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Review

The Triple Immune Argument; Surveillance/Evasion/ Senescence and the Increased Incidence of Acute Myeloid Leukemia Observed with Age

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Abstract: AML originates from genetic insults of hematopoietic stem and progenitor cells (HSPCs/HSCs) that was identified earlier as leukemia stem cells (LSCs). In quiescent state, trafficking immune cells are crucial for eradication of aberrant clones and obtaining balance between proliferation and apoptosis to maintain HSCs pool. Regulatory T-cells shield the HSCs from the inflammatory reactions by suppressing T- and B- cells. Cancer immunoediting characterize the interaction between the tumor cells and the immune system during cancer evolution. Both branches of the immune system; innate and adaptive can identify AML blasts, eliminating them completely or keeping a balance state that prevents tumor excrescence. However, the AML blasts are struggling to survive and induce many evasion mechanisms ranged from suppression of natural killer and T cytotoxic cells up to the support of suppressor cells and creating a tumor permissive microenvironment. Upon aging, the immune system is restructured in a process termed immunosenescence. The most sticking event in immunosenescence is thymic involution with reduced T-cell output and diversity that will affect the immune surveillance properties, in addition to inflammaging that prepare a convenient environment for the evolution of AML. In this age-impaired immunity background, together with the other age related changes occur in HSPCs and bone marrow microenvironment would initiate and promote the development of AML that is indeed observed in older patients. Realizing this relation would help in proper choice of therapy and the development of new lines of immunotherapy against this difficult disease in that critical age.

Keywords: Aging, AML, Immune Surveillance, Immunevasion, Immunosenescence, Inflammaging

Introduction

Aging and development of malignancies are considered to be interrelated biological phenomena. However, there is no direct causative relation and the two processes seems to be contradictory (Bonafe *et al*., 2011). Aging is characterized by organ damage, wastage and decline in tissue regeneration (Granger *et al*., 2016). Contrarily, proliferation, resistance to apoptosis and acquisition of novel aberrant functions are hallmarks of cancer (Campisi, 2013). Lately, four new cancer criteria were proposed: Capability to escape cleverly from the immune surveillance, existence of inflammation, inclination to genomic instability and uncontrolled metabolism (Hanahan and Weinberg, 2011).

The incidence of cancers in the above 65 age group is > 60% of the newly diagnosed cases and the death rate due to malignancy is more than 70% (Fulop *et al*., 2010). This high incidence copes with the age-associated deterioration of the immune function and its capacity for immune surveillance that adds more fuel to the potentially carcinogenic and transformational insults to which an elderly patient already exposed to (Sportès and Hakim, 2009). The complex interaction between the

malignant cells, the stromal cells and the immune cells modulates the process of cancer pathogenesis (Yaqub and Aandahl, 2009). There is a substantial series of proofs entails the wear out of immunity with senility, a phenomenon named immunosenescence. In aging, both branches of the immune system are distorted and a low - grade inflammation evolves. These factors participate in increased tumorigenesis. Perception of the immunosenescence role in the evolution of malignancies and assistance of cancer advancement to critical stages could help with superior medical support and treatment in the elderly (Fulop *et al*., 2013).

The hematopoietic system in the BM is an ideal organ to study the relationship between malignancy and aging of the immune system being the location where the immune cells develop and interact with the malignant blasts. Some leukemias show increased incidence with aging (Rossi *et al*., 2007). In elderly people, B-chronic lymphocytic leukemia is the commonest type of chronic leukemia (Chiorazzi *et al*., 2005), while acute myelogenous leukemia (AML) is considered the recurrent type of acute leukemia (Pollyea *et al*., 2011). More than 60% of the newly diagnosed AML cases are above the age of 60 with a median age 68 years (NCI, 2017).

In this study we hypothesize that immune frailty associated with aging termed immunosenescence is a central factor in the evolution of AML in the aged population that together with the aged BM microenvironment and hematopoietic stem cell (HSC) complete the circle and start the disease. The relevance of the immune pathophysiology in context to the emergence of AML in the elderly including surveillance, immune evasion, senescence and inflammation are going to be highlighted in this review with a special reference to the clinical relevance of this relation.

AML and Aging

Hematopoietic failure is a hallmark of myeloid disorders particularly AML (Schroeder *et al*., 2016). AML originates from genetically defective hematopoietic stem and progenitor cells that were termed previously as leukemic stem cells (LSCs) or Cancer Stem Cells (CSCs) (Wang *et al*., 2017).

Normal stem cell function is closely related to the embracing cells in the surrounding milieu; named ‘‘stem cell niche’’ (Orford and Scadden, 2008; Carlesso and Cardoso, 2010), that consists of macrophages and stromal cells (Ehninger and Trumpp, 2011; Gyorki *et al*., 2009), the stromal cells are arranged into endosteal and vascular niche according to their anatomical locations. The core difference between the vascular and the endosteal niches is the oxygen content. HSC lies mainly in the endosteal niche that has a lower oxygen tension. When the HSC are stimulated by growth factors (e.g., granulocyte-macrophage colony-stimulating factor), interleukins (e.g., IL-3, IL8, IL-7 and IL-12), chemokines (e.g., CXCL12) and flt-3 ligand, they move towards the vascular niche. In the vascular niche higher oxygen supply enables cells to recommence their cell cycle and proceed to mitosis and cellular differentiation occurs. Afterwards, HSCs return to endosteal niche. The HSCs mobilization between endosteal and vascular niche is compulsory for hematopoietic balance (Iwasaki and Suda, 2010). HSCs are under control of cytokine network responsible for their maturation, pluripotency and interaction with immune cells. In quiescent state, trafficking of the immune cells is crucial for eradication of aberrant clones of HSCs and maintenance of equilibrium between proliferation and apoptosis to keep the HSCs pool constant (Giles *et al*., 2016). Regulatory T cells (Treg) in the bone marrow microenvironment (BMM) are prevailing to shield them from the annoying inflammatory reactions by suppressing both T and B cells (Camacho *et al*., 2017).

