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REVIEW ARTICLE

Myeloid-derived Suppressor Cells in Cancer: A Review on the Pathogenesis and Therapeutic Potentials

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Abstract: Myeloid-Derived Suppressor Cells (MDSCs) are multifarious group of immature cells that arise from the myeloid and amass in individuals with cancer, sepsis, burns, or chronic inflammation. It has been evidenced that these group of cells are efficient in modifying adaptive and innate immune responses, coherent with their assumed key biological roles. It is evidenced that MDSCs inter-communicate with Tumor-Associated Macrophages (TAM), Tumor-Associated Neutrophils (TAN), Dendritic Cells (DCs), Receptor for Advanced Glycation End-products (RAGE), Toll-Like Receptors (TLRs), Matrix Metalloproteinase (MMPs) as well as High Mobility Group Box 1 (HMGB1) during carcinogenesis. This interaction although elaborated in various studies and reviews still does not explain in details as to how their interplay results in cancer pathogenesis. We noted that MDSC contributed to cancer immune suppression *via* TLR-4 receptor and lipopolysaccharideas (LPS). Furthermore, MDSC contributed to cancer development *via* MMPs (MMP-9 and MMP1-12) as well as RAGE. In the cancer microenvironment, HMGB1-driven MDSC amassment expedites cancer development and metastasis *via* PMN-MDSCs, macrophages, DCs and Immature Myeloid Cells (IMC). Also, HMGB1 intermediation with MDSCs *via* RAGE and/or TLR-4 leading to cancer development. Nevertheless, MDSCs have already proven potent in some cancers and are currently been used as treatment options although further studies are needed in some other cancers. Our review, therefore, explores the pivotal pathogenic and therapeutic roles of MDSCs in cancer.

Keywords: MDSC, HMGB1, MMPs, RAGE, TLRs, Macrophages.

1. INTRODUCTION

Myeloid-derived Suppressor Cells (MDSCs) are multifarious group of immature cells that arise from the myeloid and amass in individuals with cancer, sepsis, burns, or chronic inflammation. It has been evidenced that these group of cells are efficient in modifying adaptive and innate immune responses, coherent with their assumed key biological roles [1, 2]. Their principal role is to escape or lessen tissue injury during an extreme or a tenacious immune reaction or during inflammation. MDSCs have now been categorized into two distinctive subtypes. These are the monocytic MDSCs and granulocytic MDSCs (M-MDSCs and G-MDSCs) [3].

Studies have shown that the enlargement and stimulation of MDSCs trigger several tumors- or tumor stromal cell-derived factors [3 - 5]. One of such factors is tumor-derived Granulocyte-Colony-Stimulating Factor (G-CSF). This factor is principally required for the differentiation of M-MDSCs. Also, tumor-derived Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) has demonstrated to partake in M-MDSC generation [3, 6]. Nevertheless, the proportion of G-MDSC to M-MDSC in diverse cancer models is extremely unpredictable and relies on factors that still need further investigation into. Furthermore, in tumor environment, the proportion of G-MDSC and M-MDSC is far lesser than in lymphoid organs. This may have a positive or negative feedback on the immune flora suppression usually seen at the cancer environment. The means *via* which M-MDSC in tumor environment preferential buildup is still a matter of debate. The potential preferential movement of M-MDSC to the cancer location is postulated to be as result of a flora of chemokines generated by cancer cells. Furthermore, the cancer microenvironment , which is depicted with

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hypoxia, low pH and several other factors which might not sustain subsistence of G-MDSC [1, 2].

In humans, MDSCs are typically outlined as $CD33^{+}$, $CD11b^{+}$, $HLA^{-}DR^{-}$/low; M-MDSCs are $CD14^{+}$, $CD15^{-}$/low and G-MDSCs CD14-$CD15^{+}$ (and $CD66b^{+}$), coherent with their individual granulocytic and monocytic morphological characters [1, 7]. Studies have evidenced that MDSCs involve dual healing target due to their essential immunomodulatory tasks such as elimination or suppression of hypothetically positive immune response, as seen in tumor or cancer immunotherapy and expansion of endogenous MDSCs seen in conditions in which alteration of the immune responses is advantageous as in the therapy of graft *versus* host disease or autoimmunity [1, 8]. It has also been postulated that immature MDSCs infiltrates into a particular cancer microenvironment and can differentiate into Tumor-Associated Macrophages (TAM) [3, 9]. Therefore, numerous MDSCs has proven to partake in cancer-triggered immunosuppressive actions. On the other hand, averting the expansion of MDSCs is being investigated as an auspicious modality of combating various cancers [3].

It has been evidenced that Programmed cell Death protein 1 (PD-1) receptor is naturally secreted in stimulated T cells 26 and partakes in moderating immune responses [1, 10]. It is also proven that triggered MDSCs and some Antigen-Presenting Cells(APCs) release the PD-1 ligand (PD-L1), which after binding to PD-1 triggers apoptosis in T cells [1, 11]. Studies have further evidence that IL-6 performances a downregulatory action of IL-1β during inflammatory reactions and because MDSC secretes IL-6R but not IL-1R a direct influence of IL-1 on MDSC is also very possible [12]. These influences which are primarily linked to IL-1 could essentially be triggered by IL-6. Also, IL-1 triggers IL-10 generation *via* MDSC as well as downregulates IL-12 generation *via* macrophages [12].

2. MDSCS IN MICE AND HUMANS

Primarily, MDSC in mice were outlined as cells of the Gr-11CD11b1 phenotype and deficient in the secretion of markers characteristic of mature Macrophage (MF) and Dendritic Cell (DC) [13, 14]. In humans, however, MDSC were outlined as cells that co-sanitizes mononuclear cells, deficient of markers of lymphocytes, natural killer cells, monocytes, and DC as well as secreted by myeloid cell markers CD33 and CD11b and in some reports, granulocyte markers [13, 15]. Studies have shown that in mice G-MDSC have a phenotype of CD11b1Ly6G1Ly6Clow, while M-MDSC has a phenotype of CD11b1Ly6GLy6Chigh [15, 16]. The Ly6G molecule is identified to be secreted predominantly on granulocytes while Ly6C is characteristically extremely secreted on monocytes [13, 17]. It is also apparent that Gr-1 antibody (RB6-8C5) can be found on both Ly6G and Ly6C epitopes. Studies have proven that successive grouping with Ly6G, but not with Ly6C-specific antibody, is expressively diminished when Gr-1 antibody is used at the initial phase of staining for MDSC [13, 18]. In humans however, the phenotype of these cells is less distinctly outlined, though current reports have linked CD15 and CD66b as extra markers permitting the recognition of G-MDSC and M-MDSC [13, 19]. Studies have shown that G-MDSC and M-MDSC vary not only in the morphology and phenotype, but also in the machinery *via* which they subdue immune function [13, 20]. Therefore, in humans, G-MDSC predominantly utilizes Reactive Oxygen Species (ROS) as the contrivance of immune suppression while M-MDSC predominantly utilizes upregulation of inducible Nitric Oxide Synthase (iNOS), arginase, and a collection of immune suppressive cytokines to subdue numerous immune functions [13].

