Review Article

Exploring the tumor promoting role of anti-tumor macrophage: a developmental perspective

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Abstract: Tumor-associated macrophages (TAMs), in close proximity or within tumor masses, are a type of cell belonging to the macrophage lineage that constantly shift their functional states in response to changes in the tumor microenvironment (TME). The percentage of macrophages in human malignancies is reported to be between 10% and 65% in cancer surgical specimens, representing a prominent cellular component in TMEs. These cells dampen inflammation, promote tissue remodeling and tumor progression, and their density is associated with adverse outcomes and shorter survival in several cancer types. TAMs have been proposed to originate from blood monocytes, attracted by recruitment signals produced by tumor cells, instructed by TMEs, and eventually developing into potent tumor-supporting cell populations. Although great efforts being made toward TAM-centered research, there is still a lack of systemic understanding of this complex cell population. In this review, we summarize how TAMs transform, with particular focus on recruitment and function adaptivity, and try to provide an insight into the progression of TAMs. Finally, we will review some emerging TAM-related therapies for cancer treatment.

Keywords: Tumor associated macrophage; M1/M2 phenotype; transformation

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Introduction

Macrophages, are versatile cells that play many roles including sensing inside from outside, motility throughout the organism, phagocytosis and degradation. Tumors are abundantly populated by macrophages, wherein macrophages adapt into a protumoral phenotype. Elevated levels of recruiting signals recruit tumor-associated macrophage (TAM) precursors (basically monocytes) into the tumor. Once in the tumor, they migrate into specific areas (usually in a hypoxic condition) and mature into macrophages. They are retained in these areas, and adapted into a protumoral phenotype.

As the relationship between macrophages and their progenitors, including monocytes, has been intensively studied (1-4), we won't discuss it further here. It is worth noting, however, that given the feasibility and versatility of mouse models, most of our current knowledge is derived from them, not human cases, and not even involving cancer (2,5,6). This makes the results of the research less convincing when making analogies to the origins of TAMs, despite the fact that organization of macrophage networks of humans and mice are nearly parallel and have already been discussed (7).

Historically, activation status of macrophages is designated into M1 and M2 phenotypes. M1 macrophages (classically activated macrophages), whose prototypical activating stimuli are interferons (IFN)-γ and lipopolysaccharides (LPS), exhibit potent microbicidal properties and promote strong interleukin (IL)-12-mediated

T helper (Th) 1 responses. In contrast, M2 macrophages are activated by IL-4/IL-13 (alternatively activated macrophages), support Th2-associated effector functions and may play a role in the resolution of inflammation through endocytic clearance and trophic factor synthesis (2,8-10). However, profiling of monocyte-derived cells reveals that monocytes can acquire a much broader transcriptional repertoire than the suggested linear M1/M2 scale (1). Recent work also showed that macrophages *in vivo* can exhibit mixed phenotypes instead of clearly defined M1/M2 classification, especially in complex pathological settings (typically TME), where they are exposed to potentially opposing polarizing factors (11). So it is suggested that these states exist on a spectrum of overlapping phenotypes and gene expression patterns related to M1/M2 classification (3,12). Despite the attempts that have been made to identify TAMs' heterogeneity, there still lacks a defined basis.

Our review seeks to analyze the mechanisms by which TAMs transform and further contribute to tumor progression. In hope of understanding how the paradigm of TAMs may contribute in part to macrophage-centered therapeutic strategies and to the control of cancer progression, we will discuss TAM recruitment, differentiation, localization, entrapment, and function adaptivity, with a particular focus on recruitment and function adaptivity.