Hypoxia is a main feature of the endosteal niche; hypoxia reduces the flow of extracellur fluid that will reduce the exposure of HSC to the harmful toxins and proinflammatory cytokines that can promote cancer development (Eliasson *et al*., 2010). Additionally, hypoxia regulates HSC self-renewal as it potentiates cellular turnover, which reduces the accumulation of genetic damage that mostly ends in cancer evolution (Takubo *et al*., 2010). In the aged BMM, the HSCs reside away from endosteum that would increase oxidative insult to the DNA with subsequent augmentation of mutation (Takubo *et al*., 2010; Henry *et al*., 2011). Moreover, the adipose tissue reacts by increasing lipolysis as a metabolic disturbance in old age, with increases free fatty acid oxidation and ATP consumption. Thus, maintains a stressful BMM that represses HSCs and initiate resistance to chemotherapeutic agents (Silberstein *et al*., 2016).

In an aged BMM, the human HSCs prefer being differentiated into the myeloid lineage and became more clonal. Furthermore, the HSC clones are supposed to carry disease-inducing genetic and epigenetic changes. These two factors entail a higher risk for development of age related clonal hematopoietic disease, such as myelodysplastic syndrome, myeloproliferative disorders, or AML. The aged BMM may preferentially chose the senile HSC clones as a consequence of the changes that accompany aging (Pang *et al*., 2017).

Once the LSCs originated from mutated HSCs, they start to show considerable hostile features (Zhang *et al*., 2015). LSCs modulate BMM and participate in reprogramming of the LSC niche into a malignant niche that favors malignant cell survival and proliferation (Pleyer *et al*., 2016; Li and Neaves, 2006) and anticipate multiple pathways to evade immune response (Ashley *et al*., 2013).

Immune Surveillance in AML

Cancer immunoediting signifies the interaction between the immunological and malignant cells during the state of neoplasm evolution. This hypothesis describes three consists of three consecutive stages: (i) Elimination that involves complete effacement of malignant cells, (ii) Equilibrium where the evolution of an immune- reluctant malignant clone arises and (iii) Escape where the tumor cells have elaborated strategies to evade immune detection or destruction (Kim *et al*., 2007).

The antileukemic immune effect is evident after allogeneic hematopoietic stem cell transplantation (Cooley *et al*., 2010) where the donor immune cells namely natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) perform anti leukemic effect (Godder *et al*., 2007).

Both branches of the immune system; innate and adaptive can identify AML blasts, eliminating them completely or keeping a balance state that prevents tumor outgrowth (Schreiber *et al*., 2011; Lion *et al*., 2012). Despite the fact that most of the immunological cells participate in immune surveillance, NK cells are considered the essential effector cells from the innate system and the T cells are the indispensable cell from the adaptive system.

Innate Immune Response

The dendritic cells (DCs) are a fundamental link between innate and adaptive systems (Rainham *et al*., 2010). They are central in tumor antigen presentation to the T cells. Also, they commence and organize antigen specific adaptive immune response (Schuurhuis *et al*., 2006). DCs may fall into one of two subsets: Myeloid DC (mDC) that express CD11c and present antigens to the naïve CD4 T cells (Steinbrink *et al*., 2009) or the plasmacytoid DCs (pDC) that express CD123 (Liu, 2001) and have a humble competence in phagocytosis and production of type I interferon (Gilliet *et al*., 2008). In different types of solid malignancies, the existences of higher percentages of tumor-infiltrating DCs show a mutual relationship with favorable prognosis that highlights their fundamental role in immune surveillance (Yang *et al*., 2013). Furthermore, the DC can energize the T cells to overcome the impaired antileukemic T-cell response created by the tumor microenvironment (Schick *et al*., 2013).

The macrophages (MQ) also perform antigen processing and presentation for T cells. However, the two macrophages phenotypes play adversative roles. In early stages of tumor development, type 1 macrophages (M1) that actively inhibits cell proliferation and causes tissue damage (Mills, 2012) dominates in the tumor microenvironment (Zamarron and Chen, 2011). Later on with advanced malignancies, M2- macrophage phenotype that support tissue repair, remodeling and angiogenesis (Zamarron and Chen, 2011) predominates (Biswas *et al*., 2001)

NK cells are cytotoxic cells that are highly efficient in killing virally infected and malignant cells (Farag *et al*., 2003). NK cells are classified into two subsets; $CD16^{+ve}$ $CD56^{dim}$ and the $CD16^{-ve/dim}$ $CD56^{bright}$ (Poli *et al*., 2009). $CD56^{dim}$ population shows a high cytotoxic ability and constitutes the major percentage of NK cells. $CD56^{bright}$ cells function mainly as immunomodulators via the production of immunoregulatory cytokines such as IL-10, IL-13, TNFα, IFNγ that can activate DCs and launch adaptive immune response (Camous *et al*., 2012).

NK cells can identify and eradicate malignant cells without previous antigenic sensitization (Bigley and Simpson, 2015) using their cell surface receptors that includes killer activation receptors (KARs) and killer inhibitory receptors (KIRs). KIRs have a high affinity to HLA class I and function to repress the NK cells preventing them from destruction of normal cells (Bottino *et al*., 2004). However, absence or abnormal expression of HLA molecules that commonly occurs with malignant transformation set free the NK cells from the inhibitory signals and stimulate their cytotoxicity (Farnault *et al*., 2012).

NK cells can induce target cell lysis by two central mechanisms; granule exocytosis and liaison of death receptors (Cullen and Martin, 2008). TNF-related apoptosis inducing ligand (TRAIL) expressed by NK cells is qualified for apoptosis induction in TRAIL sensitive cells. Also, NK cells are capable of induction of caspase- dependent apoptosis via Fas/FasL interaction (Smyth *et al*., 2005).

Siegler *et al*. (2005) proved that NK cells are key players in immune surveillance in AML. They isolated the NK cells from AML cases before treatment and studied their function *in vitro*. They demonstrated a high potency in proliferation in response to IL-2 and exhibited proper cytotoxicity towards HLA class I - deficient leukemia cells and they were able to reduce AML load. On the same hand, the activating receptor (NKG2D) and the major natural cytotoxicity receptor (NKp46) were normally expressed and they were efficiently releasing interferon gamma. Further studies pointed to the pivotal role of NK cells in AML, Boeck *et al*. (2017) describe clearly the association of high NK cells percentage with good prognosis. Similarly, the presence of ≥5% circulating NK cells was considered as an independent indicator of ameliorated overall and leukemia-free survival reflecting the clinical importance of NK cells in tumor eradication (Alcasid *et al*., 2017). However, other researchers demonstrated reduced NK cell cytotoxicity in AML and referred this finding to the different

strategies of immune evasion made by AML cells (Costello *et al*., 2002).