3. MDSCS IN BONE MARROW CELLS

Studies have shown that Ly-6G and Ly-6C are both markers of primary myeloid extraction obligatory in the downregulation and differentiated of macrophages and DC. In isolation, Ly-6G is upregulated during their advancement into neutrophils [17, 18]. It is now clear that Ly-6C is extremely released by monocytes in the Bone Marrow (BM) and lowest by BM granulocytes [18, 21]. The secretion of Ly-6C has also been demonstrated on memory CD81 T cells, γδ, T cells, a subset of NK cells as well as plasmacytoid DC [18, 22]. Nevertheless, the practical responsibilities of Ly-6G and Ly-6C molecules in the myeloid expansion is still a matter of debate. However, it evidenced that in bone marrow cells Gr-1-specific antibody trigger signaling pathways through STAT1, STAT3, and STAT5, analogous to the consequence of GM-CSF. Thus, Gr-1 antibody triggers myeloid cell development and up-regulation of MF markers [18, 23]. Experimentally, Gr-1 antibody injection had suppressive action on both Gr-1high and Gr-1low MDSC. This practically means that the Gr-1 molecule has some responsibilities in both MDSC function and differentiation. Nonetheless, this further implicates Gr-1 receptor as a natural ligand and a subtype of Gr-1high MDSC which might have conspicuous immune suppressive actions [24].

Additionally, this means that the peculiarities in practical roles of MDSCs and the distinctive quantities of Gr-1 secretion might be considered as differences in the expression of this molecule by G-MDSC and M-MDSC, rather than

a suggestion that Gr-1 performs a role as a direct marker of cells with immune suppressive actions. Moreover, for eradication of neutrophils, Gr-1 Ab injections also have been utilized in the deplete MDSCs [24].

4. MDSCS, TUMOR-ASSOCIATED MACROPHAGES AND CANCER

Macrophages are also a distinct group of myeloid cells that expedites cancer advancement through machineries such as immunological as well as nonimmunological pathways [25, 26]. Macrophage is morphologically determined *via* their parochial tissue microenvironment. In the cancer microenvironment, they piquantly differentiate towards an M2-like morphology so they are referred as "Tumor or cancer Associated Macrophages" (TAMs) [25]. TAMs, can be distinguished from M-MDSCs morphologically due to their active secretion of F4/80, minimal-to-transitional secretion of Ly6C as well as minimal or indiscernible secretion of S100A9 protein. Furthermore, IRF8 a marker of terminal macrophage amplifies M-CSF receptor as well as CD115 aid in the expression of TAM as compared to M-MDSCs [26].

Macrophage-specific indicators CD68 and CD163 and minimal or vague secretion of S100A9 can be utilized to distinguish TAM and cancer M-MDSCs in human beings. Studies have evidenced that TAMs facilitate cancer advancement *via* numerous non-immune machineries such as f angiogenesis, cancer cell invasion, metastasis, as well as safeguarding cancer cells from chemotherapy-triggered apoptosis [25, 27, 28]. Biologically, macrophages are categorized morphologically into M1-like or classically triggered macrophages and M2-like or alternatively triggered macrophages [25, 29]. It is now clear that M1-like macrophages are characteristically stimulated *via* lipopolysaccharideas (LPS) as well as IFN-γ axis and are depicted with the extraordinary secretion of IL-12 as well as minimal secretion of IL-10. Furthermore, IL-12 facilitates the expansion type 1 T cell reaction which augments anti-cancer immunity [25].

It is also well known that M1-like macrophages can eliminate cancer cells while M2-like macrophages are stimulated *via* glucocorticoid hormones, IL-4, IL-13 as well as IL-10 leading to excessive generation of IL-10 and minimal generation of IL-12 resulting in cancer advancement [25]. Seven morphologically dissimilar macrophage subgroups inside cancers have been found which means that macrophages are multifaceted [25, 26]. Studies have shown that M1-like macrophages that have cancer elimination potentials have similar morphological appearances just like IL- $12^{hi}IL\text{-}10^{low}$ and are triggered *via* LPS and IFN-γ axis. Nevertheless, culturing of LPS and IFN-γ led triggered peritoneal macrophages and stimulation of cancer MDSC for 16 h reduced macrophage generation of IL-12 more than 80% [25, 30].

Studies have proven that MDSC-facilitated down-regulation of IL-12 necessitates MDSC–macrophage cell interaction just as MDSC subduction of T cell stimulation [31, 32]. Furthermore, MDSC generates extreme quantities of IL-10 and IL-10 which are strategic cytokine for modifying IL-12 transcription [33, 34]. Nevertheless, Amplified MDSC generation of IL-10 and diminished macrophage generation of IL-12 may influence $CD4^+$ T cells, Natural Killer (NK) cells and Th2 cells [25]. Moreover, IL-10 champions the differentiation of type 2 $CD4^+$ T (Th2) cells. On the other hand, IL-12 triggers the differentiation of type 1 $CD4^+$T (Th1) cells as well as NK cells. Also, Th2 cells neutralize the expansion of cytotoxic $CD8^+$ T cells (CTL) as well as the generation of IL-4 which partake in the progress of TAMs [25, 35]. Studies have demonstrated that MDSC-generation IL-10 may accelerate the advancement of $CD4^+$ T regulatory cells (Tregs) since IL-10 is an effective trigger of Tregs [34, 36]. It is evidenced that MDSC and macrophage bi-directionally communications also changes macrophage secretion of MHC class II molecules. Furthermore, MHC II reduction necessitates MDSC-macrophage cell-to-cell communication. Trials with IL-10-deficient MDSC suggested that the down-regulation was interceded by IL-10 generated by MDSCs [25].

