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Review

RAGE in tissue homeostasis, repair and regeneration

Guglielmo Sorci [a,b], Francesca Riuzzi [a,b], Ileana Giambanco [a], Rosario Donato [a,b,*]

[a] Department of Experimental Medicine and Biochemical Sciences, University of Perugia, Via del Giochetto, 06122 Perugia, Italy
[b] Interuniversity Institute of Myology, University of Perugia, Via del Giochetto, 06122 Perugia, Italy

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ABSTRACT

RAGE (receptor for advanced glycation end-products) is a multiligand receptor of the immunoglobulin superfamily involved in inflammation, diabetes, atherosclerosis, nephropathy, neurodegeneration, and cancer. Advanced glycation end-products, high mobility group box-1 (amphoterin), β-amyloid fibrils, certain S100 proteins, and DNA and RNA are RAGE ligands. Upon RAGE ligation, adaptor proteins (i.e., diaphanous-1, TIRAP, MyD88 and/or other as yet unidentified adaptors) associate with RAGE cytoplasmic domain resulting in signaling. However, RAGE activation may not be restricted to pathological statuses, the receptor being involved in tissue homeostasis and regeneration/repair upon acute injury, and in resolution of inflammation. RAGE effects are strongly dependent on the cell type and the context, which may condition therapeutic strategies aimed at reducing RAGE signaling.

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1. Introduction

RAGE (*r*eceptor for *a*dvanced *g*lycation *e*nd-products) is a multiligand receptor of the immunoglobulin superfamily long implicated in inflammation, diabetes and its complications, atherosclerosis, nephropathy, neurodegeneration, and cancer [1–9]. RAGE is a ~47–55 kDa protein consisting of an extracellular region made of V-, C1- and C2-type domains, a short membrane-spanning domain, and a relatively short cytoplasmic and transducing domain devoid of kinase activity. Thus, RAGE needs to associate with adaptor proteins for intracellular signaling.

RAGE engagement results in the activation of multiple downstream signaling pathways eventually impinging on canonical NF-κB, AP-1, CREB, STAT3 [1–9], NFAT [10], and myogenin [11] with consequent regulation of transcription of cytokines, inflammatory enzymes, chemokines, chemokine receptors, adhesion molecules, matrix metalloproteinases and/or cytoskeletal constituents, and of cell proliferation, survival, differentiation and migration, phagocytosis and authophagy (Fig. 1). However, the signaling pathways activated and functional consequences of RAGE engagement are strongly dependent on the cell type, the context and the identity and local concentration of its ligands, and impact the organization of the cytoskeleton besides transcription.

RAGE is expressed in a variety of cell types during prenatal and postnatal development and repressed at completion of development excepting type I alveolar cells in the lung and a few other cell types [1,2]. This suggests that RAGE signaling may play an important role during development, although deletion of *Rage* does not result in fertility disturbances or overt phenotypes excepting hyperactivity and increased sensitivity to auditory stimuli in mice [12]. However, RAGE is sharply upregulated in a large number of cell types under pathological conditions, and RAGE ligands upregulate its expression [1–11] (Fig. 1). These observations probably represent one main reason why RAGE expression and signaling mostly have been investigated in the context of the pathophysiology of chronic inflammatory statuses and cancer. However, recent evidence suggests that RAGE signaling may play an important role in the resolution of inflammation and in tissue homeostasis and repair/regeneration after acute injury, highlighting the pleiotropic activities of this receptor.

2. RAGE is a pattern recognition receptor

The multiligand nature of RAGE is highlighted by its ability to bind such diverse ligands as advanced glycation end-products (AGEs) [13–15], high mobility group box-1 (HMGB1, amphoterin) [13,14,16], β-amyloid fibrils [17], certain S100 proteins [3,18,19], and DNA and RNA [6] (Fig. 1). AGEs form from condensation and oxidation processes between proteins or peptides and sugars, an event occurring in diabetes and recognized as a major cause of diabetic complications such as accelerated atherosclerosis and cardiovascular disorders [5], nephropathy [7,20,21], and chronic inflammation [4,6,22], in part via RAGE binding. HMGB1 is confined to the nucleus in normal physiological conditions, functioning as a regulator of chromatin dynamics [23]; however, in case of tissue injury it moves to the cytoplasm and then is released, acting as a danger signal [24,25]. HMGB1–RAGE interactions also participate in tumorigenesis [4,6]. β-Amyloid results from proteolytic cleavage of the

* Corresponding author at: Department of Experimental Medicine and Biochemical Sciences, University of Perugia, Via del Giochetto, 06122 Perugia, Italy. Tel.: +39 075 585 7453; fax: +39 075 585 7451.
E-mail address: donato@unipg.it (R. Donato).