Adaptive Immune Response

Concerning the role of adaptive immunity in tumor immune surveillance, the tumor specific cytotoxic T lymphocyte plays the starring role (Dunn *et al*., 2002). TCLs recognize tumor antigens processed and presented by antigen presenting cells (APCs) in context to HLA class I molecules (Ochsenbein *et al*., 2001). Schneider *et al*. (2015) proved that T cells are stimulated against various leukemia associated antigens (LAA) and some of them showed very high immunogenic response for example but not limited to receptors for hyaluronic acid-mediated motility (RHAMM), preferentially expressed antigen of melanoma (PRAME) and Wilm's tumor 1 (WT1) and can induce a considerable suppression of colony forming unites (CFUs) in AML culture.

CTLs share the same mechanisms of tumor cell killing with NK cells; granular exocytosis and induction of apoptosis by FAS/FASL interaction and TRAIL (Barrett and Le-Blanc, 2010). However, tumor -specific T helper (Th) cells are fundamental for the induction and maintenance of felicitous cytotoxic and memory T cells response (Lai *et al*., 2011). The memory T cells are able to remember previously experienced antigens leading to faster responses and may help with relapse prevention (Schreiber *et al*., 2011; Dobrzanski, 2013).

Th cells collaborate with CTLs in immune surveillance by grant a license to the DC to permit the cross presentation of LAA to the naive CTLs. Additionally, T helper cells can eliminate tumor cells independently of CTLs as they produce inflammatory cytokines that intensify the phagocytosis and killing ability of the tumor infiltrating macrophages (Haabeth *et al*., 2011).

In AML, the role of lymphocytes in immune surveillance was highlighted by Le Jeune *et al*. (2014) who stated that low circulating levels of absolute lymphocyte at diagnosis is a prognostic indicator for shorter overall survival (OS) and leukemia free survival (LFS). Similarly, another study demonstrated that high percentages of BM lymphocytes and T cells were correlated with achievement of complete remission and prolonged OS (Ismail and Abdulateef, 2017). These data are not conflicting with the studies that demonstrated NK cells as a good prognostic factor in AML as it was assumed that both cells are activated in AML but each function in different phases. Where NK cells are activated at early phase, T cells are stimulated later on with disease progression (Wang *et al*., 2015).

AML Evasion from Immune Surveillance

AML cells together with the microenvironment stimulate many mechanisms that favor their survival and evade riddance by the different immune mechanisms. Generally, these mechanisms are negative regulator for the immune system and they include:

DCs Evasion

The tumor microenvironment is actively engaged in maturation of DCs. The maturation process could be biased with formation of immunosuppressive DC subsets (Steinman *et al*., 2003) or convert the conventional DC into regulatory DCs having the potential to stimulate Tregs, secrete transforming growth factor beta (TGF-β) and promoting myeloid-derived suppressor cells. Hence, supporting evolution and expansion of malignant cells (Shurin *et al*., 2011).

Gangliosides, neuropeptides and nitric oxide (NO) are factors released in the tumor microenvironment that decrease the life span of DCs (Shurin *et al*., 2012). This decreased longevity will negatively affects the duration and extend of immune response leading to feeble anti-tumor immune response and tumor elopement from immune recognition (Chen and Wang, 2011). Furthermore, the DCs are often functionally defective with reduced both antigen presentation capabilities and expression of co-stimulatory molecules (Yang *et al*., 2013). The tumor infiltrating DCs show many functional abnormalities such as inhibited endocytic activity, depressed antigen processing, abnormal migration and decreased IL-2 production (Bennaceur *et al*., 2009) and moreover, the tumor milieu suppresses the generation and survival of DCs (Onishi *et al*., 2002).

Evasion of Phagocytosis

Calreticulin (CRT) is a chaperone protein located in the endoplasmic reticulum (ER). CRT prohibits the abnormally folded proteins from being trans-located to Golgi apparatus. However, stress or apoptosis will cause exportation of CRT to the surface of the cell (Golden *et al*., 2012). On this new location, CRT will motivate CD91 expressed on the surface of macrophages; hence stimulate phagocytosis (Gardai *et al*., 2005). The malignant cells can inhibit CRT- stimulated phagocytosis by expression of anti-phagocytic proteins; CD47 (Chao *et al*., 2010). CD47 interacts with its ligand; signal regulatory protein-A expressed on phagocytes and sending them an inhibitory signal (Subramanian *et al*., 2007). The human AML blasts demonstrated excessive expression of CD47 which would explain the potentiality of AML blasts to evade phagocytosis (Majeti *et al*., 2009).

NK Cells Evasion

Patients with AML have dysfunctional NK cells at diagnosis (Le Dieu *et al*., 2009) and higher percentages of immature NK cells during first complete remission (CR) (Dauguet *et al*., 2011). The NK cells obtained from

all FAB subtypes of AML cases had a skewed receptors phenotype from the normal. They demonstrated low expression of the activating receptor; NKp46 and over expression of inhibitory receptors such as CD158b and NKG2A (Sandoval-Borrego *et al*., 2016). The repertoire of NK cell receptors in more than 50% of AML patients revealed the expression of a phenotype that supports tumor evasion from NK cells (Verheyden *et al*., 2004). Also, the capability of NK cells to secrete IFN-γ is frustrated in AML patients leading to defective immune responses (Coles *et al*., 2011). This impairment of NK cells cytokine production is linked to early relapse in AML (Lion *et al*., 2012). TGF-β released from the tumor microenvironment reduces NK-cell activation and constringes its cytotoxicity. In acute leukemia, elevated levels of TGF-β were consistent with inferior prognosis and were related to diminished NK-cell activity and low expression of the activating NK cell receptors; NKp30/NCR3 and NKG2D (Baier *et al*., 2013). Furthermore, TGF-β antagonizes the functions induced by IL-15 that include stimulation of NK-cell proliferation and their activation (Baier *et al*., 2013; Wilson *et al*., 2011). These functional abnormalities are at least in part induced by the tumor itself as proved by *in vitro* studies where direct contact between leukemic cells and NK cells induces a loss or decrease in natural cytotoxicity receptors producing a dull phenotype which associates with inferior OS (Fauriat *et al*., 2007).

