Skewed Signaling through the Receptor for Advanced Glycation End-Products Alters the Proinflammatory Profile of Tumor-Associated Macrophages

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Abstract

Tumors are complex tissues composed of variable amounts of both non-cellular components (matrix proteins) and a multitude of stromal cell types, which are under an active cross-talk with tumor cells. Tumor-associated macrophages (TAMs) are the major leukocyte population among the tumor-infiltrating immune cells. Once they are infiltrated into tumor stroma they undergo a polarized activation, where the M1 and M2 phenotypes represent the two extreme of the polarization heterogeneity spectrum. It is known that TAMs acquire a specific phenotype (M2), oriented toward tumor growth, angiogenesis and immune-suppression. A growing body of evidences supports the presence of tuning mechanisms in order to skew or restraint the inflammatory response of TAMs and thus forces them to function as active tumor-promoting immune cells. The receptor of advanced glycation end-products (RAGE) is a member of the immunoglobulin protein family of cell surface molecules, being activated by several danger signals and thus signaling to promote the production of many pro-inflammatory molecules. Interestingly, this receptor is paradoxically expressed in both M1 and M2 macrophages phenotypes. This review addresses how RAGE signaling has been drifted away in M2 macrophages, and thus taking advantage of the abundance of RAGE ligands at tumor microenvironment, particularly HMGB1, to reinforce the supportive M2 macrophages strategy to support tumor growth.

Keywords Receptor for advanced glycation end-products · Tumor microenvironment · Macrophage polarization · Alarmins · Tumor-associated macrophages

Introduction

It is estimated that almost 25% of all cancers are somehow associated with chronic infection and inflammation [1–4]. In addition, evidences derived from both epidemiological studies and basic research has demonstrated that organ-specific carcinogenesis is linked to a chronic and local inflammatory milieu, for instances, the *H. pylori*-induced gastric inflammation and the occurrence of gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma have become in a classic example [5]. The presence of inflammatory elements at the

microenvironment of neoplastic tissues is now well accepted, thus inflammation has been suggested to represent the 7th hallmark of cancer [6, 7].

Cancer and inflammation are mainly connected by two pathways [2, 8]. In the intrinsic pathway, both oncogenes and tumor suppressor genes drive the expression of inflammation-related programs, thus generating an inflammatory microenvironment. The extrinsic pathway is based on different conditions that cause non-resolving smoldering inflammation, and it is driven by inflammatory cells and a myriad of mediators produced by these cells. As masterpieces in the intersection of both pathways, different elements have been identified including transcription factors, such NF- κ B, STAT3, cytokines, chemokines and cellular components, such as tumor-associated macrophages (TAMs) [9–15].

Among the most relevant cytokines in the context of cancer-related inflammation, it should be firstly mentioned TNF- α . It plays an important role in the triggering and

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maintenance of inflammation. Tumor-derived TNF- α has been consistently associated with tumor growth [16, 17], and its constitutive release has been associated with increased release of chemokines (CCL2, CXCL8, CXCL12), IL-6, VEGF and macrophage migration inhibitory factor (MIF-1). Thus, TNF- α is able to generate an autocrine tumor-promoting network [18]. IL-1 also promotes tumor growth and metastasis by inducing several pro-metastatic genes such as metalloproteinases, chemokines, growth factors and TGF- β [19]. Furthermore, patients with IL-1 producing tumors have generally bad prognosis [20]. IL-1 also stimulates the expression of endothelial adhesion molecules [21]. Strikingly, IL-1 can be also released from necrotizing tumor/stroma cells and may then function as an alarmin [22]. Whereas some tumors acquire the ability to down-regulate alarmins able to induce apoptosis or recruit antigen-presenting cells, other tumors hijack normal alarmin function to send out fraudulent SOS signals as a means to promote their survival [23].

IL-6 is another key growth-promoting and anti-apoptotic inflammatory cytokine [24, 25]. IL-6 protects normal and premalignant intestinal epithelial cells from apoptosis and promotes the proliferation of tumor-initiating cells by a mechanism involving STAT3 [26, 27].

Different studies carried out on gene-targeted mice have clearly demonstrated the key roles of chemokines in cancer biology, particularly as mediators of chronic inflammation, and thus supporting initiation and/or tumor progression in many solid tumors [28, 29]. There is a growing body of evidences supporting that CXCR4/CXCL12 is one of the most efficient pair of chemokine receptor/chemokine to enhance tumor growth, being associated with tumor progression in many tumor types, including gastric cancer [30], as well as in the homing of cancer cells to metastatic niches and in the recruitment of different cells types to the tumor microenvironment [31–33].