Several authors have evidenced that NK cells differentiation is depicted with the secretion of CD27 on immature NK cells as well as amplified secretion of CD11b and KLRG-1 as NK cells mature [25, 37]. Nevertheless, in the cancer microenvironment, cancer cells and stromal cells such as MDSC and macrophages, creates a proinflammatory milieu. Also, diverse cancer cells generate multiplicities of pro-inflammatory intermediaries such as IL-6, TNF-α, prostaglandins and cyclooxygenases [25, 38]. Studies have shown that inflammation champions MDSC buildup as well as subdue their effectiveness [31, 39]. Nevertheless, *via* a feedback mechanism, MDSC generation inflammatory intermediaries which also triggers a downgrade inflammation *via* the generation of the anti-inflammatory cytokine IL-10 [40]. Also, MDSC extra reduce inflammation by reducing macrophage generation of the pro-inflammatory cytokine IL-6 [39]. This suggests that MDSCs at the inflammatory cancer milieu may be beneficial.

5. TUMOR-ASSOCIATED NEUTROPHILS, POLYMORPHONUCLEAR MDSCS AND CANCER

Tumor-Associated Neutrophils (TAN) are multifarious group of cells with pro-carcinogenic as well as anti-cancer actions [26, 41]. Classification of circulating neutrophils and TANs is founded on features like gradient density, phenotypical roles as well as tissue type [26, 42]. Systematic substantiation on definitive maturation and differentiation phases of the subtypes of neutrophils is still not established. Further studies are needed in this direction. Terminologies like anti-tumorigenic N1 and pro-tumorigenic N2 mouse neutrophils were introduced to depict distinctive groups of TAN [41]. Recently, polymorphonuclear (PMN)-MDSCs which are a subset of MDSCs have been identified. The exact difference between TAN and PMN-MDSCs is still a matter of debate because both cells have similar morphological appearances [26].

Most researchers used the terminology 'granulocytic MDSC' to depict PMN-MDSC, but it is now clear that the latter terminology well depicts this MDSC subset, because PMN-MDSC is morphologically different from steady-state neutrophils. PMN-MDSC have fewer granules, distorted buoyancy, decreased CD16 and CD62L, and amplified arginase 1, peroxynitrite, CD11b as well as CD66b) [26]. PMN-MDSC and TAN can be distinguished from mononuclear cells within the $CD11b^{+}$ myeloid cell segment because of their secretion of Ly6G granulocytic cell marker in mice. On the other hand, eosinophils can be identified based on their secretion of sialic acid-binding immunoglobulin-like lectin F [43].

Morphologically, TAM can be differentiated from M-MDSCs because of their amplified secretion of F4/80, minimum-to-intermediary secretion of Ly6C as well as minimum or unnoticeable secretion of S100A9 protein. Furthermore, IRF8, an indicator of terminal macrophage differentiation amplifies M-CSF receptor and CD115 resulting in the expression of TAM compared to M-MDSCs [26]. It is very difficult to distinguish neutrophils from PMN-MDSCs because these cells share similar morphological features. It is, however, possible to distinguish between them using functional tests. It is now clear that macrophage-specific indicators like CD68 and CD163, together with minimal or deficient secretion of S100A9 can be utilized in distinguishing TAM from cancer M-MDSCs in humans [43]. However, the glitches in differentiating cancer PMN-MDSCs from TAN are the same as in mice. There are currently no clear cell-surface indicators that can directly to use to distinguishing of TAN from PMNMDSCs.

6. MDSCS, DENDRITIC CELLS AND CANCER

Dendritic Cells (DC) are cells that process and present antigen for the stimulation of $CD4^{+}$ as well as $CD8^{+}$ T cells [25]. It is evidenced that the quantities of mature DC diminished equitably with rising quantities of MDSC in an *in-vitro* investigation utilizing mouse MDSC differentiated from c-kit^{+} BM progenitor cells in the presence of IL-4, GM-CSF, and PGE2 [44]. A study revealed that IL-10 generated by hepatocellular carcinoma-triggered MDSC resulted in reduced DC generation of IL-12 [45]. The decrease in mature DC as seen in cancer individuals is because of distortion in MDSC/DC progenitor cells towards the preferential differentiation of MDSC at the expense of DC. This distortion occurs because MDSC and DC share a common progenitor cell [44].

Studies with MDSC from melanoma individuals revealed that MDSC compromised DC maturation *via* the diminishing of antigen uptake, aversion of movement of immature and mature DC, inhibiting DC triggering of IFN-γ generation of T cells as well as distortion of DC cytokine generation towards anti-inflammatory kinds [46, 47]. Furthermore, DC generation of pro-inflammatory cytokine IL-23 and its down-regulatory triggering of Th17 cells may contribute to the consequences of MDSC on DC. Therefore, IL-23 and IL-17 facilitate cancer advancement and MDSC may decrease cancer advancement by restraining IL-23 and IL-17 generation [47].

7. MDSCS, TOLL-LIKE RECEPTORS AND CANCER

Toll-Like Receptors (TLRs) have a fundamental responsibility in the stimulation of innate immune responses. It is evidenced that signaling *via* TLR-4 characteristically comprises of the bonding of LPS to the LPS bonding protein, which consequently relocates LPS to the membrane-bound receptor CD14 [25]. It is also now clear that MDSC-macrophage inter-communication utilizes LPS. LPS has also been confirmed as a stimulate of macrophages [48]. A study has shown that CD14 inter-communication with TLR-4 to triggers TLR-4 signaling as well as down-regulatory triggering of NF-κB [48] (Fig. **1**). Studies have proven that CD14 concentrations are amplified on inflammatory MDSC during inter-communication with macrophages. This amplification is TLR4-dependent since TLR4-deficient inflammatory MDSC do not exhibit raised concentrations of CD14 (Fig. **1**) [39, 49].