Exhaustion of T Helper (Th) Cells

Persistent antigenic stimulation of T-cell results into a state of hyporesponsiveness termed exhaustion (Wherry and Kurachi, 2015). The myeloblasts express CD86 and inducible T- cell costimulator ligand (ICOS-LG) that support Th cell stimulation and proliferation. The persistent stimulation of T cells leads to their functional fatigue. The exhausted Th cells are identified by increased expression of programmed cell death 1 (PD-1) and the inhibitory receptors such as cytotoxic T-lymphocyte antigen 4 (CTLA-4), lymphocyte activation gene 3 (LAG-3) and mucin domain-containing protein-3 (TIM-3). These enervated T cells are reluctant to proliferate and produce reduced quantities of IL-2, TNF-α and IFN-γ. Interestingly, T helper cells with the exhausted phenotype were recognized with CD86 (+) and/or ICOS-LG (+) myeloblasts in the BM of AML patients (Ozkazanc *et al*., 2016).

T Cell Evasion

The cytotoxicity of T- cells are reduced that may be a direct cause of the over expression of the suppressor molecules such as PD-1(Bos *et al*., 2012; Shi *et al*., 2013). Additionally, its ligand; PD-L1 was found to be over expressed in myelobasts (Zhou *et al*., 2010). The interaction between PD-1 and its ligand would participate in T-cell failure that may be related to persistence of minimal residual disease and development of relapse (Bos *et al*., 2012; Norde *et al*., 2011). Furthermore, PD-L1 advocate Tregs by enhancement of their development, maintenance and function (Francisco *et al*., 2009), which may explain the link between increased Tregs and high PD-1 expression on CTLs and tumor progression (Zhou *et al*., 2010; Ustun *et al*., 2011).

Tim-3, a type I membranous glycoprotein, is expressed on CTLs and its ligand; galectin-9 (gal-9) is found on myeloblasts in both animal and human. Tim-3/gal-9 pathway possibly contributes with the PD-1/PD-1L pathway in regulating CTL responses. In animal studies, monoclonal antibodies that blocks Tim-3 fusion protein and PD-L1 could restore the antitumor function of exhausted T cells with better AML survival (Zhou *et al*., 2011). Additionally, hypoxic and acidic conditions created as a result of different metabolic processes in the malignant environment can cause deterioration of the different T cells functions (Teague and Kline, 2013; Calcinotto *et al*., 2012).

Regulatory T Cells (Tregs)

Some studies highlighted the role of Tregs in AML patients. One of these studies demonstrated a significant higher percentage of Tregs than the control and the antileukemic activity of T cells was negatively correlated with Tregs (Schick *et al*., 2013). Furthermore, another study established a link between the presence of elevated CD25 levels on T helper cells and reduced survival rate (Bołkun *et al*., 2016). These studies pay the attention towards the Tregs as a factor implicated in impairment of T cell function and antitumor response either directly or indirectly (Wilke *et al*., 2011).

Tregs isolated from adult AML cases can synthesis and release IL-35; a novel inhibitory cytokine. IL-35 expands Tregs and inhibits CD4+ve, CD25-ve effector T cells (Teffs) thus promoting AML blasts immune escape. Moreover, IL-35 enhances the proliferation of AML blasts and impairs apoptosis (Tao *et al*., 2015). Tregs also induce apoptosis in T helper effector cells through the granzyme B-dependent mechanism in mice (Gondek *et al*., 2005).

Tregs can suppress Teffs through APC- dependant numerous rotes, including competing them for the same costimulatory receptors (e.g., CD80/86) and prevention of steady interaction between DCs and conventional T cells (Tadokoro *et al*., 2006). Tregs inhibit transcription of IL-2 mRNA in the responding T cells. Supposing that IL-2 is produced normally from the Teff, Tregs expresses a high affinity receptor for IL-2; CD25 that binds to it and decrease the IL-2 available for other T cells (Thornton *et al*., 2004;

Pandiyan *et al*., 2007). Away from APCs, direct contact between Treg and Teff can cause suppression or programmed cell death of the latter cell (Bopp *et al*., 2007). In AML, Tregs are highly qualified in hydrolysis of ATP with resultant increase in Treg cAMP levels (Ustun *et al*., 2011); this cAMP is transferred to Teffs on contact with Tregs. cAMP will decrease IL-2 production with subsequent inhibition of Teff proliferation (Bopp *et al*., 2007). These findings would oblige us to think that the increased Treg cAMP levels in patients with AML might explain why Tregs in AML patients are more suppressive than Tregs in control patients (Szczepanski *et al*., 2009).

DCs residing in the BMM in AML have a vigorous chemotactic effect on Tregs, which may be a considerable factor in the accumulation of Tregs (Olsnes *et al*., 2008). On the other hand, the increased Tregs in AML impair the maturation of normal DCs (Curti *et al*., 2010). The immature DCs express indolamine (IDO), giving rise to immune inhibition both by depleting tryptophan, which interrupt cell cycle progression in T cells and inhibits their proliferation. Increasing kynurenines; tryptophan metabolites which is toxic to T cells, will promote T-cell apoptosis (Mellor and Munn, 2004). Both IDO activity in the serum of AML patient (Corm *et al*., 2009) and its expression in myeloblasts (Curti *et al*., 2007) were found to be increased. Interestingly, AML patients with IDO +ve myeloblasts were shown to have extra Tregs compared with IDO -ve patients and *in vitro* studies showed that IDO +ve myeloblasts in humans and mice can transform CD4+ve, CD25-ve (Th) cells into CD4+ve, CD25+ve (Tregs) cells (Curti *et al*., 2009). Regarding the effect of IDO on AML patient's survival, it was reported that high IDO mRNA expression in leukemic blasts (Chamuleau *et al*., 2008) and high IDO activity(Corm *et al*., 2009) were associated with poor survival.

CD200 is over expressed in leukemic blasts in 43% of AML patients (Tonks *et al*., 2007). CD200 interact with its ligand on T- cells, B- cells and DC results in their suppression (Gorczynski *et al*., 2005). Interestingly, the expression of CD200 on the AML blasts was correlated with a more frequent Tregs in the BM (Coles *et al*., 2010) and it directly inhibits the cytotoxic activity of NK cells (Coles *et al*., 2011) (Fig. 1).