Tumor Microenvironment Tumors are complex tissues composed of variable amounts of both non-cellular components (matrix proteins) and a multitude of stromal cell types, in addition to the ever-evolving neoplastic cells [34, 35]. It is important to highlight that in tumor microenvironment converge the persistent and abundance of a myriad of soluble signals in a hypoxic niche. In this context, tumor cells orchestrate microenvironment modifications by attracting or activating many of these non-tumoral cells. Thereby, there is a consensus that dynamics changes occurred in tumor microenvironment during the progression towards advanced tumor stages, thus determining the outcome of tumor growth, tumor dormancy, tumor invasion, metastasis and resistance to therapy [36].

This dynamics changes are mainly produced by the active cross-talk between tumor cells and tumor-infiltrating cells, which not only fail to mount an effective anti-tumour immune response, but also interact intimately to actively modified

tumor development particularly by their actions towards promoting tumor progression, invasion, and metastasis. Of note, tumor-associated macrophages (TAMs) are the major leukocyte population among the tumor-infiltrating immune cells.

Tumor-Associated Macrophages (TAMs) TAMs represent the major inflammatory component of the stroma of many tumors [37]. They are recruited early at tumor site where they promote tumor growth, switch to an angiogenic program, the resistance of tumor cells to apoptotic stimuli, tissue remodeling, invasion of tumor cells and the suppression of cytotoxic T-cell activities [38, 39].

Although the interactions between macrophages and tumor cells are incompletely defined, it is evident that the macrophage-dependent production of proteases, growth factors and cytokines regulates tumor seeding and the metastatic process [40]. The presence of immunocompetent cells, particularly T lymphocytes has been considered as a proof of an immunological antitumor response. Indeed the degree of T-lymphocytes infiltration has been consistently associated with more favorable clinical outcome [41]. In contrast, TAMs densities inversely correlate with patient prognosis in most solid tumors [42–44].

Macrophages Plasticity Macrophages are highly plastic cells, which undergo polarized activation. In this context, the “classically activated” or **M1** phenotype ($TNF-\alpha^{high}$, $IL-1^{high}$, $IL-12^{high}$, $IL-10^{low}$, $TGF\beta^{low}$) and the “alternatively activated” or **M2** phenotype ($TNF-\alpha^{low}$, $IL-1^{low}$, $IL-12^{low}$, $IL-10^{high}$, $TGF\beta^{high}$) represent two extreme phenotypes in this heterogeneity spectrum [45–47] (Fig. 1). Classical or M1 macrophages activation is produced in response to microbial products (LPS) or interferon- γ and display a classical expression pattern in regard to high IL-12 and IL-23 production and elicit antitumor and tissue destructive reactions. On the contrary, M2 cells respond to IL-4, IL-13, IL-10, immune complexes or glucocorticoids displaying a low IL-12, high IL-10 production pattern, poor antigen-presenting capacity and suppression of Th1 adaptative immunity, thus promoting tumor cell survival, proliferation and dissemination [48, 49].

TAMs as M2 Polarized Macrophages It is known that TAMs acquire a specific phenotype (M2), oriented toward tumor growth, angiogenesis and immune-suppression. This M2 polarization is promoted by signals presented at the tumor microenvironment such as PGE2, TGF- β , IL-6, IL-10 which are produced by tumor cells and by TAMs themselves. The M2 phenotype of TAMs is associated with profound effects on tumor progression [50]. It is well accepted that NF- κ B activation in cancer cells is mainly promoted by signals derived from the microenvironment itself, such as a cytokines/chemokines network, hypoxic conditions, and oxidative stress. NF- κ B activation on cancer cells is known to contribute to their proliferation and survival [51]. In contrast, TAMs from

Fig. 1 Schematic representation of the two extreme phenotypes (M1 and M2) in the heterogeneity spectrum derived from macrophage polarization. M1 phenotype arises as a response to interferon- γ and LPS while M2 are generated in response to IL-4, IL-13, IL-10, immunocomplexes (IC), or glucocorticoids (GC). The classical M1 phenotype supports proinflammatory and tumoricidal responses. On the contrary M2 macrophages are supportive of anti-inflammatory and protumorigenic responses

advanced neoplasias display defective NF- κ B activation. Accumulation of p50 homodimers, which act as repressor of NF- κ B activation, has been reported in TAMs [52], thereby impairing the production of cytotoxic mediators such as nitric oxide (NO), cytokines, TNF- α , IL-1 and IL-12.