Recruitment

TAM precursors in responses to recruitment signals

To understand the pathophysiology of TAMs, there must be an understanding of precursor contributing to TAM population. It's has long been thought that TAMs are almost entirely derived from peripheral blood monocytes (13) but recent evidence challenges this long-held view. Recently, the ability of spleen to maintain its reservoir capacity throughout tumor progression has been evaluated (9). Splenic macrophage progenitors and their descendants were also identified in clinical specimens. These studies shed light on the origins of TAMs, and position the spleen as an important extramedullary site which continuously replenishes tumors with these cells. To further complicate the matter, several tissue resident macrophages were confirmed to contribute to the TAM pool, typically in the brain. Macrophage ontogeny analyzed in mouse models of brain cancer indicated that both resident microglia and blood-derived monocytes contribute to the pool of macrophages that infiltrate brain tumors of either primary or metastatic regions (14). Also, one study identified a reservoir of fully mature F4/80^{high}GATA6^{+} peritoneal cavity macrophages which rapidly invaded a sterile injury in liver via a non-vascular route [depending on cluster of differentiation 44 (CD44) and damage associated molecule pattern (DAMP) molecule adenosine triphosphate (ATP)] which resulted in the changing of the macrophage to an M2 phenotype (15). Although this observation did not involve malignancy, a rapid invasion of mature macrophages from a body cavity with the capacity for induction of reparative phenotypes may impact altered tissues ranging from infections to cancer. Works in other mouse cancer models have suggested that locally derived TAMs are progressively diluted by monocyte-derived TAMs during tumor progression and growth (16), further proving the point that bone marrow-derived monocyte remain the main contributor of TAM pool.

In summary, TAMs are largely derived from bone marrow hematopoietic stem cells through monocytic intermediates, with minor contributions from locally derived and tissue-resident macrophages. In that case, we will focus on myeloid-derived monocyte precursors in our following discussion.

How TAM precursors respond to these signals

Monocytes enter tumors throughout the life span of tumors. This replenishment sustains tumor progression; however, the underlying mechanisms are not fully known. Several factors have been shown to support this ongoing replenishment, including chemokines, cytokines and other molecules.

Chemokines

According to the traditional model of cell trafficking, the combination of chemokine receptors (on circulating cells) and chemokines (produced by target tissues) enables the recruitment of circulating cells. Of these circulating cells, CCR2/CCL2-axis, CCR5/CCL5-axis, CX3CR1/CX3CL1-axis and CXCR4/CCL12-axis are the best-researched.

CCL2, also known as monocyte chemotactic protein-1 (MCP-1) has been heavily demonstrated to positively correlate to TAM numbers in tumors (17). In a severely immunodeficient (SCID) mice model combined with *CCL2* gene transfer, the level of monocyte infiltration correlated with the level of expression of the chemokine (18). Monocytes are preferentially recruited to metastatic site in

a CCL2-dependent way; depletion of CCL2 also inhibits metastatic seeding (19). As the sole receptor for CCL2, CCR2 is highly expressed in circulating inflammatory monocytes ($Gr1^{+}$/Ly-$6C^{high}$/$CD43^{-}$/$CD62L^{+}$/$CX3CR1^{low}$/$CCR2^{+}$/$VEGFR1^{high}$ cells in mice and $CD14^{high}$/$CD16^{-}$/$CD62L^{+}$/$CX3CR1^{low}$/$CCR2^{+}$/$VEGFR1^{high}$ cells in human), which is additional strong evidence that CCL2 may be a critical determinant of monocyte recruitment (4).

CCL5, also known as RANTES (regulated on activation, normal T cell expressed and secreted) shares similarities with CCL2 in acting as a chemoattractant (17). CCL5 directly stimulates protein expression on monocytes to promote monocyte migration. For example, CCL5 stimulates human monocytes to express CCL2, CCL3, CCL4 and CXCL8 as well as the chemokine receptor CCR1 (20).

CX3CL1, also called fractalkine in humans and neurotactin in mice, is the only known member of the CX3C chemokine family. CX3CL1 is primarily expressed in endothelial cells. The cleavage of membrane-bound CX3CL1 by metalloproteinase produces a soluble form of CX3CL1 which chemoattracts monocytes (21), while cell-bound chemokine promotes strong adhesion of leukocytes to activated endothelial cells (22). CX3CL1 exclusively binds CX3CR1 expressed on non-classical monocytes ($Gr1^{-}$/Ly-$6C^{low}$/$CD43^{+}$/$CD62L^{-}$/$CX3CR1^{high}$/$CCR2^{-}$/$VEGFR1^{low}$ cells in mice and $CD14^{low}$/$CD16^{+}$/$CD62L^{-}$/$CX3CR1^{high}$/$CCR2^{-}$/$VEGFR1^{low}$ cells in humans) (4), which also elicits its adhesive and migratory functions.