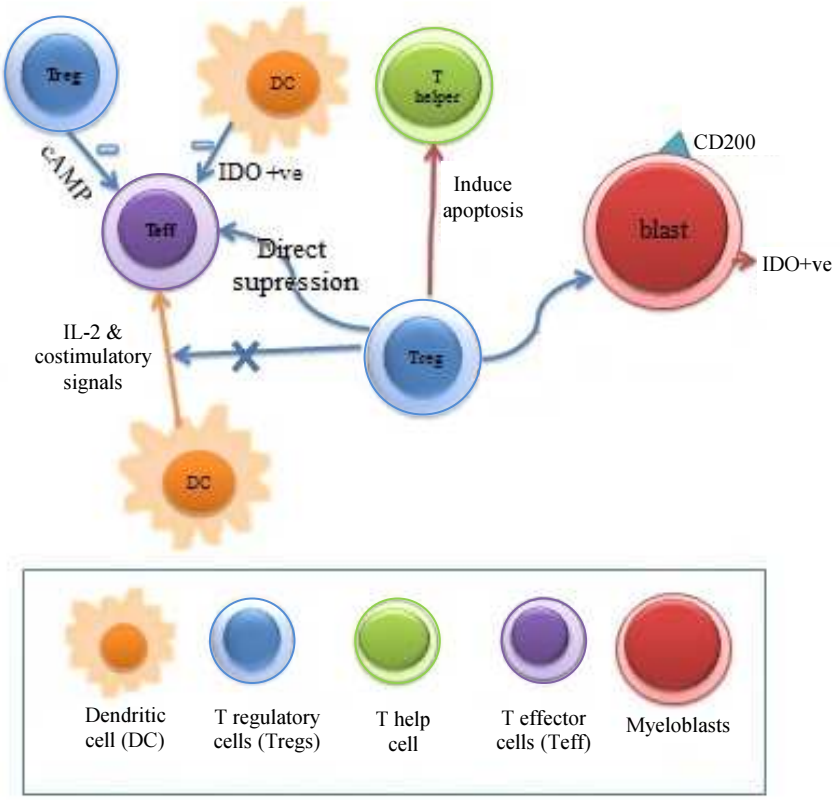

Fig. 1: Interaction between T regulatory cells and other immune cells in acute myeloid leukemia. Tregs produces IL-35 that inhibits T helper cells and directly reduces the apoptosis of AML blasts and promotes their proliferation. Tregs directly inhibit Teff cells either directly or via inhibition of DC. Tregs inhibit Teff by cAMP pathway. both DC and blast cells express Indoleamine 2, 3-Dioxygenase (IDO), which causes immune suppression

T Helper 17

In AML patients, either newly diagnosed or not in remission, Th17 (CD3+ve, CD4+ve, IL-17+ve) was considerably increased in relation to the control (Abousamra *et al*., 2013; Musuraca *et al*., 2015; Yu *et al*., 2014) and reduced significantly after remission completion (Abousamra *et al*., 2013). Additionally, the circulating IL-17 in acute leukemia showed remarkable elevated levels compared to the control and decreased to a notable level after 6 months of chemotherapy (Musuraca *et al*., 2015; Xiang *et al*., 2016). Also, Th17 release IL-10 with its known immunosuppressive properties (Musuraca *et al*., 2015). An inverse relationship was found between depletion of Th17 and restoration of IFN-γ production from T cells in AML. These findings denote that altered Th17 cells actively promote AML escape by induction of an immunosuppressive state (Musuraca *et al*., 2015).

Myeloid Derived Suppressor Cells (MDSCs)

MDSCs have a characteristic phenotype being CD33+ve, CD11b+ve, HLA-DR low/-ve. They are closely related to neutrophils and monocytes. MDSCs are not present under normal conditions (Gabrilovich, 2017). Cytokines and growth factors derived from the malignant cells can induce shift of hematopoiesis towards the development and proliferation of MDSCs (De Sanctis *et al*., 2016). They can inhibit T cells, NK cells and APCs and frustrate the advantageous immune reactions (Meirow *et al*., 2015) hence promoting tumor growth (Malek *et al*., 2016).

MDSCs can hinder the proliferation of tumor specific T cells and inhibit their cytotolytic potential (Chesney *et al*., 2017) by many mechanisms including; damaging lack of amino acids essential for T cells, inducement of oxidative stress, interference with T cell trafficking and hamper their viability (Motallebnezhad *et al*., 2016) as well as by promoting expansion of Tregs. Thereby, dampening the host immune responses against the tumor (Chesney *et al*., 2017) and enhance shifting of the immune system towards tumor tolerance (Parker *et al*., 2015). In addition, tumor-infiltrating MDSCs can express IDO in animal models (Jia *et al*., 2010) that play a critical role in Tregs induction in the tumor microenvironment (Ustun *et al*., 2011). Sun *et al*. (2015) reported that, in the BM of newly diagnosed adult AML, MDSCs were found to be increased and significantly reduced after complete remission. Also the achievement of remission was inferior in the group that had higher MDSCs count. High count of MDSCs was correlated with WT-1 protein and extramedullary spread denoting a possible role of these cells in AML prognosis.

Immunosenescence

Immunosenescence involves age-associated restructuring changes of innate and adaptive immune functions (Baeza *et al*., 2011). The aging process that affect the innate immunity results in reduced ability to initiate adaptive immunity, together with enhanced inflammatory reactions (Panda *et al*., 2009; Shaw *et al*., 2010). Consequently, immunosenescence would affect the immune surveillance properties of the immune system and add more burden together with the evasion mechanisms created by AML blats that collectively promote the development of the disease (Fig. 2). These changes will be highlighted in the following section.

Aging of the Innate System

The drastic changes that occurs in the innate system due to senility mainly results in the deterioration of the different functions of NK and DC cells as a consequence, contribute to the increase prevalence of malignancy as a result of diminished tumoricidal effect of NK cells and impaired activation of T cells (Henry *et al*., 2011). In addition, the aging process that affect innate immunity result in enhanced inflammatory reactions; inflammaging that usually precedes the development of malignancy (Panda *et al*., 2010; Shaw *et al*., 2010).