Intracellular signaling networks are tightly regulated in both M1 and M2 macrophage phenotypes. The cytokine signaling protein suppressor family (SOCS) represents a negative regulator for various cytokine-mediated signaling [53, 54]. This family is linked to macrophage polarization, SOCS3 member is essential to M1 polarized macrophages [55], whereas SOCS1 is up-regulated in M2 macrophages, being critical in sustaining the anti-inflammatory phenotype [56].

The Interferon Regulatory Factor (IRF) family also participates in signal transduction triggered by pattern recognition receptors [57]. Both IRF5 and IRF4, are key players in the commitment of macrophage polarization into M2 or M1 macrophages phenotypes, respectively [58, 59].

Additionally STAT3, a member of the STATs transcription factors, has been reported to be constitutively activated in tumor cells as well as in TAMs [60, 61], leading to the inhibition of proinflammatory mediators production.

The Receptor of Advanced Glycation End-Products (RAGE)

RAGE is a member of the immunoglobulin protein family of cell surface molecules, being activated by several danger signals, and

thus functioning as a pattern-recognition receptor [62, 63]. In addition to the full-length receptor, RAGE undergoes extensive alternative splicing. However, endogenous soluble RAGE isoform may be generated by mechanisms different from alternative splicing, such as the participation of membrane associated-proteases, including the sheddase A disintegrin and metalloprotease-10 (ADAM-10) and the matrix metalloproteinase-9 (MMP-9) [64, 65]. Of note, soluble RAGE (sRAGE) may function as a decoy for ligands, and thus preventing the interaction with the membrane anchored full-length RAGE [66].

RAGE as a Multiligand Receptor Advanced glycation end-products (AGEs) were the first identified RAGE ligands, particularly N-carboxymethyllysine-modified proteins [67, 68]. The presence of AGEs has been even detected in human cancer tissues [69].

Of particular importance, S100/calgranulins and high-mobility group box 1 (HMGB1) have been also identified as RAGE ligands. S100 proteins are responsible for different roles in cell cycle, but some members of the family, have relevant extracellular roles, particularly at sites of chronic inflammation, being able to activate, via RAGE, different cell types, including macrophages [70]. HMGB1 belongs to the so-called damage-associated molecular pattern molecules or alarmins, which are released in response to infection or inflammatory stimuli, especially during tissue damage [71]. Both S100/calgranulins and HMGB1 are expressed and secreted not only by cancer cells but also by stroma-infiltrating cells [72, 73].

Noteworthy, the ligand HMGB1 may signal through RAGE and via TLRs (TLR2/TLR4). Activation of these receptors results in the activation of NF- κ B, AP-1, thereby promoting inflammation [74]. Very recently, new data have highlighted the cross-talk between TLRs and RAGE, when both TIRAP and MyD88, two adaptor proteins for TLR-2 and TLR-4, also function for RAGE once it is phosphorylated by PKC- ζ upon binding of ligands, and thus partly share intracellular signaling pathways [75].

RAGE and Tumor Microenvironment There is a growing body of evidences that clearly support that RAGE axis activation plays a central role in strengthening the inflammatory milieu at tumor microenvironment [76]. In this context, many open questions still remain to be answered particularly on the role of RAGE axis on different tumor infiltrating cell populations. In addition to the cancer cells themselves, tumors are also comprised of many RAGE-positive cell types, such as stromal cells. All these cellular components are under a very complex cross-talk mediated by a myriad of biological mediators. From the mechanistic point of view, a considerable amount of new pieces of knowledge has been added in the last years; however, much more remains to be understood regarding the role of RAGE in tumor biology, particularly in this complex cross-talk located at tumor microenvironment and where the net response favors tumor growth and progression. Although the functionality of RAGE in some tumor infiltrating cells has been described, the role of RAGE on tumor-associated macrophages have been recently started to be clarified.

RAGE and Macrophage Functionality We and others have demonstrated that RAGE engagement activates redox-sensitive transcription factors such as NF- κ B, and subsequently induce the production of pro-inflammatory molecules such as IL-1, IL-6 and TNF- α , NO and superoxide [77–84]. Very interestingly, sRAGE was shown to bind and induce monocytes survival and differentiation into macrophages, which paralleled by increases in the expression of mannose receptors and in CCR5 chemokine receptor [85]. Mannose receptor engagement by tumoral mucins modulates cytokine production by TAM toward an immune-suppressive profile [86]. Furthermore, the CCR5 ligand CCL5, is known to increase the presence of tumor-associated macrophages (TAM) and inhibiting potential anti-tumor T cell activities, at least in breast cancer [87].