CXCL12 is also known as stromal derived factor-1α (SDF-1α). Although identified as a lymphocyte chemoattractant itself, it is capable of arousing chemotactic effects on monocytes and macrophages via CXCR4 expression, which are receptors for this chemokine (23). However, studies have found that tumor cells express either little or no CXCL12 (24), thus making this CXC chemokine less likely to play a critical role in the attraction of monocytes into tumors.

Cytokines

Several cytokines have been implicated in the recruitment of monocytes into tumors. CSF-1 functions mainly in mononuclear phagocyte biology including cell growth, differentiation and cell survival, but also acts as a potent chemoattractant for monocytes and macrophages. Induced CSF-1 gene expression can exhibit a significant increase of TAM infiltration in mammary tumors (25) whereas in CSF-1 knock-out mice, monocyte infiltration into tumors was remarkably reduced (25). In various types of human tumors, typically in breast cancer, expression levels of CSF-1 and its only receptor CSF-1R were elevated (17).

Vascular endothelial growth factor (VEGF) production can be induced in cells which are not receiving enough oxygen. Other than acting as an angiogenesis promoter, increased VEGF expression in the hypoxic region acts as a chemoattractant for monocytes and macrophages, and is likely to play a major role in the recruitment of monocytes into the hypoxic region (26), probably via activation of one form of the VEGF receptor VEGF-R1 (27). There also exists a reciprocal dialogue between CSF and VEGF involving TAM recruitment and localization (8). Hypoxia-induced Semaphorin 3A (Sema3A) also acts as an attractant for TAMs by triggering VEGF-R1 phosphorylation through the associated holoreceptor, which is composed of Neuropilin-1 (Nrp1) and PlexinA1/PlexinA4 (28). Actually, VEGF-R1 and Sema3A cooperate to function in monocyte recruitment, localization and entrapment processes.

Others

CD62L, also known as L-selectin, is a cell adhesion molecule found on classical monocyte. Due to the expression of CD62L on classical monocytes and CD62L ligands on inflamed endothelium, this interaction has been strongly implicated in the recruitment of classical monocytes into the perivascular tumor region. Engagement of CD62L and integrins synergize to slow monocyte rolling, generate transmembrane signals leading to activation of intracellular signaling pathways, consolidate adhesion of the leukocyte to the vascular endothelium and eventually, extravasation of monocyte ensues (29). CD62L together with several ligands [including GlyCAM-1, CD34, MadCAM-1, PSGL (26)], are heavily implicated in the recruitment of monocytes in the perivascular tumor region, which will be discussed further.

Differentiation

Upon emigration from the vasculature, monocytes interact with subendothelial matrix components and mature into macrophages (30). Monocyte-to-macrophage differentiation is accompanied by pronounced phenotypical changes involving the selection of specific gene expression programs. However, the molecular events governing this specific differentiation process are poorly understood. Transcription factor knockout mice have shown some deficiencies in mononuclear-phagocyte networks, as these

transcription factors often display broad effect in multiple cell types (31), revealing a complex network of transcription factors, enhancers and promoters which require further investigation.

ETS (E-twenty six) family transcription factor PU.1 plays an important role in monocyte-to-macrophage differentiation. Gain-of-function and retroviral reconstitution experiments of PU.1-deficient cells demonstrated its critical role in the early steps of myeloid lineage commitment (32). PU.1 also has additional key selector gene functions at several branch points of myeloid lineage diversification, particularly during the late macrophage versus dendritic cell (DC) choice of monocytes by overruling key regulators of other pathways. For example, inhibitory interactions with GATA-1 shut down the megakaryocytic/erythroid pathway; repression of GATA-2 blocks mast cell development; antagonizing C/EBPα overcomes neutrophil fate-inducing effects; activation of the macrophage-specifying zinc finger transcription factors Egr-1 and Egr-2 is required for macrophage fate commitment; antagonizing the macrophage-inducing transcription factors c-Maf and MafB induces dendritic fate. To be more specific, intermediate expression of PU.1 overcomes the neutrophil fate-inducing effects of C/EBPα and activates the macrophage-specifying effect of Egr-1 and Egr-2. High expression of PU.1 is required to induce a DC fate in monocytes and to antagonize the macrophage-inducing effect of c-Maf and MafB [reviewed in (33)]. Ectopic expression of the transcription factors MafB, c-Maf, Egr1, ICSBP/IRF8, KLF4 in early progenitors also drive monocyte/macrophage fates [reviewed in (2)].

