworthy portion of T lymphocytes. MAIT cells are a major component of T cells found in the liver and are also found in other tissues such as the lung, female reproductive tract, adipose tissue, and to a lesser degree, the gut. These cells are mainly found in peripheral tissues, indicating a tissue-resident phenotype. They express markers associated with tissue-resident T cells and do not express lymph node homing receptors. Recent findings suggest that while most tissue MAIT cells are resident populations, some subsets may possess the capacity to recirculate. The frequency of MAIT cells is determined by genetic and environmental factors, with the frequency decreasing with age and in certain diseases, but expanding in response to infection or inflammation. Environmental factors may have a greater influence on MAIT cell frequency than genetic factors. However, additional investigation is required to validate these results. using specific techniques for MAIT cell identification [9].

MAIT cells' T cell receptor (TCR)

MAIT cells demonstrate a Vα7.2-Jα33/12/20 TCR alpha chain which links alongside Vβ2 or Vβ13, and their αβ TCR are primarily composed of an invariant TCR alpha chain connected with a biased set of Vβ chains. This enables MAIT cells to distinguish between the short peptide antigens given by polymorphic MHC Class I or MHC Class II molecules, which typical T cells identify, and non-peptide ligands coupled to monomorphic MHC Class I-like molecules, such as riboflavin metabolites bound to MR1 [9].

Phenotypes

MAIT cells, with a majority of DN (20%), some CD8+ (90%), and a small population of CD4+ cells (about 1/5000), have a unique phenotype and are distinguished by the demonstration of various exterior markers, cytokine receptors, and transcription factors, and are typically recognized by means of markers like Vα7.2 positive CD161 high T cells and MR1 tetramers [13].

MAIT cells Thymic and Peripheral Development

Selection

The selection of MAIT cells is driven by their interaction with MR1-expressing double positive (DP) thymocytes containing endogenous ligands, although the identity of these ligands remains unknown, and while the position of endogenous ligands in MAIT cell selection is assumed, the process of negative selection has not been extensively investigated[14] **Fig. 1**.

Differentiation

MAIT cell development can be classified on the basis of manifestation of CD161 and CD27 within 3 periods, namely, first Period, cells found exclusively in the thymus, second period, cells occurring at a little incidence in the periphery, and the evolution from Phase 2 to Phase 3 involving the raised levels of IL-18R and PLZF, as well as the gaining of functional prospective, and marked by the expression of CD161. In contrast to mice, there is no functional branching of MAIT cells into MAIT seventeen or MAIT one cells during their intra-thymic progress in humans [15] **Fig. 1**.

Expansion

The proliferation of MAIT cells is thought to be induced by the introduction of external ligands from symbiotic bacteria, with MAIT cells being discovered in great quantities in human blood but rarely in the thymus, suggesting that MAIT cells experience gradual expansion following their departure from the thymus, peaking at around 25 years old, and then gradually decreasing in number, representing just under one percent of T lymphocytes by the time an individual reaches 70 years old, although the precise mechanisms governing the peripheral development, proliferation, and stability of MAIT cells remain unclear [16] **Fig. 1**.