The DC and MQ phenotype in aging shows low levels of MHC- class II expression (Strohacker *et al*., 2010; Garbe *et al*., 2012) that will be associated with decreased antigen presentation to T cells (Plowden *et al*., 2004). The competence of these professional APCs to introduce costimulatory signals to the T cells is diminished as a result of reduced expression of CD80 (Strohacker *et al*., 2010). Prostaglandine E2 synthesis and release by MQ is enhanced that can also repress T cell functions (Solana *et al*., 2012).

Signaling via toll like receptors (TLRs) is absolutely necessary for DCs activation. In old age, there is decreased TLR signaling that may be related to down regulation (Rosenstiel *et al*., 2008; Montoya-Or Tiz, 2013) or unresponsiveness (Gomez *et al*., 2005; Shaw *et al*., 2013) this will ends in aberrant secondary immune cell activation (Rosenstiel *et al*., 2008; Montoya-Or Tiz, 2013). Reduced TLR signaling will results in defective upregulation of TLR- dependant expression of CD80 and CD86 this in turn will impair the function of DC and MQ as APCs due to their failure to supply T cells with the costimulatory signal (Van Duin *et al*., 2007).

With advanced aging, the movement of DCs towards the concentration gradient of chemokines

(MIP-3β, SDF-1) is reduced, which might negatively affects their migration to lymph nodes and induction of immune responses (Agrawal *et al*., 2007). Also, their potentiality to form cytokines like IL- 15, INF-α and TNF-α is reduced (Stout-Delgado *et al*., 2008). TNF-α is a pivotal cytokine in CTLs activation via DC hence, its reduction will impedes stimulation of T cells (Liu and Zheng, 2012).

Defective NK cells cytotoxicity is observed during aging that may be related to many factors (i) Defective signal transduction due to reduced release of IP3. (ii) Defective granule exocytosis (Mariani *et al*., 1998). (iii) Diminished capacity to release perforin that consequently results in reduced killing effect on target cells (Hazeldine *et al*., 2012).(iv) Deficiency of the natural cytotoxicity receptors e.g. NKp46 (Hazeldine *et al*., 2012) and NKp30 (Almeida-Oliveira *et al*., 2011). However, the $CD56^{dim}$ NK population is increased in number as a trial to compensate this defective cytotoxicity (Di Lorenzo *et al*., 1999) but this expansion occurs on the expense of the $CD56^{bright}$ population (Chidrawar *et al*., 2006) that mainly functions as immunoregulator and an amble source of IFN-γ which is reduced in the elderly by 75% in relation to the younger samples (Chidrawar *et al*., 2006; Solana *et al*., 2012).

Aging of the Adaptive System

The primary process in age associated immune frailty is the decrease in the thymic output that occurs as a result of thymic involution (Hakim and Gress, 2007). Measurement of TCR excision circle that denotes recent emergence from the thymus gland (Sempowski *et al*., 2001), revealed that the output of the naive T-cell in old age decreases up to 80% (Arnold *et al*., 2011), which affects both T helper and cytotoxic but the cytotoxic cells are more affected. Consequently, T cell diversity will be reduced, which put a fixed T-cell immune repertoire in front of rapidly growing tumor cells and tumor permissive microenvironment (Czesnikiewicz-Guzik *et al*., 2008). Thus initiating an unjustified battle that ends in cancer propagation. With respect to the response of the naïve T cells to IL-2 stimulation, the naïve cells show reduced proliferation and differentiation in senility compared to the young age (Zediak *et al*., 2007).

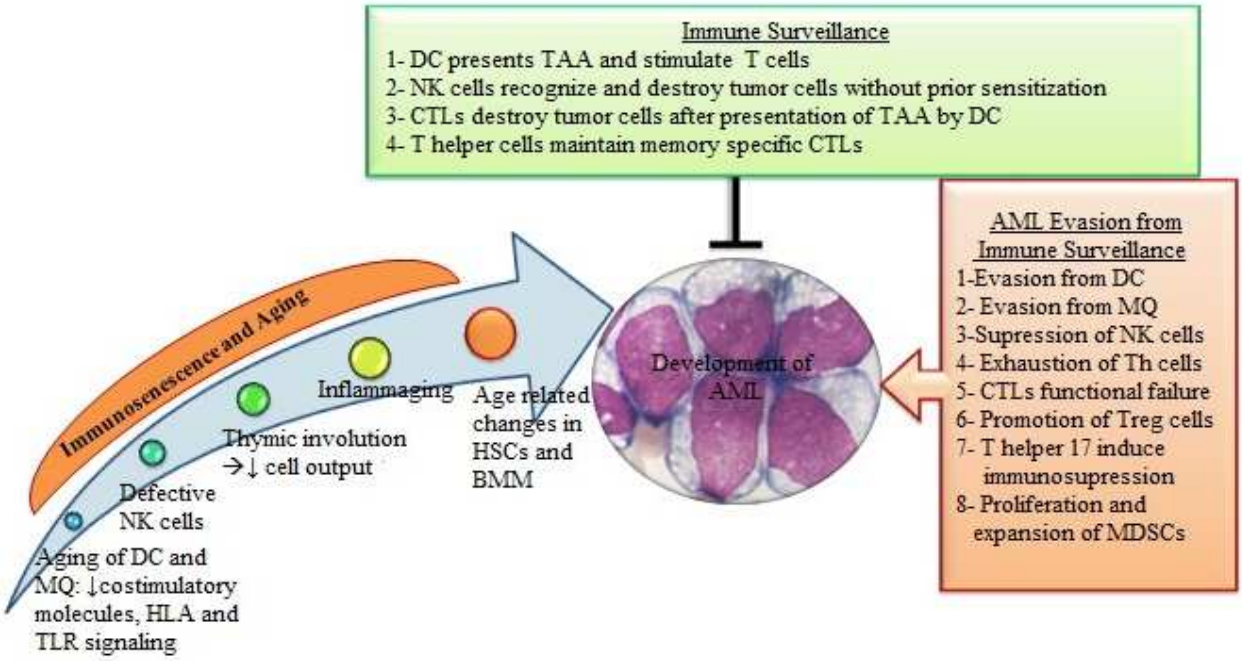

Fig. 2: Outline of the immune mechanisms that affect the development of acute myeloid leukemia in old age. Immune surveillance can eradicate the tumor cells or maintain an equilibrium state, however this function is opposed by the evasion mechanisms created by AML blasts and additionally became weaker with immunosenescence and age related changes in BMM and HSCs. AML: Acute myeloid leukemia, BMM: Bone marrow microenvironment, CTL: Cytotoxic T lymphocytes, DC: Dendritic cells, HLA: human leukocyte antigen, HSCs: Haematopoietic stem cells, MDSC: Myeloid derived suppressor cells, MQ: Macrophages, NK: Natural killer cells, TAA: Tumor associated antigens, TLR: Toll like receptors

The costimulatory molecules on CTLs shows reverted distribution in caducity were CD28 is decreases, CTLA-4 is increased which binds to CD28 ligands (CD80 and 86) on APCs and inhibits CTLs (Parish *et al*., 2010a). Additionally, the CD28 negative T cells can causes non reactivity of T helper cells (Effros, 2010).