Integration of cytokines also influence signaling and transcription factor activity, typically CSF-1 and its receptor CSF-1R, encoded by c-fms proto-oncogene. PU.1 trans-activates the c-fms proximal promoters c-ets-1 and c-ets-2. And, PU.1 is assembled in a primed chromatin conformation on both the proximal promoter and the *fms* intronic regulatory element (FIRE) enhancer. This indicates that cell-intrinsic commitment events induce the up-regulation of the c-fms receptor which precedes the appearance of c-fms on the cell surface. However, c-fms expression cannot restore macrophage differentiation in PU.1-deficient cells, indicating that c-fms signaling is insufficient to drive macrophage differentiation in the absence of PU.1 [reviewed in (33)].

Besides intrinsic gene expression change, extracellular matrix (ECM) is also involved in the differentiation process. Human peripheral blood mononuclear cells (PBMCs) undergo a rapid rate of differentiation when maintained *in vitro* in a three dimensional environment compared with two dimensional, suggesting that the topology clue provided by the three dimensional matrix also influences monocyte-to-macrophage differentiation (34). In turn, monocytes and macrophages synthesize many of the molecules participating in ECM formation and function (35).

Localization

A growing body of evidence indicates that monocytes migrate into tumors, differentiate into macrophages and accumulate in distinct tumor microenvironments (TMEs) including: (I) tumor perivascular region (the region immediately beyond the external elastic lamina); (II) tumor epithelial region (the region between normal cells and tumor cells separated by a basement membrane); (III) tumor hypoxic region (visualized by immunolabeling of the reductively activated hypoxic-specific marker pimonidazole).

CD62/CD62L is responsible for the localization of TAMs in the perivascular region. High endothelial venules (HEVs) are specialized post-capillary venules which support the recruitment and extravasation of leukocytes, and have recently been found to exist in the endothelium of most solid human tumors, including: melanomas, breast, ovarian, colon, and lung carcinomas (36). HEV density within tumors correlates with increased CD62L-expressing immune cell infiltration (26). HEVs express many CD62L ligands, including 6-sulfosialyl Lewis X ligands, peripheral lymph node addressins (PNAd), and MAdCAM-1 (26,36), that mediate the initial gathering and rolling interactions of CD62L-expressing cell along the endothelium. TAMs localization to perivascular region ensues.

CCR2/CCL2 is also responsible for TAM localization in the epithelial region. Expression of CCL2 is not evenly distributed throughout tumors, with significantly higher levels of CCL2 expression in the epithelial region of various tumors, including ovarian, breast, and prostate cancers (26), both at mRNA and protein levels (37). Furthermore, CCL2 expression levels positively correlate with TAM accumulation in breast, ovarian, squamous cell, and non-small cell lung cancers and also glioblastoma (26). Overall, these findings support the point that the tumor epithelial region is a major target site for TAM localization, which is CCR2/CCL2 pathway dependent.

Cancer cell proliferation always outpaces the rate of new blood vessel growth, which results in widespread hypoxia in solid tumor. Cells in these regions become hypoxic

and exhibit robust induction of hypoxia-responsive gene expression to initiate angiogenesis (17). Several ligands, including EMAPII, endothelin, and VEGF, are known to be related to macrophage recruitment into tumor hypoxic regions [reviewed in (17)]. The VEGFR1/VEGF axis is regarded as the most important receptor-ligand pair in this process. In avascular and perinecrotic areas of human tumors, elevated expression levels of VEGF were found both in tumor cells and macrophages (17). Gene expression profiling studies have also shown that various tumor cell lines up regulate VEGF in response to hypoxia (38,39). Overexpression of VEGF has been demonstrated to be directly correlated with extensive recruitment of macrophages into tumors (40). Significantly impaired migration of macrophages in a VEGFR1-deficient mouse model provided still more compelling evidence (26). Hypoxia inducible factor (HIF) induced expression of CXCL12, along with CXCR4, also directs localization of monocytes to hypoxic area (41). Besides, CX3CR1/CX3CL1 directs localization into perivascular and hypoxia regions (26).

Entrapment

After recruitment into the tumor, macrophages become tethered by diminishing their mobility. Several factors have been postulated to participate in the entrapment of TAMs.