CCL2 is one of the highly represented chemokines in a wide range of tumor, as well as one of the important determinants of human tumor macrophages content [88]. RAGE over-expression has been linked to the induction of CCL2 expression [89].

One of the earlier events downstream RAGE engagements is the activation of reactive oxygen species (ROS)-generating enzymes such as NADPH oxidase (NOX), thereby

contributing to the activation of redox signaling pathways. TAMs in thyroid carcinoma displayed strong immunostaining for NOX2, the catalytic subunit of NAPH oxidase [90]. Although ROS appear to be related more to “classic” M1 macrophages phenotype, is important to highlight the contribution of ROS to an immunosuppressive environment [91], as well as to invadopodia and podosome formation which facilitates tumor invasive behavior [92].

Macrophages are key elements of innate immunity and host defense, and where pattern recognition receptors are able to sense “danger signals” resulting from tissue damage and necrosis. In the innate immune system, many receptor systems are capable of adapting their responsiveness to marked and sustained increases in the concentration of extracellular ligand(s) (as occurs in tumor microenvironment) and use the steady-state levels to generate appropriate negative feedback mechanisms that effectively shut down signal transduction [93].

In this sense, the nature of the “tuning machinery” displayed by M2 macrophages might involve not only the recruitment of negative feedback pathways affecting RAGE/TLRs downstream signaling but also other gene expression regulation mechanisms, such as chromatin modification and microRNAs, thereby promoting the skewed profile ascribed to M2 macrophages. Strikingly, it has been suggested that acute inflammatory state in macrophages is transient and unstable and evolves to a tolerant state associated with features of the “alternative” macrophage activation [94].

Restraining or Skewing Inflammatory Response in TAMs

A growing body of evidences supports the presence of tuning mechanisms in order to skew or restraint the inflammatory response of TAMs and thus forces them to function as active tumor-promoting immune cells. Some major mechanisms have described, particularly those based on the acquisition of a tolerant state, the induction of epigenetic changes as well the marked changes in the miRNAs profile.

Tolerance As mentioned above, TAMs displayed a defective NF- κ B signaling, resembling the classical LPS tolerance [52]. Furthermore, recent data derived from microarrays and advanced bioinformatics analysis determined that gene expression pattern in endotoxin tolerance is very similar to that found in M2 macrophages [95].

Taking in mind that RAGE is now considered as a member of pattern recognition receptor family, it is noteworthy that macrophage tolerance can be also induced by stimulation through TLRs, thus representing a general regulatory strategy to control inflammation triggered by TLRs signaling [96]. In the classical endotoxin tolerance, TLR signaling is

suppressed, either by TLR4 desensitization or by induction of molecules able to inhibit TLR signaling such as IRAK-M, SHIP, SOCS1 and A20 [97]. TAMs produce low amounts of proinflammatory cytokines, a condition that may resemble some aspects of tolerance, which may then contribute to the immunosuppressive tumor microenvironment. Strikingly, recent reports have highlighted the relevance of chromatin modifications leading to a tolerant phenotype [98].

Epigenetics Inflammation involves a very complex regulatory network. In addition to transcription factors families, chromatin structure modification has been shown to be a key regulator of many inflammatory genes. Chromatin remodeling via histone modification is one of the key epigenetic mechanisms that plays a pivotal role in the maintenance of both active and suppressed states of gene expression depending of the site of methylation [99, 100]. Of note, epigenetic regulation has been recently reported in alternative phenotype of murine macrophages, particularly a decreased in H3K27 (histone H3 at lysine-27) methylation at the promoter of M2 marker genes and a paralleled increased in the demethylase Jumonji domain containing-3 (Jmjd3) expression [101]. Furthermore, transcription-prone histone modification at the IL-10 promoter has been described in TLR signaling in TAMs, thereby enhancing IL-10-mediated immunosuppression [102]. Noteworthy, RAGE activation by S100B is able to induce the expression of thioredoxin-interacting protein (TXNIP),

the endogenous inhibitor of ROS-scavenging protein thioredoxin (TRX). Additionally, TXNIP over-expression abolished H3K9 tri-methylation, a marker for gene inactivation, and increased H3K9 acetylation, an indicator of gene induction, at proximal Cox2 promoter [103].