The process of cancer immunediting indicates that tumor cells continuously produce novel antigens due to their genetic instability. Thereafter, these novel antigens are presented by APCs to the CTLs and assigned for immune destruction. However, in old age the CTLs have a limited diversity and will lose their eligibility to interact with the novel TAA (Beatty *et al*., 2009). In aged AML patients, senescent T cells (CD28-ve, CD57+ve and short telomerase) have been isolated. These cells have a weaken ability to perform most of the effector functions such as proliferation, cytokines release, or degranulation despite their ability to recognize different epitopes derived from TAA (Beatty *et al*., 2009).

Aged naive Th cells live longer as a consequence of reduced expression of the proapoptotic molecule; Bim (Tsukamoto *et al*., 2010) but proliferate less mostly due to shorter telomerase (Kilpatrick *et al*., 2008), produce reduced levels of IL-2 when stimulated and are not influential in assisting B cell (Eaton *et al*., 2004). This longer life span keep sufficient number of the cells to compensate for the reduced production but the side effect of this longevity is the development of T helper functional impairment (Tsukamoto *et al*., 2009).

The effector T cell response is counting on the rapid expansion and subsequent cell survival to form long-lived memory T cells. Proliferation is associated with considerable genomic stress and the activation of DNA damage response pathways, which are increasingly compromised with immune aging (Cavanagh *et al*., 2012). Best known is telomeric erosion due to a decline in repair mechanisms, in particular the expression of telomerase (Hodes *et al*., 2002). Age-associated telomeric erosion is seen in naïve T cells and extra in the effector CTLs, in which telomerase appears to limit clonal expansion (Parish *et al*., 2010b).

Finally differentiated CTLs overexpress miR-24, which down-regulates the expression of histone variant; H2AX (Brunner *et al*., 2012). As a consequence, DNA damage responses to genotoxic stress are impaired in these cells with reduced serine phosphorylation of ataxia telangiectasia mutated (ATM) and p53. This will be translated functionally into increased apoptosis susceptibility and a decreased replicative capacity, which dampens T cell responses (Brunner *et al*., 2012). A variation in the signal transduction pathways NF-κβ and MAPK was noted (Deruy *et al*., 2014; Jing and Lee, 2014) together with reduced miR-181a. This would be associated with lose control upon lymphocyte activation with poor response (Mariani *et al*., 1998).

Senility is associated with progressive reduction in memory formation as proved from vaccination studies (Bouree, 2003). This would impair one of the main advantages of the adaptive immune system; formation of memory. The hazard of losing efficient memory especially to the newly emerging tumor antigens is deterioration of the immune system ability to hinder disease recurrence in elderly patients (Foster *et al*., 2011).

One of the features of the immunosenescence is the increase in Tregs that enforces the tendency towards immune suppression in old age (Cusi *et al*., 2010). In AML, Tregs are also increased (Schick *et al*., 2013) representing one of the immune evasion mechanisms (Watanabe *et al*., 2010). This double increase in Tregs would critically impair immune response in old AML patients.

Inflammaging

It is low- grade chronic sterile inflammation that occurs in old age (Franceschi and Campisi, 2014) probably occurs as a result of persistent subjection to antigens together with a substandard immune functions mostly characterized by aged MQ and T cells in addition to increased proinflammatory cytokines (Campos *et al*., 2014).

Cellular senescence is accompanied by accumulation of danger-associated molecular patterns (DAMPs) (Rubartelli and Lotze, 2007) that enhance innate immunity (Feldman *et al*., 2015) via stimulation of three different groups of receptors; TLR (Piccinini and Midwood, 2010), NOD-Like receptors (NLRs) (Strowig *et al*., 2012) and cytosolic DNA sensor (Keating *et al*., 2011). DAMPs will stimulate TLR leading to stimulation of the pro-inflammatory transcription factors; NF-κβ with subsequent elevation in an amble of inflammatory cytokines such as TNF-α, IL-1β and IL-12 and enhancement of type I interferon-dependant immune response (Piccinini and Midwood, 2010). DAMPs warn the NLRs that cause increase in IL-1β and IL-18 via inflammasome assembly that promote maturation of the inflammatory cytokines (Strowig *et al*., 2012). Also, inflammasome signaling and type I IFN response can be stimulated by dsDNA (Keating *et al*., 2011). Enhanced activation of the coagulation system and inadequate regulation of the complement system are extra sources for inflammaging (Franceschi and Campisi, 2014).

Another crucial component of the inflammatory responses is the aging of the immune system itself, which in favor of supporting the proinflamatory status by the following mechanisms (i) The considerable changes of monocyte subsets with age with increase in non-classical

monocytes ($CD14^{+ve}$, $CD16^{+ve}$) (Iida *et al*., 2011); a major source of proinflammatory cytokines e.g. IL6, IL1β (Sadeghi *et al*., 1999). (ii) Release of proinflammatory cytokines comprising IFN-γ and TNF-α, by $CD8^{+ve}$ T cells. The increase in TNF-α level has a mutual relationship with dismal prognosis in hematological malignancies (Malaguarnera *et al*., 2010). (iii) Augmentation in the number Th17 cells that release IL-17 with its well known proinflammatory properties (Ouyang *et al*., 2011) and it is demonstrated to be increased in AML (Abousamra *et al*., 2013).