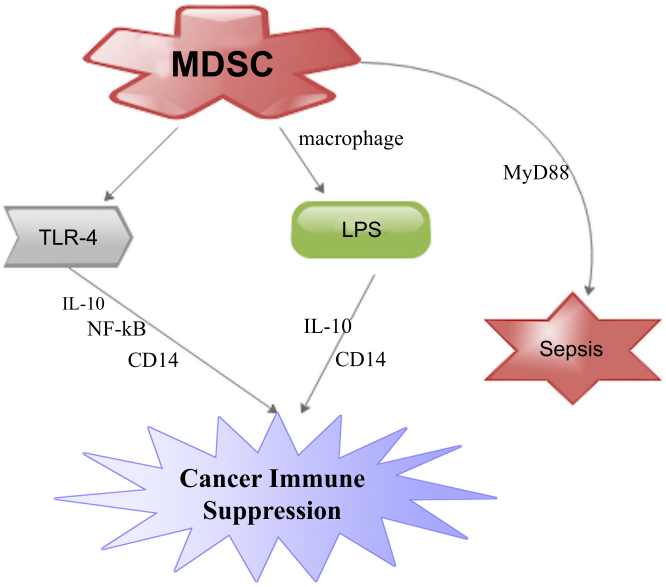

Fig. (1). MDSC contributed to cancer immune suppression *via* TLR-4 receptor and lipopolysaccharideas (LPS).

Gabrilovich and Nagaraj proposed that inflammation probably amplified CD14 concentrations thereby making MDSC more receptive to LPS and TLR-4 stimulating ligands. They argue that this interaction led to MDSC generation of IL-10 and a significant suppression of immune system [50]. A study has shown that amplification of MDSC subgroups in the spleen is dependent on the TLR adaptor molecule myeloid differentiation primary-response gene 88 (MyD88) [51]. This was evidenced when polymicrobial sepsis triggered by the ligation and perforation of the caecum led to secretion of microbial products into the peritoneum and systemic circulation. Nevertheless, study involving wild-type mice and mice deficient of efficient TLR-4 protein revealed an analogous amplification of MDSC during polymicrobial sepsis (Fig. **1**). This means that signaling *via* TLR-4 may not be prerequisite for MDSC amplification. This further means that MyD88-dependent signaling pathways that might have been activated by other TLRs perhaps participated in the amplification of MDSCs in sepsis [50, 51] (Fig. **1**). This also suggests that the triggering of MDSCs is a primary consequence of the host innate immune response to pathogens that secretes TLR ligands. We proposed further studies gear towards the functional roles of TLR and MDSCs in inflammatory cancer microenvironments.

8. MDSCS, RAGE AND CANCER

Receptor for advanced glycation end-products (RAGE) is an MHC class III encoded

protein, considered as a damage associated molecular pattern (DAMP) molecule receptor [52]. It functions as the kindred receptor for the archetypal DAMP, HMGB1 as well as numerous S100 proteins such as S100A8 and S100A9 [53]. Several studies have shown that RAGE signaling intermediates in the pathogenesis of epithelial derived cancers. Furthermore, RAGE also triggers fundamental survival pathways like autophagy in cancer cells and promulgating as well as withholding pro-cancer host inflammatory reactions [54, 55].

It has been evidenced that RAGE actively participated in intratumoral MDSC amassment in triggered skin cancer model experiment involving $RAGE^{-/-}$ mice [52, 56]. Several studies have also demonstrated that mice defective for the RAGE ligand, S100A9, display a substantial decrease in the rate and encumbrance of colitis-associated colorectal cancers and a demonstration of reductions in intratumoral and splenic MDSC rates [40, 57]. On the other hand, RAGE is not prerequisite for the expansion of MDSCs from myelopoietic progenitor cells or their precise blockade endeavor. This is because MDSCs are located in both RAGE-null and KCR mice phenotypes and therefore are morphologically and functionally stable [40].

Studies have indicated that a larger population of myeloid cells ($CD11b^{+}$) display extreme mature phenotype exhibited by the secretion of mature macrophage marker F4/80 and a deficiency of Gr1 secretion during pancreatic neoplasia deficient in RAGE [40, 58]. It is also known that pro-inflammatory proteins S100A8/A9 triggers MDSCs by interrelating with RAGE and other glycoproteins on the surface of MDSCs and facilitated their migration through NF-

κB determined signaling pathway [40, 53] (Fig. **2**). Furthermore, RAGE over-secretion inside cancer and stromal sections are simultaneously ligated by S100A8/A9 production by MDSCs which in turn triggers a monitoring chemokine cancer gene silhouette and functions as a positive feed-back loop for the conscription of MDSCs [40, 52] (Fig. **2**). Also, DCs and macrophages have proven to express RAGE ligands like HMGB1 in reaction to numerous maturational stimuli. Therefore, HMGB1 expression by MDSCs characterizes an extra machinery for MDSC conscription and so warrants more investigations [59]. We also propose further investigation into the paradoxical roles of RAGE and MDSC in cancers.

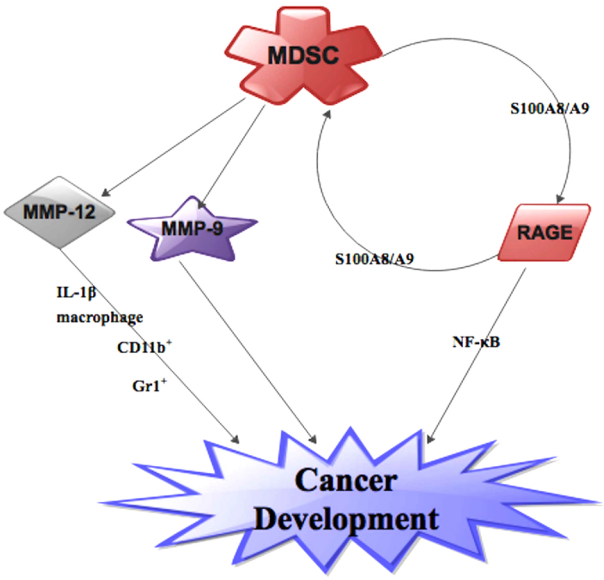

Fig. (2). MDSC contributed to cancer development *via* MMPs (MMP-9 and MMP1-12) as well as RAGE.

9. MDSCS, MATRIX METALLOPROTEINASE AND CANCER

MMPs are an essential group of zinc enzymes conscientious to the mortification of ECM constituents [60, 61]. Several studies have shown that pro-inflammatory factor MMP-12 or macrophage elastase, is secreted principally by macrophages as well as a prerequisite for monocyte conscriptions [62, 63]. It has been demonstrated that extreme secretion of MMP12 in myeloid cells results in anomalous expansion of hematopoietic progenitor cells [64]. Numerous investigators have implicated macrophage-derived MMP-12 in destructive melanoma [65, 66]. Furthermore, MMP-12 polymorphism has also been implicated in breast cancer prognosis [64].