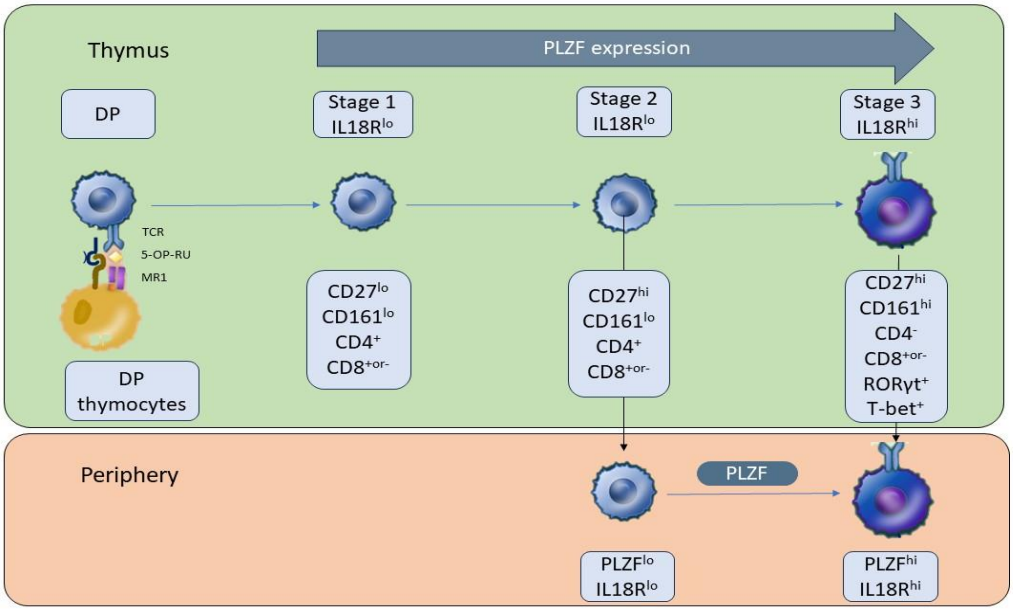

Fig. 1: MAIT cell development.

The development of MAIT cells occurs in three stages primarily within the thymus, starting with the trafficking of 5-OP-RU to the thymus and loading onto MR1 on double positive (DP) thymocytes. Subsequently, MAIT cells are positively selected on double positive thymocytes in stage 1, followed by the acquisition of effector functions and prototypic phenotype in stages 2 and 3 driven by PLZF (promyelocytic leukemia zinc finger)expression, with the display of distinguishing markers and regulatory co-factors.

MAIT cell Activation

Activation Influenced by TCR

TCR binding with riboflavin compounds presented on MR1 activates MAIT cells. However, additional co-stimulation through CD28, cytokines, bacterial products, or TLR agonists is needed for full activation. Cytokines like IL-7, TNF, IL-1b, IL-23, and/or type-one IFNs can provide the necessary co-stimulatory signals [17] **Fig 2**.

(A) MR1 ligands

The reactivity of MR1-dependent MAIT cells relies on the occurrence of the riboflavin. The gene RibD is crucial in this process as it encodes an enzyme that generates the precursor molecule 5-A-RU, and its expression is linked with the response of MAIT cells [18].

(B) MR1, major histocompatibility complex-related protein-1

MAIT cells differ from conventional T lymphocytes in their detection of antigens displayed by MR1 rather than MHC molecules. antigen presentation by a non-polymorphic molecule called MR-1 that is widely expressed in various tissues. Unlike MHC molecules, MR-1 isn't continuously displaying self-ligands and typically resides in the endoplasmic reticulum (ER) in a somewhat folded conformation. After being carried to the ER, riboflavin derivatives attach to MR1, causing full folding and binding with b2-microglobulin. The complex then travels to the cell membrane. MR1 transduction of signals is able to be triggered by non-bone marrow (BM) derived epithelial cells or BM derived antigen-presenting cells (APCs), and it needs signaling through the transcription factor NF-kB [19]. MAIT cell activation requires signaling through MR1 and their TCRs, as well as costimulation through various factors such as CD28, cytokines, bacterial products, and TLR agonists. Cytokines, including TNF, type one IFNs and/or IL-7 perform a part in MAIT cell activation. MAIT cells express various cytokine receptors, and their TCR chains exhibit some variability. Non-cognate TCR-dependent activation of MAIT cells has been observed in response to bacterial superantigens[20].

TCR Unrestricted Activation

MAIT cells carry a variety of cytokine receptors, such as IL-1R, IL-7R etc., which enable them to be activated by a variety of mediators regardless of TCR-mediated antigen recognition. The MAIT cells' activation by cytokine-dependent mechanisms typically requires the presence of at least two cytokines, expanding their range of pathogen response. Although IL-12 or IL-15 alongside IL-18 may immediately stimulate MAIT cells to create IFN-γ and produce cytotoxic chemicals, IL-7 can trigger the production of cytolytic effector molecules. However, type-I IFNs or TNF-like protein 1A (TL1A/TNFSF15) can activate MAIT cells only when combined with, IL-18, IL-12 or both [21]**Fig 2**.

MAIT cell Effector Functions

Upon activation, MAIT cells undergo expansion and exhibit innate-like immune responses, producing antimicrobial cytotoxic products, chemokines, and cytokines. IL-17A and IL-22 are generated by MAIT cells from human tissues, while their role in producing cytokines for TH2 helper T cells or anti-inflammatory cytokines remains unclear. MAIT cells also activate other cells in their vicinity, such as dendritic cells and NK cells, potentially triggering a cascade of downstream effector cells[22] **Fig 2**.