Senile hematopoietic stem cells display an enhancement of the inflammatory pathways as well (Franceschi and Campisi, 2014). It was proposed that the potentiality of hematopoietic cell in humans is conserved during the whole life and the main changes are due to reconstruction of the hematopoietic cytokine network with advanced age (Bagnara *et al*., 2000). Intriguingly, it was noticed that age dependant modulation of the stem cell pool are responsible for deviation towards myeloid series (Woolthuis *et al*., 2011) which in turn leads to increased macrophages; the major player in inflammaging (Franceschi *et al*., 2007). The inflammatory cytokines produced by macrophages, e.g., TNF-α, boosts proliferation of malignantly transformed cells by induction of death of the normal cells. Hence, giving a space for proliferation of cancer cells (Karin *et al*., 2006). Furthermore, chronic inflammation promotes recruitment of MDSCs with their mentioned inhibitory properties (Meyer *et al*., 2011). Overall, these observations supports the concept that the age-related shift of the hematopoietic microenvironment toward a proinflammatory phenotype can contribute to hematopoietic malignancy.

Clinical Significance and Conclusion

Away from the immune system, senility had a negative effect on many protective mechanisms against malignancy. These negative effects includes defective DNA repair, telomere shortening, chromosomal instability, modulation of intercellular communication and scarcity in apoptosis- controlling genes (Campisi, 2013). Then again, malignant cells are distinguished by sustained proliferation, uncontrolled expansion, resistance to apoptosis and the capability to evade immune surveillance (Fouad and Aanei, 2017). These criteria of aging and malignancy appear to be contradictory but it emphasizes the mission of the microenvironment which directs both cellular and molecular events in the surrounding tissue. Tumor microenvironment is dictated and promoted by the malignant cells and in turn, it actively promotes tumors. In AML, the immune cells interact with the tumor cells and all other components within this microenvironment. This interaction generates a network of immunosuppressive mechanisms, while activation of the normal immune protective responses are impeded to evade the immune surveillance (Whiteside, 2010). However, the immune cells responsible for surveillance together with the tumor microenvironment have already been altered with aging leading to a state of immune frailty that adds more to the evasion mechanisms.

A clear view of the aging changes and the evasion mechanisms mediated by AML malignant cells demonstrate that the AML cells can perform several mechanisms to evade from the killing potential of NK and CTLs and potentiate the immune inhibitory cells such as Tregs and MDSCs. With aging the NK cytotoxic ability per cell is diminished, the potentiality of the DC to perform antigen presentation is hampered and T cell diversity decreases due to thymic involution with defective proliferation. Those factors together with the previously mentioned evasion mechanisms would fasten the transition from the equilibrium to the escape phase of tumor development. Moreover, inflammaging creates a hazardous microenvironment that promotes oncogenic events. In this setting of age-impaired immunity, together with the other age related changes occur in HSC and BMM would initiate and promote cancer cells resulting in increased frequency of hematological malignancies that is truly perceived with advanced age.

AML in elder age group has a dismal outcome with 5 years OS less than 5%, as compared to 40% in the young (Alibhai *et al*., 2001). This poor outcome is related to both patient and disease-related factors. Ageing often coexists with enfeeblement and co-morbidities that negatively affect their tolerance to intensive treatment modalities (Mohammadi *et al*., 2015). AML in the elderly has distinct biological criteria different from the young age group with higher incidence of multiple chromosomal abnormalities, mutations in genes coding for epigenetic regulators, kinases and cell cycle regulators and transcription factors (Almeida and Ramos, 2016). Additionally, immunosenescence adds more to the different biological properties of AML in elderly.

Understanding the role of immunosenescence and evasion mechanisms in the development and progress of AML will help with proper choice of therapy. Naturally, the immune cells are anatomically and functionally close to the myeloid cells in the BM. This interaction provides a unique area for development of immunotherapeutic strategies that targets the blasts and enforces immune surveillance. Monoclonal antibodies were used to target specific AML antigens with effective results and minimal toxicity. In recent years, a number of these antigens emerged such as CD33, CD123, CD96, CD47 and CD25 (Majeti, 2011). Despite that most efforts have focused on CD33, CD47 have revealed potent efficacy against AML-LSC in

xenotransplantation models that would both target the blast cells and inhibit one of immune evasion strategies. Hopefully, these antibodies will at the latest be advantageous in the treatment of AML.

Recording the negative influence of aging on NK cells with evasion mechanisms would make the NK cells a proper target for immunotherapy in old AML patients that is emphasized to be safe and effective (Rubnitz *et al*., 2010). The usage of anti-KIR antibodies that block KIRs would increases the activity of NK cells; a requirement for effective antileukemic response (Vey *et al*., 2012). Trial using IL-2 diphtheria toxin fusion protein results in depletion of Tregs proliferation, hence overcome their inhibitory effect on NK cells (Bachanova *et al*., 2014).

Targeting AML blasts with adoptive T cells is an interesting line of therapy but its benefit may be limited by the immune modalities made by the AML itself to evade the T cells that necessitates combined monoclonal antibody therapy such as PD-1 blockade, blockade of CTLA-4, administration of adenosine antagonists and IDO inhibitors may create a tumor environment that enhances the effectiveness of cellular immunotherapy (Ohta and Sitkovsky, 2014). However older patients may get benefit first from restoration of the thymic function by the use of cytokines known to improve thymopoiesis such as IL-7and growth hormone (Taube *et al*., 2012) because evidence advocate that aged precursors can complete their development normally if they are located in a young thymic environment (Garbe *et al*., 2012). To overcome replicative senescence in T cells, treatment modalities that support telomerase activity may be tried (Effros, 2010). Another prospective strategy to reduce the prevalence of cancer in old age is to impede the proinflammatory environment by exploiting currently obtainable medications used in chronic inflammatory diseases (Korkaya *et al*., 2011; Jones *et al*., 2011).

Peptide vaccines using leukemia associated antigens (e.g., WT1, proteinase 3 and RHAMM) to stimulate CTLs was tried in AML cases to stimulate antileukemic responses and thereby control minimal residual disease (Grosso *et al*., 2015). However, this would be of a limited value because of the finite response to vaccines noticed in old age with less effective development of immunological memory.

As research in the field progresses, novel therapeutic modalities to actively support the immune function, essentially in the senile age group, will occupy a prominent place in the armamentarium against this difficult disease in that critical age.

Conflict of Interest

The author declares that there is no conflict of interest.

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