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amyloid precursor protein and can assemble into fibrils the accumulation of which in the brain is a hallmark of Alzheimer's disease [26]. S100 proteins are Ca^{2+}-binding proteins acting as intracellular regulators and extracellular signals [27–29].

RAGE is found in an oligomeric or a pre-assembled state [30]; ligand binding stabilizes RAGE oligomers, an event required for RAGE signaling. The V and C1 domains form a single functional unit in the RAGE molecule and the VC1 unit is linked to the C2 domain by a flexible linker. Structural analyses have shown that with the exception of S100A6 which interacts with RAGE C2 domain [31], all other RAGE ligands interact with the VC1 domain [32]. This would predict that AGEs, HMGB1, β-amyloid and the majority of RAGE-activating S100 proteins should elicit similar if not identical effects in the same cell type upon RAGE ligation. However, structural properties intrinsic to individual ligands (e.g., their tendency to form oligomers of variable complexity and sensitivity to the non-reducing conditions of the extracellular milieu), the ligand concentration, the context, the cell type and the number of RAGE molecules expressed on the cell surface may condition RAGE signaling.

RAGE VC1 domain has a net positive charge whereas the C2 domain has a net negative one [33–35]. It has been proposed that the negatively charged HMGB1 C-domain (which harbors the RAGE-binding site [24,25]), AGEs and the acidic S100 proteins are attracted by the positively charged area of RAGE's VC1 domain, implying that HMGB1–, AGE– and S100 protein–RAGE interactions are electrostatic in nature [33–35]. Thus, AGEs, HMGB1, S100 proteins and DNA and RNA should compete with each other for RAGE binding; however, information about this issue is surprisingly scant. RAGE in phagocytes also interacts with phosphatidylserine (an "eat-me" signal) [36] on the surface of apoptotic cells thereby promoting efferocytosis, i.e. the phagocytosis of apoptotic cells [37,38]. While these observations point to a beneficial role of RAGE in the clearance of apoptotic cells in tissue development, homeostasis and repair and in resolution of inflammation, one would predict that phosphatidylserine binds to the VC1 domain positively charged area and that the reported HMGB1-dependent inhibition of phagocytosis [39,40] may be due to the blockade of phosphatidylserine by HMGB1, competition between HMGB1 and phosphatidylserine for RAGE binding and/or to blockade of access of phosphatidylserine to HMGB1-bound RAGE.

Conflicting conclusions have been drawn concerning the mode S100B and perhaps other S100 proteins interact with RAGE. According to one view these proteins bind to the positively charged area of the VC1 domain [34], whereas according to another view they bind to the C'D loop and at least part of a nearby hydrophobic surface located in another region of the V domain [35].

RAGE also interacts through its V domain with heparan sulfate with high affinity, an interaction reported to be essential for HMGB1-stimulated RAGE signaling in endothelial cells [41]. These studies have established that RAGE binds heparan sulfate irrespective of the absence or presence of HMGB1, suggesting that RAGE forms a complex with heparan sulfate on the cell surface, i.e. heparan sulfate may act as a RAGE coreceptor amplifying ligand-induced RAGE signaling. RAGE also might bind to extracellular matrix heparan sulfate, and potentially, HMGB1 (and other RAGE ligands as well) might regulate the extent of RAGE interactions with extracellular matrix heparan sulfate. This