MicroRNAs In the context of innate immunity and particularly on macrophages gene expression profile changes during the course of an inflammatory reaction, microRNAs have emerged as important regulators [104]. Of note, miR-155 also regulates inflammatory cytokine production in TAMs by targeting the enhancer binding protein C/EBP β [105]. Conversely, miR-155 has been reported to target IL-13R α 1, which is known to trigger an M2 phenotype [106]. Noteworthy, IL-10, a crucial anti-inflammatory cytokine, inhibits miR-155 transcription by an STAT-3 dependent mechanism [107]. RF5 is a member of the interferon regulatory factor family, which is crucial in the up-regulation of the M1 phenotype markers and inhibits transcriptional activation of IL-10, a marker of M2 phenotype [108]. Strikingly, miR-146a is known to dampen down inflammatory response, by targeting genes such as IRF-5 and other signaling molecules down-stream MyD88, such as TRAF-6 and IRAK1 [109]. Of note, MyD88 blocking largely abrogated the RAGE-mediated intracellular signaling [75]. miR146a over-expression also results in a decrease of proinflammatory signals such as CXCL8 [110], IL-6 [111] and TNF- α [112]. Furthermore, miR21

Fig. 2 Skewing RAGE signaling seems to be an emerging mechanism to reinforce the anti-inflammatory and protumorigenic actions of M2 macrophages. Although during polarization active transcriptomic reprogramming occurs on of macrophages, RAGE still remained expressed and functional on M2 macrophages but its canonical proinflammatory signaling has been drifted away, either by increasing

expression of NFkB activation inhibitors such as SOCS1 and SHIP1 or by transcription-prone histone modification at the IL-10 promoter, thus taking advantage of the abundance of its ligands on tumor microenvironment, particularly HMGB1, to reinforce a supportive tumor growth strategy

controls inflammation by down-regulation the translation of the pro-inflammatory tumor suppressor programmed cell death 4 (PDCD4), an inhibitor of IL-10 production [113].

Skewing RAGE Signaling. An Emerging Mechanism

We have recently reported that RAGE is equally expressed in both M1 and M2 macrophages polarized phenotypes and that RAGE activation by the alarmin HMGB1, highly abundant at tumor microenvironment, promotes protumoral activities of M2 macrophages based on their abilities to enhance tumor cell invasion and promoting angiogenesis. All these effects were abrogated by RAGE-targeting knockdown [114].

Additionally, RAGE activation by HMGB1 in M2 macrophages did not produce NF κ B activation supporting how cell signaling triggering by RAGE activation in these cells has been drifted away from its classical NF κ B activation-dependent proinflammatory response, by a mechanism that involved the induction of both the suppressor of cytokine signaling 1 (SOCS1) and the Src homology-2 domain-containing inositol 5-phosphatase 1 (SHIP-1), which are negative regulators of NF κ B activation [114].

Another important finding supporting the fact that RAGE activation-mediated proinflammatory signaling has been skewed in M2 macrophages was that RAGE activation by HMGB1 in this phenotype induced a transcription-prone histone modification at the IL-10 promoter, and this epigenetic imprinting correlates with increments of HMGB1-induce IL-10 production, as reported independently by two groups [115, 116] (Fig. 2).

In summary, new data has emerged demonstrating how complex are the cellular cross-talk in tumor stroma which may even skew the canonical responses that we can expect for individual cell types. This is particularly interesting based on the fact that many tumor stroma cells undergo a process of phenotypic polarization, and most of them also express RAGE.

Finally, during the last years, TAMs have been recognize as an active and bidirectional modulator of immune response, and therefore a particular interest has raised to be considered as target for the treatment of tumors. It is known that TAMs are able to even modulate the efficiency of chemotherapy, radiation therapy, and immunotherapy in different stages of various tumors [117]. Of note, reeducation of TAMs towards an anti-tumor cell population is now a promising approach for the treatment of tumors. However, this goal will be only reached when we fully understand all cellular and molecular mechanisms underlying the switch from tumor-suppressing to tumor-promoting phenotypes.

Conclusion Once macrophages infiltrate tumors they undergo a polarized activation, where the M1 and M2 phenotypes

represent the two extreme of the polarization heterogeneity spectrum. At present, there is a consensus about the presence of tuning mechanisms in order to skew or restraint the inflammatory response of TAMs and thus forces them to function as active tumor-promoting immune cells. The activation of the receptor of advanced glycation end-products by HMGB1, a the highly abundant alarmin at tumor microenvironment, has emerged as a new mechanism which is able to drifted away the canonical proinflammatory signaling observed in classically activated macrophages and thus strengthening their supportive tumor growth behaviour.

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