MAIT cells Function in Infection

Antibacterial Defense

Various, fungal, bacterial and mycobacterial microbes it has been demonstrated to activate MAIT cells in the lab by utilizing TCR-dependent mechanisms and riboflavin pathway. However, it has been difficult to find a distinct and essential phenotype associated with pure MAIT cell deficiency, possibly due to their multiple roles in mucosal immunology [23] **Fig 2**.

Antiviral Defense

MAIT cells, which can activate immune responses independently of TCR stimulation, are involved in defending against viral infections. They can respond to various viruses and be modulated by them. MAIT cells require the production of cytokines, specifically IL-18 and IL-12, in order to respond to viruses. The significance of MAIT cells in overcoming influenza infection has been demonstrated through evidence in both humans and mice [24] **Fig 2**.

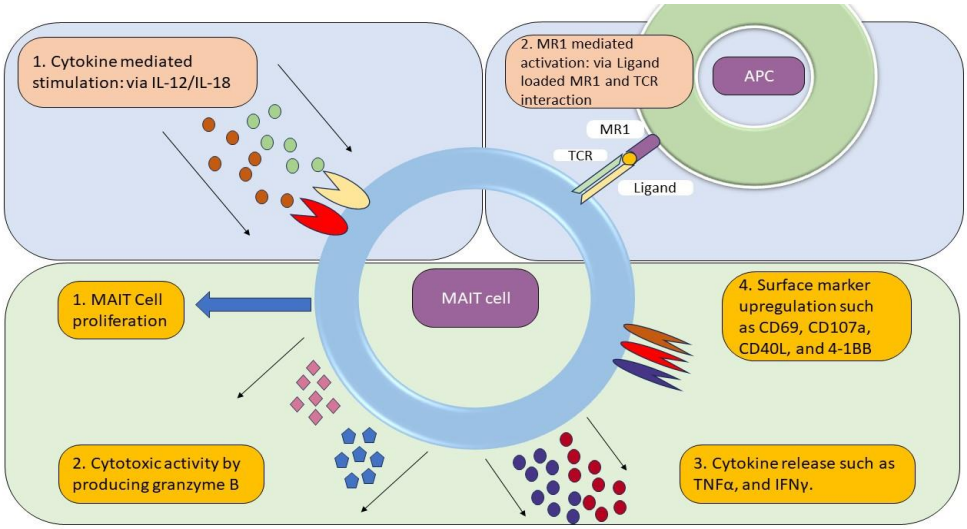

Fig. 2: MAIT cell activation and Effector Functions.

Activation of MAIT cells involves presentation of bacterial-derived vitamin B metabolites to TCR of MAIT cell through MR1, as well as cytokine stimulation via IL-12/IL-18, leading to cell proliferation, upregulation of cell surface markers such as CD69, CD107a, CD40L, and 4-1BB, and secretion of proinflammatory cytokines such as IFNγ, TNFα, and cytotoxic granzyme B.

MAIT cells Function in Repair and Homeostasis

Commensal organisms are vital for the growth and operation of the host defense mechanism. The presence of such organisms induces a growth of cutaneous MAIT cell populations and initiates a program for tissue healing. MAIT cells are primarily found in organs where naturally occurring bacteria became established and are essential for pathogen defense and restoring homeostasis in the presence of tissue damage or infections [25].

MAIT cells Function in inflammation and autoimmunity

Despite the various causes of autoimmune and autoinflammatory diseases, consistent findings regarding the phenotypical and functional Modifications in MAIT cells have been documented. Patients' disorders such as systemic lupus erythematosus, systemic sclerosis, inflammatory bowel disease and rheumatoid arthritis showed significant reductions in MAIT cells in their PB. Not all subsets concerning MAIT cells decreased equally, with differences observed in population composition in certain diseases. Additionally, cytokine production characteristics of MAIT cells have been shown to vary among people with autoimmune diseases and normal subjects. The penetration of MAIT cells within affected tissues during immune-mediated diseases has been observed, indicating that MAIT cells may have a part in autoimmune pathologies [26].

MAIT Cells in Transplant against the host Pathology

The existence and development of MAIT cells are dependent on the transfer of donor cells and the presence of certain bacteria, according to several studies that have looked into the contribution of MAIT cells in the immune system's rehabilitation following stem cell transplantation. Reconstituted MAIT cells, however, exhibited compromised function and were susceptible to chemotherapy; their role in graft-versus-host disease has been investigated[27].