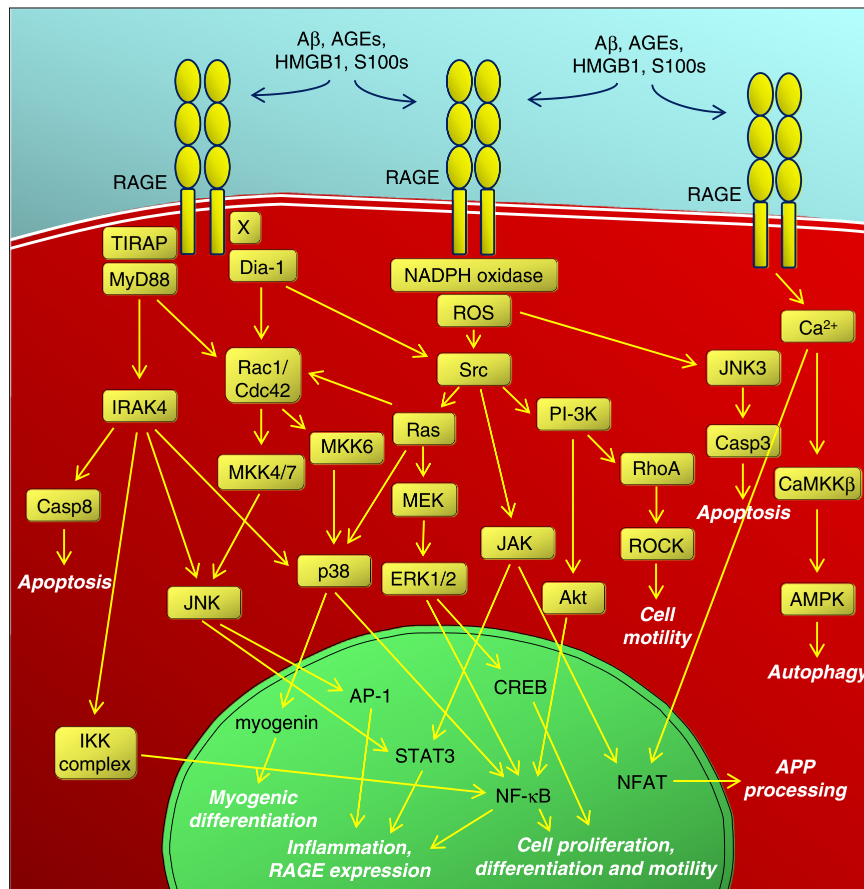

Fig. 1. RAGE engagement by multiple ligands activates various signaling pathways in a cell-specific manner. Ligand binding causes RAGE oligomerization (or stabilization of RAGE oligomers) and association of the RAGE cytoplasmic domain with the adaptors Dia-1, TIRAP-MyD88 and/or as yet unidentified adaptors (X), which in turn activate signaling molecules impinging on transcription factors NF-κB, AP-1,CREB, STAT3, and/or myogenin. In so doing, RAGE regulates the inflammatory response and/or cell proliferation, survival, differentiation and motility in a cell-specific manner. RAGE signaling-dependent regulation of cell motility also occurs independently of its effects on gene transcription via a Dia-1/Src/Ras/PI3K/RhoA/ROCK and a Dia-1/Rac1/Cdc42/RhoA/ROCK pathway.

might have important implications for RAGE functions in physiology and pathology.

3. RAGE signaling requires adaptor proteins

One adaptor protein involved in RAGE signaling transduction is diaphanous-1 [42], a member of the formin family that mediates the effects of the small GTPase of the Rho family, RhoA, on cell motility and the cytoskeleton [43–45] and of Cdc42 and Rac1 signaling [46]. Diaphanous-1 recruits Rac1 and Cdc42 in glioma cells thereby driving RAGE-dependent cell migration [42] (Fig. 1). Also, following RAGE ligation by S100B in microglia, diaphanous-1 recruits Rac1/Cdc42 with ensuing activation of a RhoA/ROCK and a Src kinase/Ras/PI3K/RhoA/ROCK pathway governing microglial motility and a JNK/AP-1 pathway responsible for chemokine expression [47]. However, diaphanous-1 is not required for S100B/RAGE-dependent activation of a Ras/MEK/ERK1/2/NF-κB pathway concurring to chemokine expression in microglia [48] (Fig. 1). Thus, additional adaptors may be recruited by activated RAGE in microglia. Also, diaphanous-1 may not mediate RAGE signaling to Rac1/Cdc42 in myoblasts because HMGB1-dependent stimulation of RAGE in these cells results in the acceleration of myogenic differentiation and inhibition of proliferation via activation of a Rac1/Cdc42/MKK6/p38 MAPK pathway and p38 MAPK-dependent inhibition of ERK1/2 and JNK [48–50] whereas diaphanous-1 activity supports myoblast proliferation [51]. Other adaptor proteins involved in RAGE signaling transduction are TIRAP and MyD88, two adaptor proteins for Toll-like receptor (TLR)-2 and -4 [52] (Fig. 1). Specifically, upon binding of ligands the cytoplasmic domain of RAGE is phosphorylated at Ser391 by protein kinase Cζ, which promotes TIRAP and MyD88 recruitment and activation of inflammatory pathways. Incidentally, these results point to cooperation between RAGE and TLRs in immune response. Whether RAGE ligation recruits other adaptor proteins, possibly in a cell-specific manner, remains to be determined.