Initially, it was suggested that to retain TAMs at specific sites, TAMs or cancer cells down regulate chemokine receptors chemokines respectively. CCR2/CCL2 is an important determinant of macrophage infiltration in tumors, as discussed above. Previously, down regulation of tumor necrosis factor (TNF)-α-induced CCL2 mRNA and protein was evaluated (42), and defective CCR2 expression of TAMs was also found to be largely dependent on local TNF-α production at the tumor site, which could be rescued by neutralizing antibody of TNF-α (43). Based on these observations, it was supposed that the entrapment of TAMs may involve two integral mechanisms. The initial step is that TNF-α deactivates MAPK and inhibits the intracellular signaling cascade needed for migration in response to certain TAM chemoattractant receptors, followed by a second mechanism involving such immunomodulatory molecules as TNF-α and IFN-γ, which down regulate the expression of CCR2 and other chemoattractant receptor. Deceased responsiveness to major migration signals result in TAMs entrapment. However, further experiments demonstrated that the inhibition of migration was not dependent on TNF-α or any other soluble factors. Cells still respond to chemoattractant such as CCL2, with an elevation of intracellular calcium (44). Then, it was supposed the decreased mobility was due to metabolic changes. However, cells were still able to migrate to CCL2 when their metabolism was affected in different levels, with consistent up regulation of mitogen-activated protein kinase phosphatase 1 (MKP-1) (45). Series of works suggest that activation of MKP-1 by hypoxia leads to chemotaxis arrest [reviewed in (17)], which may play central role in the entrapment of TAMs in hypoxic sites within tumors.

As discussed earlier, Sema3A also tightly controls localization of TAMs by interacting with VEGF-R1. Notably, whereas Nrp1expression is down regulated in hypoxic environment, Sema3A continues to regulate TAMs in a Nrp1-independent manner. Nrp1 gene knockdown in macrophages favors TAM entrapment in normoxic tumor regions (28). Collectively, Sema3A trap TAMs within the hypoxic niche rather than normoxic environment. Besides, macrophage migration inhibitory factor (MIF) may also retain TAMs in hypoxic niche. However, the functions of MIF on macrophage migration are somewhat controversial at present [reviewed in (17)].

Function adaptivity and TAM-related cancer therapy

Macrophages are extremely malleable cells that constantly adapt their phenotype with changing microenvironments. This plasticity probably associates with the capacity to turn on and off different gene transcriptional programs and thus express various sets of proteins. Because of their location within a tumor, TAMs are exposed to high concentration gradients of tumor factors and are more prone to receive the combined effects of additional cells and molecules at TME. In fact, peripheral, non-TAMs as well as systemic blood monocyte precursors are also significantly altered in tumor-bearing hosts [reviewed in (46)]. In selected preclinical and clinical conditions, coexistence of cells in different activation states and unique or mixed phenotypes have been observed (11), reflecting dynamic changes and complex tissue-derived signals in TAMs. However, a note of caution should be taken into consideration regarding the concept of macrophage M1/M2 polarization. This concept should not be understood as an irreversible cellular differentiation in one of two distinct subsets, but as dynamic, adaptive and reversible changes constantly occurring as macrophages

respond to varying microenvironments (47). TAMs do not correspond to clearly defined M1 or M2 activation profiles. TAMs in established tumors generally resemble an M2 phenotype with defective production of interleukin (IL)-12 and high IL-10. How do macrophages switch from tumor-suppressing (M1-like) to tumor-promoting (M2-like) macrophages after their recruitment and entrapment in TME is not fully understood yet.