Studying of MAIT cells

Although describing MAIT cells in various tissues or in the setting of disease could not be possible using certain antibodies, the development of MR1 tetramers loaded with 5-OP-RU has made it possible to conduct new research and directly assess surrogate phenotypes for the examination of human MAIT cells[28].

MAIT cells in hematological malignancies

The rising curiosity in oncology has led to a surge in the exploration of MAIT cells, which are abundant and capable of secreting inflammation mediators, particularly due to the increasing number of MR1 ligands, such as riboflavin-related antigens and folate-derivatives, emphasizing the importance of comprehending the role of MAIT cells in hematological malignancies and hematological cancer immunity, as well as their potential in developing immunotherapy[29]. However, little is known about the role that MAIT cells play in hematological cancers, particularly leukemia.

Multiple myeloma

The first study concentrated on the role of MAIT cells in hematologic cancers, especially multiple myeloma (MM). Reduced numbers of CD1d-restricted NK-T cells, altered cytokine production, and impaired activation by NK-T cells were among the findings of the study, which also revealed a drop in circulating MAIT cells in newly diagnosed patients. Surprisingly, PD-1 expression on MAIT cells was greater in MM patients; yet, NK-T cell activation was partially restored by PD-1 blocking antibodies[30]. Rapid validation of initial results demonstrating reduced quantities and functions of circulating MAIT cells in MM patients at diagnosis was given by two investigations. It's interesting to note that while MM cell lines expressed MR1 and were susceptible to being killed by MAIT cells when exposed to a particular ligand, 5-OP-RU, refractory or relapsed MM patients secreted normal amounts of IFNγ. These findings suggest significant changes in MAIT cell homeostasis and function in relation to this blood cancer [15].

Chronic lymphocytic leukemia

It has been previously shown that circulating CD8+CD26hi T cells are less common in patients with chronic lymphocytic leukemia (CLL)[31]. Studies have demonstrated that MAIT cells express CD26 at higher levels. Studies have also confirmed that MAIT cells

predominate in the CD8+CD26hi fraction. Thus, studies suggests that CLL could have an effect on the physiology of MAIT cells, but more research is required to confirm this [17, 32].

Acute Myeloid Leukemia

AML is the malignant growth of progenitor cells along with a blockage in their differentiation. AML is the utmost prevalent kind of leukemia. Recent research has significantly improved our understanding of the genetics and pathobiology of AML. Inhibitors targeting specific genetic abnormalities in AML, such as FLT3 and IDH1/IDH2 mutations, have been approved for clinical use, improving response rates and outcomes. However, challenge to these targeted treatments endures a challenge, and ongoing studies aim to develop new treatments. AML is categorized via repeated chromosomal irregularities as well as mutations that affect disease progression and treatment response. Identifying these mutations is crucial for risk assessment and guiding treatment decisions. Despite having fewer alterations compared to solid tumors, the majority of AML patients have at least one driver mutation, with many having multiple mutations. Analysis of AML patients has identified 11 distinct subtypes, including three recently defined subtypes with specific genetic abnormalities. AML is a complex disease with multiple genetic, epigenetic, and clinical factors that affect the accumulation and proliferation of immature myeloid cells, leading to impaired hematopoiesis. Despite advancements in genomic and epigenomic research, chemotherapy remains the primary treatment with limited success, highlighting the urgent need for alternative therapies such as immunotherapy to target chemo-resistant clones and provide sustained disease control[33].

AML symptoms and indicators

The diagnostic signs and symptoms of AML primarily result from the replacement of healthy blood cells by leukemic cells, which results in a reduction in red blood cell count and an impairment in the formation of white blood cells. This can cause symptoms such as fatigue, paleness, and shortness of breath, as well as easy bruising or bleeding. Early signs of AML may resemble those of influenza or other common illnesses, and can include fever, weight loss, anemia, and persistent infections. Enlargement of the spleen is mild and asymptomatic in AML, and lymph node swelling is rare. In some cases, gum inflammation, solid leukemic masses, or incidental detection during routine blood tests may indicate AML[34].

Risk factors

Several risk factors have been identified for the development of AML, including other blood disorders, chemical exposure, radiation, and genetic predisposition. Hematological disorders like MDS and MPN have the potential to progress to AML, while the presence of clonal hematopoiesis further increases the risk. Exposure to certain chemotherapy agents and ionizing radiation also contribute to AML development. Genetic variables linked to an elevated risk of AML include Down syndrome and GATA2 deficiency. The specific genetic abnormalities associated with AML vary between children and adults [35].