4. RAGE ligation activates signaling pathways in a cell-specific manner

Whereas RAGE-dependent stimulation of ERK1/2, Akt, p38 MAPK and JNK in monocytes/macrophages/microglia, astrocytes, endothelial cells, chondrocytes and vascular smooth muscle cells causes cell activation and/or proliferation during the course of inflammation, arthritis and/or atherosclerosis [3,5], RAGE-dependent stimulation of ERK1/2 results in enhanced survival of neuronal cells under oxidative stress conditions [53–55] and enhanced proliferation of low-density myoblasts [56], whereas HMGB1/RAGE-dependent stimulation of p38 MAPK in myoblasts results in myogenic differentiation and reduced proliferation and migration [48,49] (Fig. 1). Moreover, excess RAGE stimulation in neurons causes excessive ERK1/2 activation resulting in neurotoxic oxidative stress leading to apoptosis [53]. Also, as mentioned above RAGE signaling in microglia stimulates migration via a diaphanous-1/Src/Ras/PI3K/RhoA/ROCK, an X/Ras/PI3K/RhoA/ROCK (where X is an unidentified adaptor protein) and diaphanous-1/Rac1/RhoA/ROCK pathway [47], and in several cancer cells it stimulates invasiveness via activation of ERK1/2, p38 MAPK, JNK, Akt, Rac1, NF-κB and caspase-1 and production of matrix metalloproteinase 9 [14,57–60] (Fig. 1). However, RAGE engagement by HMGB1 in myoblasts and in rhabdomyosarcoma cells induced to express the receptor, reduces migration, invasiveness and release of matrix metalloproteinases 1 and 2 via p38 MAPK activation [48–50]. Aside from the nature of the adaptor protein recruited by RAGE in different cell types, which may differentially condition the intensity and duration of the activity of downstream signaling molecules, the overall effect of RAGE ligation may be strongly dependent on intervening intracellular events such as the amount of produced reactive oxygen species (ROS), the redox status, energy metabolism and cell-specific transcription and activity of definite genes.

5. S100 proteins and β-amyloid form oligomers

In the extracellular space S100 proteins assemble into multimeric (tetrameric, hexameric, octameric and/or higher-order) complexes [61–66], which stabilize RAGE oligomers thus promoting the close association of intracellular domains of RAGE molecules required for the recruitment of adaptor proteins and/or enzymes [30,32]. Possibly, the larger the amount of S100 oligomers the greater the stabilization of RAGE aggregates and the more intense and/or sustained the RAGE signaling. This mechanism may explain the different outcomes of, e.g. S100B-stimulated RAGE signaling in neurons and microglia: S100B at low doses promotes neuronal survival, stimulates neurite outgrowth and counteracts microglia activation [53,54,67], whereas at high doses it kills neurons [53,54] and activates microglia [68,69] and astrocytes [70]. As another mechanism, the extent of ligand-induced RAGE oligomerization/stabilization, which may be larger at high S100B concentrations (i.e., in the presence of high amounts of high-order S100B oligomers) and/or in the presence of β-amyloid fibrils, and the cell type identity may dictate the nature of the adaptor protein recruited. For example, the different ability of neurons and of microglia and astrocytes to manage oxidative stress may explain the different outcomes of highly intense RAGE signaling in these cell types. Moreover, as RAGE ligands upregulate RAGE expression [2], the greater number of expressed RAGE molecules at high ligand concentrations may translate into a more sustained RAGE signaling via the recruitment of different adaptor proteins. Lastly, different ratios of levels of RAGE and advanced glycation end products receptor 1, which counteracts RAGE [71], may be responsible for the different outcomes of RAGE ligation of high S100B in neurons and microglia.