The first notable change in TAMs is the pro-inflammatory capacity. Interactions between tumors and immune system of the host shape the course of cancer progression. Inflammation and immune-suppression are two opposing responses of the immune system, linked in different ways to cancer progression (48). TAMs exhibit depressed mRNA and protein levels of pro-inflammatory molecules IL-12 and inducible nitric oxide synthesis (iNOS), and diminished expression of NFκB as well as C/EBP (49). This seems to contradict previously established elevated constitutive NFκB activity in tumor cells and myeloid cells from the tumor host [reviewed in (50)]. Further studies have found that these defects were associated with impaired binding activities of NFκB and C/EBP to their corresponding sites on the IL-12 and iNOS gene promoters, under the influence of factors derived from tumors, including IL-11 (50). An up regulation of NFκB in mice bearing smaller tumors (1–2 weeks) and decreased constitutive expression and activity of NFκB in macrophages from mice bearing advanced (4 weeks) tumors was later reported. This indicates that tumor initiation is associated with inflammation (increased NFκB activity and the downstream pro-inflammatory cytokines NFκB regulates), whereas tumor progression is associated with immune-suppression (decreased NFκB) (46). TAMs down regulate IL-12p70 but up regulate IL-12p40, IL-23, IL-6 and IL-10. NFκB p65 is profoundly diminished in TAMs; p50, in contrast, is dramatically up regulated with inhibiting p50 homodimers formation. STAT1/pSTAT1 and STAT3/pSTAT3 are over expressed in TAMs (51), resulting in a shift toward features that support tumor progression.

Metabolic changes in TAMs also shape their functional plasticity. The metabolic profile of TAMs is characterized by increased oxidative phosphorylation (OXPHOS), enhanced fatty acid oxidation (FAO) and up regulated arginase1 (ARG1) (52). To provide the substrate for energy supply via fatty acid oxidation, they improve their fatty acid (FAs) uptake. FAs interact with their sensors to regulate cellular gene transcription (52), tipping the balance of a complicated network in macrophage activation. In TAMs, ARG induction enhances a phenotype shift towards an M2-like phenotype and tumor cell growth by providing them with polyamines, while suppressing tumor cytotoxicity by reducing nitric oxide (NO) production (52). TAMs also process iron in a different way, characterized by high iron release. Decreased intracellular iron availability attenuates inflammatory response by negative regulation of NF-κB activity and translation of TNF-α and IL-6 (53). The influence of increased availability of iron in the extracellular milieu in TAMs remains to be further investigated.

Harnessing TAMs for therapeutic purposes has major implications for infectious disease, vaccination, transplantation, tolerance induction, inflammation and cancer immunotherapy [reviewed in (7)]. As the paradigm of TAMs now emerges with greater clarity, the identification of mechanisms and molecules associated with TAM recruitment, differentiation, localization, entrapment and function adaptivity provides a basis for macrophage-centered therapeutic strategies. Clinical evidence shows that an increased number of M2-like TAMs correlates with treatment failure and poor prognosis in different cancers types (54). Manipulating this cellular population could lead to clinical benefits. The elaboration of TAM biology provides three main approaches to target this critical cell population. The first one is to repress macrophage recruitment to tumors, followed by specific interference with M2-like TAM survival or inhibition of signaling cascades, and the last one is to reverse protumoral M2-like TAMs to a tumoricidal M1-like phenotype. For example, targeting tumor-derived chemokines, including CCL2, has shown pre-clinical anti-tumor success (55). Manipulation of environmental stimuli to revise M2-like TAMs to a tumor suppressive phenotype under pathological conditions is also a potential clinical strategy for cancer therapy. Administration of IL12 alters the functional phenotype of M2-like TAMs, reducing the production of tumor-promoting cytokines and inhibiting tumor growth (56). CpG-DNA and CpG-DNA combined with anti-IL-10R Ab could reverse TAM polarization and lower the number of detectable lung-metastasis foci (57).

Conclusions

Overall, the combination of chemokine receptors (on monocytes) and chemokines (by tumor cells) plays a central role in monocyte/macrophage recruitment and localization into specific TMEs; both lineage-restricted (developmental) genetic mechanisms and tissue-specific

(microenvironmental) signals support monocyte-to-macrophage differentiation; function adaptivity is highly regulated at transcriptional, metabolic levels as well as environmental levels. Besides the potential impact of genetic background, TME is a critical influence on TAM transformation.

In conclusion, our understanding of TAM pathophysiology is increasing rapidly, and it represents attractive therapeutic targets because TAM functions can be augmented or inhibited to alter disease outcome. On one hand, diversity and plasticity of macrophages have frustrating attempts to develop successful focused therapies. On the other hand, their plasticity may in fact provide unique opportunities to target the transformation process selectively in the context of certain cancer type, thereby inhibiting the pathology without disturbing resident macrophage biology and maintaining normal homeostasis.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aob.2020.02.03). The authors have no conflicts of interest to declare.

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