A study has shown that there is upsurge in number MDSCs in MMP-12$^{-/-}$ cancer mice and this upsurge is directly linked to cancer development. The study further showed that macrophage-derived IL-1β stimulated extra MDSCs in bone marrow in these MMP-12$^{-/-}$ mice [64]. Another study indicated that mice lacking MMP-12 spawned metastases than their wild-type in Lewis lung pulmonary carcinoma [67]. Li *et al*. also proposed that MMP12 knockout can augment cancer development by triggering the amassment of MDSCs in the myeloid cells of mice. Their finding supports an earlier report that MMP-12 absence enhanced macrophages-derived IL-1β triggering of myeloid cells into MDSCs (Fig. **2**). They therefore concluded that MMP-12 influenced myeloid cells differentiation and IL-1β played a fundamental part in the inter-communication between macrophage and MDSCs in bone marrow milieu in MMP-12$^{-/-}$ mice [64]. Qu *et al*. demonstrated that the proportion of CD11b^{+} and Gr-1^{+} inflammatory cells were appreciably amplified in the lung of 3-month doxycycline-administered bitransgenic mice utilizing a transgenic mouse extreme secretion of MMP-12 model but had conflicting finding in the cancer milieu [68]. Also, Li *et al.* observe that generation of CD11b^{+}/Gr1^{+} cells augmented cancer development because these cells were increases in the myeloid cells of MMP-12 knockout mice [64] (Fig. **2**).

It is now evidenced that MMP-9 inhibition resulted in a cogent subduing of the immunosuppressive consequence of M-MDSCs than that of G-MDSCs in an *in-vitro* study. Furthermore, M-MDSCs augmented MMP-9 generation more than G-MDSCs and circulating MMP-9 concentrations is interrelated with early infections as well as consequent

prognosis [69]. Shao *et al.* propose that an OPN/MMP- 9 inter-communication is associated with MDSCs production in a lung cancer model. They indicated further that a distinctive OPN- 32 kDa portion was smitten by MMP- 9 which in turn led to modifications in the generation of MDSCs [61]. Initial studies have implicated VEGF as one of the factors that contributes to the secretion of MMP-9 [70, 71]. It is also confirmed that soluble MMP-9 generated by cancer cells stimulates MDSC buildup as well as cancer angiogenesis [71]. Additionally, MMP-9 is able to modify the recruitment of hemopoietic stem cells from the bone marrow niche *via* the dissolution of the membrane-bound form of c-KitL [72, 73]. Therefore, MMP-9 is a prerequisite in cancer development (Fig. **2**). We propose further studies into the roles of other subgroups of MMPs and MDSCs in cancer models.

10. MDSCS, HIGH MOBILITY GROUP BOX 1 AND CANCER

High mobility group box 1 (HMGB1), an alarming was initially recognized as a DNA binding protein in the nucleus. It performs various roles such as altering the conformation of DNA to permit the binding of modification proteins, expediting the incorporation of transposons into DNA, as well as steadying nucleosome establishment within the nucleus [74 - 76]. Its responsibility as an expressive protein and an immune chaperone has only been documented a few years ago [74, 77]. HMGB1 also act as a binding protein, stimulator, and/or modulator for many pro-inflammatory molecules [78]. Higher concentrations of HMGB1 have been implicated in various cancers. The upsurge in HMGB1 levels has shown to directly stimulate cancer development [79]. Furthermore, HMGB1 partakes in all fundamental hallmarks of cancer including unlimited proliferation, angiogenesis, invasion and metastasis [80, 81].

Several studies have demonstrated that HMGB1 is vigorously expressed by activated leukocytes or inactively secreted from stressed and necrotic cells [82, 83]. It is also evidenced that HMGB1 is momentously raised in the circulation of traumatic injury and peaks up within first 6 h post injury [84, 85]. Numerous studies have shown that extracellular HMGB1 can attract myeloid derived cells such as PMN-MDSCs, macrophages, DCs and Immature Myeloid Cells(IMC) [59, 86] (Fig. **3**). These myeloid derived cells in turn negatively modulate immune reactions in the cancer microenvironment as well as facilitates cancer development [13, 50]. HMGB1 also plays dual roles as Damage Associated Molecular Pattern Molecule (DAMP) and a pro-inflammatory molecule making it a binding protein, stimulator, and/or moderator to many pro-inflammatory molecules that drive MDSC [74, 87]. *In-vitro* studies revealed that blockage of HMGB1 averted the expansion of MDSCs from bone marrow progenitor cells which means that HMGB1 is prerequisite for the differentiation of MDSCs. Furthermore, *In vivo* knockout of HMGB1 in cancer-bearing mice decreases MDSC quantities in cancer, spleen, and blood meaning that MGB1 as a chaperone for MDSCs [74].

Several studies have shown that the expression of the protumor cytokines IL-10 and IL-1β is co-chaperone by MDSCs and high HMGB1 levels which means that HMGB1-driven MDSC amassment expedites cancer metastasis [74, 88] (Fig. **3**). Numerous studies have also implicated HMGB1 as the trigger of IL-10 drives MDSC amassment as well as T cell suppressive roles [89 - 91]. It is further proven that a combination of HMGB1 and IL-10 have augmented pro-inflammatory action as compared to either molecule alone [74, 92]. It is also proven that MDSC-intermediate in the reduction of T cell L-selectin (CD62L). This mediatory action relied on HMGB1 because HMGB1 amplified MDSC extracellular secretion of A disintegrin and metalloproteinase 17 (ADAM17), a protease that cleaves L-selectin. HMGB1 also augments the pro-inflammatory action of IL-6, TNF-α, and prostaglandin E2, three other pro-inflammatory intermediaries that drive MDSC [44, 90] (Fig. **3**).