Diagnosis

AML diagnosis is typically made by identifying abnormal results in a complete blood count. A definitive diagnosis usually requires BM aspiration and biopsy, as well as genetic studies to identify specific mutations [36].

Epidemiology

Since its establishment in 1973, Data on cancer incidence and death have been gathered in the US through the Surveillance, Epidemiology, and End Results (SEER) program. SEER now encompasses about 30% of the US population, with an initial age-adjusted incidence of AML reported at 3.43 per hundred thousand cases annually. Over time, the occurrence has increased, with rates consistently surpassing 4.2 per 100,000 individuals per year since 2010. Comparable rates have been observed in the UK, Canada, Australia, Sweden, and Denmark, while Algeria reported a significantly lower incidence rate [37].

Morphology

Morphologically, AML blasts display varying sizes and large nuclei with diverse

shapes, expressing antigens typically found on healthy immature myeloid cells. The co-expression of T or B cell lineage antigens can make classification challenging, leading to poorer overall survival in cases of mixed phenotypic leukemia [38].

Classification

Over time, various classification systems have been proposed for AML, considering factors such as etiology, morphology, immune-phenotype, and genetics, with the World Health Organization classification now being the primary framework for AML classification [39].

In 2008, the World Health Organization (WHO) updated the categorization of AML and recognized seven subtypes, including AML with alterations associated with myelodysplasia and AML with genetic abnormalities and gene mutations. AML may also be divided into three kinds according to its etiology: AML that develops from scratch, AML connected to therapy, and AML that is secondary [40].

Pathophysiology

The pathogenesis of AML arises from genetic abnormalities in blood cell precursors, resulting in the proliferation of immature myeloblasts. These cells, also known as leukemia-initiating cells or leukemic stem cells, hinder the proper production of blood cells and contribute to the various symptoms of the disease. Secondary AML encompasses cases that emerge from DNA damage caused by previous exposure to chemotherapy or radiotherapy (t-AML), non-therapeutic toxic exposures, or pre-existing blood disorders like myelodysplastic syndromes (MDS) or myeloproliferative neoplasms. It constitutes approximately 10-30% of all AML cases, with the t-AML subset accounting for around 7-15%. However, because undetected MDS instances are likely, it is difficult to determine with accuracy the fraction of really secondary AML cases [41].

Tumor Microenvironment (TME)

TME, which is made up of several cell types, is essential to the onset and spread of cancer. The TME can vary significantly throughout cancer types and even amongst people that have the same malignancy, impacting treatment results and prognoses. Hematological malignancies, such as leukemia, exhibit distinct TME characteristics and necessitate further investigation [42]. The exploration of T cells in individuals with AML has been an area of insufficient inquiry, leaving a lack of consensus due to a scarcity of available research. One all-encompassing examination contrasted the distinctive features of AML patients and healthy volunteers, utilizing immunophenotyping, TCR clonality assessment, and gene expression profiling. While the amount of T cells in BM seemed comparable in both groups, AML patients exhibited a noticeably greater count of circulating T cells, particularly CD8+ cells. Another study discovered heightened activation indicators on T cells in AML patients, aligning with the unconventional T cell activation identified through gene expression profiling and flow cytometry. The inconsistencies in the quantities of circulating lymphocytes among AML patients and healthy individuals may be ascribed to the heterogeneity of AML and the limited sample size of the studies, as well as the effect of medical histories on the immune system equilibrium [43]. Identifying a crucial antigen target for AML biology, particularly on malignant cells, presents a formidable task due to the diverse and clonal makeup of AML. LRAs, LAAs, and LSAs are classified as antigen targets in AML. LRAs, situated on leukemia cells, can be pursued through antibody-based methods or CAR T cells, yet their effectiveness is hindered by the potential harm they can cause to the intended target. Although more particular to leukemia cells, intracellular LAAs and LSAs are often detected, and their potential as targets for immunotherapy depends on their ability to be processed and presented to T cells. Additionally, neoantigens and other mechanisms like spliceosome mutations and dysregulated posttranslational modification may offer potential antigen targets in AML[44].

Immune Evasion Mechanisms in AML

The immune evasion of AML involves a multitude of intricate mechanisms. The precise role that each mechanism plays in fostering immune tolerance towards leukemia, how these mechanisms function in different bodily compartments such as the PB, BM (the primary tumor site), and extramedullary tissues, as well

as how they are impacted by AML treatment or influenced by AML genetics, necessitate additional comprehension [22].