On the other hand, studies have shown that HMGB1 intermediation with MDSCs could be *via* RAGE and/or TLR-4 [25] (Fig. **3**). Several studies have confirmed that HMGB1 binds mutually to TLR-4 and RAGE, and MDSC secretes these two receptors [40, 49, 74]. Therefore, MDSC contributes significantly to the function of HMGB1 in the cancer milieu. Initially, studies have proven that MDSC generation of IL-10 is modulated by TLR-4 [49]. Furthermore, studies have shown that ethyl pyruvate and glycyrrhizin which are HMGB1 blockers down-regulates MDSC generation of IL-10 during MDSC-macrophage inter-communication [49, 93]. Nevertheless, the differentiation of MDSC from bone marrow progenitor cells as well as ethyl pyruvate reinstated T cell stimulation in the attendance of MDSC. HMGB1 is, therefore, a powerful trigger of MDSC as well as immune suppression while MDSC, macrophages, tumor-infiltrating cells, and tumor cells contribute to the quantity of HMGB1 in the cancer microenvironment [74] (Fig. **3**).

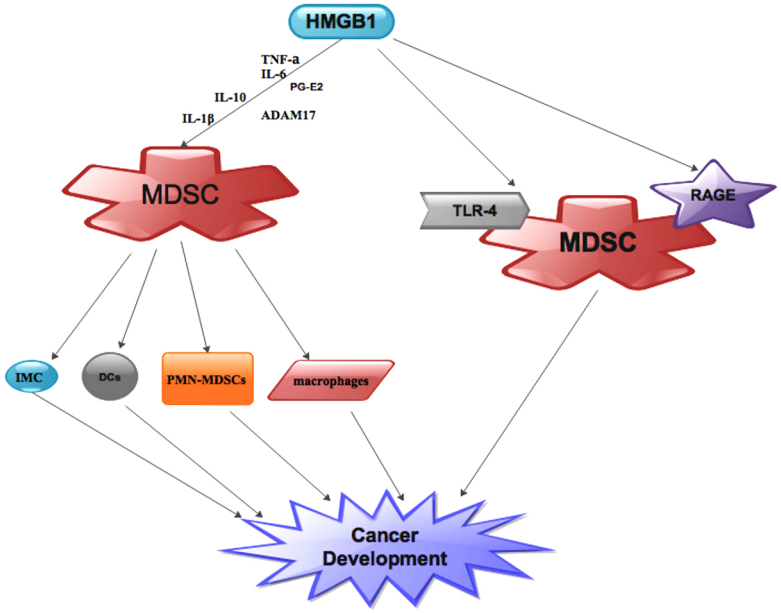

Fig. (3). HMGB1-driven MDSC amassment expedites cancer development and metastasis *via* PMN-MDSCs, macrophages, DCs and immature myeloid cells (IMC). Further HMGB1 intermediation with MDSCs *via* RAGE and/or TLR-4 leading to cancer development.

11. MDSCS IN CANCER MICROENVIRONMENT

Automatous investigations utilizing cancer or tumor conditioned media (TCM) to cultures of spleen, BM, or isolated myeloid/progenitor cell subsets have revealed mediators and arouses of MDSC function, differentiation, proliferation and survival as well as, T-cell proliferation, DC function and differentiation [24]. Cancers that triggers MDSC proliferation has also demonstrated to release VEGF, GM-CSF, Stem Cell Factor (SCF), FMS-Like Tyrosine kinase 3 ligand (FLT3-L), G-CSF, and/or macrophage-colony stimulating factor (M-CSF) [24]. It evident that using transplantable cancers associated cancer GM-CSF expressed by MDSC increasement *via* the knock down of GM-CSF in cancer cell lines led to distorted MDSC quantities and subset dissemination resulting in cancer development [24, 94]. In a study that utilizes constant haematopoiesis, GM-CSF and G-CSF not only control proliferation, but also unknowingly mobilization from the BM and spleen [95].

Studies have shown that growth factor injection or release from cancers led to myeloid hyperplasia thus augmenting prosteroid and neutral protease release. The process above resulted in steady mobilization, myeloid progenitor survival, and their dissemination between peripheral and circulating pools [24, 96]. The machineries linked to their mobilization may be analogous to those of haematopoietic progenitor cells because MDSCs comprise of myeloid-committed haematopoietic progenitors and are probably unchanging at the immature differentiation phase [24, 97]. It is now very clear that MDSCs stimulate cancer invasion *via* the release of MMPs, which partakes in extracellular matrix degradation [24, 98, 99].

Studies have proven that the utilization of a mammary carcinoma deficient in type II Transforming Growth Factor beta (TGF-β) receptor led to an augmented proportion of metastasis and an amplified MDSC infiltrate which confirms the phenomenon above [24, 98]. The augmented invasion above was MMP-dependent; though, it was not certain whether the MMPs were released by MDSCs or by the carcinoma cells in response to MDSC activation [24, 98]. It is postulated that both cell groups are probably involved in MDSCs derived from cancer bearing hosts leading amplified MMP levels as compared to "MDSCs" from non-cancer-bearing hosts [98]. This implies that the amplified invasive capability may be from MDSC-derived MMP expression. Nevertheless, MDSCs likewise appeared at a high incidence in lungs and livers, which are normal metastatic locations [24].

It has been evidenced that even when organ fragments are implanted ectopically, particular organ environment control cancer cell arrest and growth signifying that myeloid cell development and angiogenesis, are crucial, especially hormonal and organ-specific growth factors [24, 100]. Therefore, metastasis is both discriminatory and ineffective, and

only a limited number of cells survive to form a micrometastasis, a route partly controlled by MDSCs and other myeloid cells [24]. Studies have further demonstrated that splenic MDSCs partake in cancer vasculogenesis *via* directly differentiating into EPCs [24, 99]. Nevertheless, a subset of circulating progenitor cells is $CD11b^{-}170$, and as such, $Gr1^{+}CD11b^{+}$ cells may be precursors that differentiate and partake in cancer vasculogenesis (BOX 1). The machineries linked to MDSC suppression of T-cell roles depends largely on NOS2176, ROS, ARG1177, cyclooxygenase 2 (COX2), and hypothetically upregulation of IL-10 as prime machineries [24].

It is now clear that the adoptive transfer of MDSCs suggestively stimulated cancer growth in animal models, and Gr1+ cell depletion in cancer-bearing mice blocks cancer development, lessens metastasis, and lengthens survival [24, 101]. Studies have demonstrated that some chemotherapeutic agents like gemcitabine, 5-fluorouracil, and docetaxel differently suppress MDSCs [24, 102]. Numerous studies of cancer-bearing mice, and a few clinical reports utilizing medicines that target MDSCs or their function, have proven that in mice MDSC diminution slowdown cancer initiation, progression, and lengthen ssurvival [24, 103].

12. MDSCS AND CANCER METASTASIS

Cancers usually invade the neighboring tissue, travers into the circulation, seed and proliferate in a distant tolerant niche before there are able to metastasize [104]. It is becoming clearer that MDSC actively partakes in cancer metastasis at all phases. It is evidenced that MDSC stimulates malignancy or metastasis by stimulating stemness of cancer cells or by increasing the cancer stem cell groupings [104]. Studies have shown that MDSCs directly triggered malignant cell proliferation and overpowered immune elimination of malignant metastasis in allogeneic mice *via* alteration of the mTOR pathway, which offers an automatous foundation for steering MDSCs to decrease the possibilities of tumor malignancy [105, 106]. Wang *et al.* evidenced that cancer metastasis and Gr-11 CD11b1 MDSCs at postoperative period were augmented in quantity to the severity of surgery stress. They demonstrated this with tentative lung metastasis mice models [107].

Another study revealed that circulating $CD14^{+}$HLA-DRlow M-MDSC were concurrent with extra-thoracic metastases in non-small cell lung cancer (NSCLC) patients [108]. Furthermore, the upsurge in IDO-secretion $CD45^{+}$ $CD33^{+}CD14^{-}CD15^{-}$ MDSC in breast cancer tissue was also simultaneous with augmented lymph node metastasis in patients with breast cancer [104, 109]. Nevertheless, the evolution of metastases and poor survival was interrelated with an upsurge in both circulating $CD11b^{+}CD14^{-}CD15^{+}$ PMN-MDSC as well as M-MDSC in melanoma individuals [110, 111].

Several studies have shown that pro-inflammatory proteins S100A8 and S100A9 are effective chemoattractants for MDSC. These two factors have recently been incriminated in the advancement of cancer growth and metastases *via* MDSC axis [40, 57]. It is also evidenced that S100A8/A9 could directly trigger serum amyloid A (SAA) 3 which in turn magnetizes MDSC to pre-metastatic lungs *via* NF-κB signaling pathway in a TLR4-dependent manner thereby accelerating metastasis [104, 112]. Therefore, MDSC conscription to cancer locations may symbolize a rancorous circle. MDSC primarily conscripted to cancer location *via* cancer-derived chemokines may likewise expedite the conscription of other MDSC through S100A8/A9 proteins [57].

A study revealed that amassment of PMN-MDSC is interrelated with augmented bone metastasis in 4T1 model of breast cancer [98]. Also, the administration of MDSC as well as 4T1 cells together resulted in augmented lung metastasis. This study also revealed that MDSC in 4T1 cancers augmented the secretion of numerous MMPs which were very imperative in intermediating invasiveness of 4T1 cells *in vitro* and *in vivo* [98]. It is further evidence that MDSC decreases protease inhibitors like neutrophilic granule protein, a blocker of cancer intrusiveness and metastasis [113]. Nevertheless, in mammary carcinoma cells, deletion of TGF-β receptor II (Tgfbr2) led to an upsurge in MDSC insinuation into cancers intermediated *via* SDF-1 as well as CXCL5. Also, in SMAD4-deficient mice colon carcinoma, blockade of TGF-β signaling triggered MDSC conscription as well as cancer invasion *via* CCL9 dependent pathway [104, 114].

Furthermore, the meticulous deletion of Tgfbr2 in myeloid cells expressively subdued cancer metastasis. Moreover, Tgfbr2 deficiency in myeloid cells diminished arg-1 action as well as NO generation which in turn facilitated IFN-γ generation as well as an enhanced systemic immunity [104, 115]. Nevertheless, HIF-1α-dependent kit ligand secreted by hypoxic cancer cells in a mouse mammary cancer model activated $c\text{-}Kit^{+}$ $CD11b^{+}$Ly6Ghigh PMN-MDSC at the principal cancer site as well as facilitated metastasis [116]. It is further shown that M-MDSC directly triggered expansion of aldehyde dehydrogenase-1^{+} (ALDH1) pancreatic cancer stem cells in mice models of pancreatic cancer as

we as human $CD14^{+}$ $HLA\text{-}DR^{-}$ M-MDSC [117, 118].

Moreover, the buildup of Lin^{-} $CD45^{+}$ $CD33^{+}$ MDSC is interconnected to poor life expectancy in metastatic and non-metastatic ovarian cancer patients. Also, MDSC directly interrelated with ovarian cancer cells and triggered their stemness. Additionally, at principal cancer and metastatic locations, MDSC generate IL-6 which in turn bestows invasive abilities of breast cancer cells as well as triggers distant metastases *via* tenacious stimulation of STAT3 in cancer cells [104].

13. MDSCS AND CANCER ANGIOGENESIS

Angiogenesis, the sprouting of new blood vessels, happens at distinctive phases during embryonic formation, physiological activities like wound healing and reproduction. Angiogenesis also occurs in several diseases condition such as inflammation, cancer development, and metastasis [119, 120]. An earlier study indicated that neovascularization appears around cancers. In this study it was postulated that the sprouting of new blood vessel is a prerequisite source of nutrients and oxygen to cancer cells during exponential cancer growth [121]. A current study has shown that new blood vessels arise from antecedent vessels *via* stimulation, proliferation and migration of endothelial cells [122]. It is now clear that Vascular Endothelial Growth Factor (VEGF) and basic fibroblast growth factor (bFGF) trigger the proliferation and migration of innately inactive endothelial cells leading to the development of new vessel structures during embryonic formation and cancer development [119, 123]. Vasculogenesis is the amalgamation of new blood vessels from specific endothelial cells or progenitor cells. Initially, vasculogenesis was assumed to be limited to the development of the preliminary vascular tree during embryonic vascular formation [119].