When leukemia blasts are exposed to selective immune pressure after alloHSCT, they can effectively edit their immune system. This is demonstrated by the elimination of mismatched HLAs in haploidentical transplants and the epigenetic suppression of HLA class II molecules in different donor transplant situations. On the other hand, leukemia antigens presented by immature APCs or splenic CD8α+ dendritic cells (DCs) have been shown to induce deletional T cell tolerance as well as CD8+ T cell tolerance in mice with AML. Furthermore, it has been observed lately that worse survival rates and the continuation of detectable residual illness following AML therapy are associated with the lack of plasmacytoid DC differentiation [45].

The existence of T cells within the tumor location is vital for the immune system to identify and eliminate AML cells. AML patients exhibit comparable or heightened quantities of T cells in comparison to individuals in good health. Enhanced proportions of lymphocytes and T lymphocytes found in the BM are linked to improved reaction and survival rates in AML patients. Leukemic blasts have a part in altering the reaction of T cells and NK cells, resulting in apoptosis and decreased cytotoxicity. Tregs and MDSCs also contribute to impaired immune responses in AML patients, with heightened levels connected to unfavorable outcomes. More than a few enzymes expressed by AML blasts create a suppressive microenvironment, including IDO which is associated with shorter survival. Tryptophan depletion and its metabolite accumulation inhibit T cell proliferation, induce Treg generation, and suppress T cell function[46].

Immune-Based Therapies

For quite some time, it has been well acknowledged that treating AML with immune system stimulation offers potential. This is demonstrated by the successful results of donor lymphocyte infusions and allogeneic hematopoietic stem cell transplantation, both of which induce a graft-versus-leukemia response. Recently, a number of immune-based therapies have emerged and are currently undergoing evaluation for AML treatment. The goal is to develop immune therapies that are not only effective and safe, but also capable of complementing and enhancing the effectiveness of cytotoxic, targeted, and apoptosis-inducing agents [32].

The efficacy of antibodies against AML relies on multiple mechanisms, including immune effector recruitment, toxic agent delivery, and enhancement of T or NK cells. However, clinical trials have shown limited activity of unmodified monoclonal antibodies targeting specific antigens in AML. In contrast to acute lymphoblastic leukemia, bispecific antibodies in AML have not been successful in clinical studies and have shown cytokine release syndrome, necessitating careful dose escalation and symptom management. To optimize this approach, a deeper understanding of patient responses and immune-enriched microenvironments is crucial. Ongoing studies are exploring combination therapies and locally blocking the PD-1/PD-L1 checkpoint [47].

The initiation of inexperienced T cells involves a duo of signals: the TCR of T cells connecting with the MHC molecule on APCs and a supplementary signal bestowed by the APCs. Preventive checkpoints are pivotal regulators of the immune system, disengaging initiation sequences and diminishing T cell propagation and cytokine production. Malignant cells exploit this mechanism by revealing ligands that interact with checkpoint receptors, thwarting the immune system. Obstructing the interactions between checkpoint molecules and ligands could potentially overturn tumor repercussions. Immune checkpoint inhibitors (ICIs) such as CTLA-4 and PD-1 have been sanctioned for diverse cancers, with PD-1 blockade therapy being particularly pertinent in HL. Prudence is requisite when utilizing ICIs after transplantation due to the hazard of GVHD, but preliminary discoveries exhibit potential in patients with AML [48].

In the realm of triumph for chimeric antigen receptor T-cell therapies in different blood cancers, exploratory studies are presently underway for AML. Nevertheless, the hurdle resides in the quest to discover AML-specific external antigens, since potential targets are not solely exclusive to cancerous cells and may result in unintended harm. Despite numerous

approaches to bolster the security and efficacy of CAR T-cell therapies in AML, no creation has yet exhibited conclusive effectiveness and safety [49].