Kujawski *et al.* were among the first researchers to demonstrate that MDSCs might actively partake in cancer angiogenesis. They indicated that MDSCs actively triggers STAT3, which in turn increases the secretion of numerous angiogenic genes [124]. It is now obvious that VEGF a pro-inflammatory growth factor triggers angiogenesis during tumorigenesis. It is also now clear that VEGF contributes significantly to poor cancer prognosis. Therefore, tumors that generate extreme levels of VEGF will usually have a poorer prognosis. A study showed that VEGF blocks nuclear factor kappa light-chain-enhancer (NF-κB) stimulation which in turn inhibits DC advancements although concurrently, they facilities MDSC buildup [125]. It has been demonstrated that MDSCs secretes VEGF receptor empowering VEGF to serve as a chemoattractant for MDSCs. Nevertheless, Kusmartsev *et al* demonstrated that ROS generated by MDSCs amplifies oxidative stress which in turn increases MDSC secretion of VEGF receptors [126]. In solid tumors, however, so many factors actively partake in oxidative stress. The most influential among this factor is cancer microenvironment because it determines the responsiveness of MDSCs to VEGF. Kujawski *et al.* further explained that during tumorigenesis besides tumor cells, MDSCs themselves generate VEGF which in turn triggers an autocrine feedback loop that maintains MDSC amassments [124].

Mucha *et al*. demonstrated that cancer cells administered with IL-28 before and during their experiment for 6 h triggered 3D vessel sprouting by endothelial cells [127]. An earlier study had indicated that IL-28-mediated amplification of VEGF-C and IL-18 secretion in cancer cells [128].

Mucha *et al* further indicated combined culturing of HUVECs with control tumor cells or with IL-28 alone for 6 h triggered little endothelial cell bifurcations. They concluded that prolonged stimulation may trigger IL-28 cancer cells to secretion of angiogenic factors resulting in angiogenesis [127]. Therefore, MDSCs release IL-28 which in turn triggered cancer angiogenesis predominantly *via* an upsurge in expressing angiogenic proteins in cancer cells [127]. Studies have shown that MDSCs facilities cancer angiogenesis by generating angiogenic factors as well as matrix degrading enzymes like VEGF and MMP-9 [129, 130].

A Study has further indicated that unceasing upsurge of VEGF in the peripheral blood leads to an upsurge in the generation of immature Gr-11 myeloid cells. Furthermore, sustained extreme concentration VEGF resulted in substantial blockade of DC formation [131]. Moreover, researches demonstrated that the upsurge of VEGF is linked to the blockade of the movement of transcription factor NF-κB in bone marrow progenitor cells [107, 125]. Studies have also shown that management of patients with metastatic renal cell cancer with a VEGF specific inhibiting antibody avastin led to a reduction in the size of CD11b1 VEGFR11 subgroups of MDSCs in peripheral blood [107, 126]. Nevertheless, blockade of the responsibilities of MMP-9 in cancer-bearing mice reduced the quantity of MDSCs in cancer mass and spleen as well as led to a substantial deferment in the growth of extemporaneous NeuT cancers [72]. Wang *et al* also demonstrated that surgery-triggered CD11b1 CD331 HLA-DR– MDSCs vigorously accelerated to cancer angiogenesis as well as facilitated the generation MMP-9 and VEGF [107].

14. THERAPEUTIC POTENTIALS OF MDSCS IN CANCER

Studies have shown that MDSC provides double discrete beneficial curative potentials. In cancer individuals, particularly in those taking immunotherapies, the outcomes of MDSC are normally disadvantageous therefore intermediation should be angled at diminishing the consequences of MDSC [12]. This can be accomplished *via* terminating their activities, *via* lethal stimulating myeloid differentiation, *via* blocking or diminishing MDSC growth, or *via* blocking their function [12]. Studies have shown that MDSC differentiation to macrophages or DCs can be attained *via* clinically accepted medications such as vitamin D3 or derivatives, and vitamin A or derivatives like All-Transretinoic Acid (ATRA). It is clear that the use of ATRA enriches the anti-cancer outcomes of cancer vaccines in cancer-bearing mice [12, 132]. Also, it decreases the buildup of MDSC and enhances antigen-specific immune responses in patients with renal-cell carcinoma [12].

Furthermore, inhibiting pathways that contribute to MDSC development, such as those of VEGF and SCF, may also decrease MDSC buildup. Studies have proven that sunitinib a clinically accepted tyrosine kinase inhibitor that blocks c-kit, VEGFR, PDGFR, Flt3, CSF-1 and RET pathways, decreases MDSC buildup and prohibited T- cell activation and Treg expansion in cancer bearing mice, and it was linked to a diminution in the quantity of MDSC and a reversal of $CD4^{+}CD25^{hi}Foxp3^{+}$ Treg cell elevation in patients with renal cell carcinoma [12, 133, 134]. Also, inhibition of PGE2 generation by COX-2 inhibitors decreased the development of MDSC and blocked cancer growth in cancer-bearing mice [12].

It is also now clear that MDSC can be destroyed with radiotherapy, monoclonal antibodies targeting myeloid markers or chemotherapeutic medications. Gemcitabine or 5-fluorouracil has proven to effect in destroying MDSC while conserving the quantities of T or NK cells, which improves anticancer immune responses in cancer-bearing mice [12, 103, 135]. Studies have shown that blockade of enzymes such as nitro-aspirines (NO-aspirines) and phosphodiesterase 5 inhibitors led to cancer reduction. NO-aspirin inhibited both iNOS and arginase actions in cancer-associated MDSC. It is evidenced that aspirin blocked arginase, while iNOS was blocked by the NO expressed by the medication [12, 136]. It is also clear that NO-aspirin also has antioxidant action and has proven to decrease the indigenous generation of peroxynitrites, known mediators of the immune suppressive consequence. Nevertheless, blockade of the generation of PGE2 by celecoxib, a non-steroidal anti-inflammatory medication that inhibits cyclooxygenase 2 (COX-2) action, prohibited chemical stimulation of huge abdominal cancers as well as a decrease in arginase-1 and iNOS secretion and the number of MDSC in the spleen of cancer bearing mice, together with a reinstatement of $CD4^{+}$ cell quantities and functionality [12, 137].

CONCLUSION

MDSC contributed to cancer immune suppression *via* a TLR-4 receptor and Lipopolysaccharideas (LPS). Furthermore, MDSC contributed to cancer development *via* MMPs (MMP-9 and MMP1-12) as well as RAGE. In the cancer microenvironment, HMGB1-driven MDSC amassment expedites cancer development and metastasis *via* PMN-MDSCs, macrophages, DCs and Immature Myeloid Cells (IMC). Further HMGB1 intermediation with MDSCs *via* RAGE and/or TLR-4 leads to cancer development. Also, MDSCs have already proven potent in some cancers and are currently been used as treatment options although further studies are needed in some other cancers.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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