MAIT cells in AML

In a recent research, 216 individuals with newly diagnosed AML were followed up on to track the frequency and concentration of MAIT cells. It was discovered that there was an inverse relationship between activation as determined by HLA-DR expression and the decrease in MAIT cell frequency. Furthermore, the cytogenetic profile and molecular subtypes of AML were linked to MAIT cell dynamics, indicating a complex interplay between MAIT cells and tumor growth[32]. An article published recently described the clonal expansion of MAIT cells in the bone marrow of patients with NK AML M4/M5, a specific subtype of AML. Interestingly, the one patient who did not experience complete remission had higher levels of MAIT cell infiltration and upregulated a unique gene transcription signature; this is the only study to date that shows bone marrow infiltration by MAIT cells [22]. The activation of MAIT cells in AML may cause them to infiltrate the tumor microenvironment, which might have a negative impact on the course of the illness, or it may cause the cells to undergo apoptosis, which would decrease the number of MAIT cells in circulation.

Conclusions

MAIT cells work in different ways when it comes to cancer. On one hand, MAIT cells have the ability to migrate to the location of the tumor and induce a Th1-cytokine response, as well as increase the expression of cytolytic granules. On the other hand, MAIT cells may have a fatigued phenotype, which would limit their capacity to release anti-tumor cytokines like TNFα and IFNγ. Owing to their strong effector capabilities and elevated frequencies throughout the human anatomy, MAIT cells exhibit promise as a target for cancer treatment. The finding of a particular kind of MR1-restricted T cell clone that can kill different kinds of cancer in a way that depends on TCR-MR1 interactions lends credence to this. Furthermore, immune-checkpoint inhibitor treatment may target MAIT cells due to their elevated expression of PD-1, CTLA-4, and TIM-3 in malignancy. Nonetheless, MAIT cells' distinct qualities make them especially intriguing for potential cancer treatment approaches in the future. Very little is presently known regarding the possible anti-tumor actions of MAIT cells in the setting of hematological malignancies specially AML. Consequently, it is imperative that further study be done in order to fully comprehend the biology of MAIT cells and how these malignancies relate to them. This can result in the creation of fresh therapeutic philosophies.

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الأدوار المتنوعة للخلايا اللمفاوية التائية اللامتغيره المرتبطة بالغشاء المخاطي في الأورام الدموية الخبيثة

علي ع. أحمد[١*] – أمنية حسن البدوي[٢] – محمد أحمد المختار[٢،٣] – عمر ع. أحمد[٤] – مروة ثابت[٥] – أسماء م. زهران[٦] – سلوى سيف الدين[٢]

[١] قسم المكروبيولوجيا والمناعة، كلية الصيدلة، جامعة أسيوط، أسيوط، مصر

[٢] قسم المكروبيولوجيا الطبية والمناعة، كلية الطب، جامعة أسيوط، أسيوط، مصر

[٣] كلية جيلبرت وروز ماري شاغوري للطب، الجامعة اللبنانية الأميركية، جبيل، لبنان

[٤] قسم الصيدلة، مستشفى المنشاه المركزي، مديرية صحة سوهاج، سوهاج، مصر

[٥] قسم المكروبيولوجيا والمناعة، كلية الصيدلة، جامعة سفنكس، أسيوط الجديدة، مصر

[٦] قسم الباثولوجيا الإكلينيكية، معهد جنوب مصر للأورام، جامعة أسيوط، أسيوط ٧١٥١٥، مصر

سرطان الدم النخاعي الحاد (AML) هو اضطراب ورمي يتميز بالتوسع النسيلي للخلايا السلفية المكونة للدم غير اللمفاوية مما يؤدي إلى فشل تكوين مكونات خلايا الدم الطبيعيـــة. خلايـــا T الثابتـــة المرتبطة بالغشاء المخاطي (MAIT) هي مجموعة من خلايا αβ T التي تتعرف على المستضدات غير الببتيدية التي يقدمها جزيء MR1 غير متعدد الأشكال. وهي تتميز بالتعبير عن Vα7.2 مـــع التعبيـــر العالي عن CD161. تم ربط خلايا MAIT بمجموعة متنوعة من الأورام بما في ذلك الأورام الصـــلبة مثل سرطان خلايا الكبد وسرطان القولون والمستقيم والرئة والكلى ويبدو أن ترددتها في مواقع الورم ترتبط بالتشخيص. تمت دراسة خلايا MAIT أيضًا في الأورام الدموية الخبيثة مثل المايلوما المتعـــددة وسرطان الدم. في هذه المراجعة سنحدد فهمنا الحالي للعلاقة بين خلايا MAIT وسرطان الدم النخاعي الحاد (AML)، والذي سيؤكد إمكانية استهداف هذه المجموعة الفرعية لتطوير العلاج المناعي الحديث.