Among the S100 proteins that are RAGE ligands, S100B is the only one exerting different RAGE-mediated effects at low and high concentrations on the same cell type [29]. S100A4, S100A8/S100A9 and S100A12 also exert extracellular effects in part via RAGE engagement [29,72–75]. However, relatively high concentrations of these proteins are required for RAGE activation, and they mostly are involved in chronic inflammation and cancer. There are exceptions to this rule, however. One exception is represented by S100A12, shown to exert a potent neurite extension activity at concentrations between 0.1 and 1.0 μM and decreasing activity at higher concentrations [76]. However, RAGE engagement in this case was supposed, but not firmly demonstrated. Analogously, S100A4 at high but not low concentrations promotes neurite extension, yet without activating RAGE, the protein binding to heparan sulfate that presumably acts as a coreceptor of an unknown receptor [77]. Also, the S100A8/S100A9 heterocomplex at low concentrations activates RAGE to promote tumor cell growth [78] and may act as a potent pro-apoptotic agent, but this latter activity occurs in a RAGE-independent manner [79]. The three so-called calgranulins, S100A8, S100A9 and S100A12, may exert protective effects in relation to tissue repair and remodeling, acting as chemokine mediators in response to infection and activating mast cells, neutrophils, keratinocytes, macrophages and dendritic cells, upregulating adhesion molecules required for extravazation, and inhibiting microbial growth [reviewed in Refs. 29,73]. However, these proteins can also activate TLR-4 and G-protein-coupled receptors, and their antimicrobial effects are independent of RAGE.

β-Amyloid is known to form oligomers which intensely activate RAGE in neurons and microglia with deleterious effects. Indeed, the participation of RAGE signaling in neurodegenerative diseases via direct effects on neurons and indirect effects through microglia and astrocyte activation is long recognized [17,80,81]. However, in vitro data suggest that low S100B-activated RAGE counteracts the detrimental effects of β-amyloid on neuronal survival, whereas high S100B-activated RAGE potentiates these effects [54].

6. RAGE ligands upregulate RAGE expression

Re-expression of RAGE after completion of development occurs in injured tissues under the action of a ROS/NF-κB axis [2], and engagement

of RAGE ensues if its ligands are present in sufficient amounts. Also, besides activating RAGE signaling, RAGE ligands upregulate RAGE expression mostly, but not exclusively via activation of NF-κB, which translates into an increased density of RAGE molecules at the cell surface and consequent enhancement of the intensity and duration of RAGE signaling [2] (Fig. 1). This feed-forward mechanism can be interrupted by decreasing the concentration of RAGE ligands, ROS production and/or NF-κB signaling, whereas a reduced clearance of RAGE ligands and/or a continuous release of RAGE ligands from the injured tissue may perpetuate RAGE signaling and amplify RAGE-dependent cell responses. In this context, proteins acting as RAGE ligands are generally viewed as damage-associated molecular patterns [82]. However, in normal physiological conditions at least one RAGE ligand, i.e. S100B, is found in the brain extracellular space at a concentration (a few nM or less) sufficient to activate RAGE [83]. Because RAGE is expressed in low, but appreciable amounts in neurons and microglia in normal brain [84], S100B might tonically activate a low-intensity RAGE signaling in neurons resulting in trophic effects, and in microglia resulting in attenuation of microglial reactivity [54,85]. However, in the context of gliomas interaction of low S100B with RAGE may induce tolerance of microglia thus contributing to local tumor immunosuppression [85]. Whether low S100B-activated RAGE has a role in the beneficial activity of microglia [86,87] and in neuronal electric activity in normal physiological conditions remains to be investigated. Moreover, whereas early after acute muscle injury a ROS/NF-κB axis induces RAGE expression in activated muscle stem (satellite) cells, in differentiating myoblasts RAGE expression is regulated positively and negatively by myogenin and PAX7, respectively [11]; S100B and HMGB1 upregulate RAGE expression in low-density myoblasts [56], whereas HMGB1 only does so in high-density myoblasts [11].

7. Cell type identity conditions effects of RAGE ligation

Interestingly, RAGE expressing cells are not homologous to each other in terms of functional responses to RAGE ligation. On the one side, cells of the innate and adaptive immune system, endothelial and vascular smooth muscle cells and chondrocytes respond to RAGE activation by amplifying their responses in the context of inflammatory processes, diabetic complications and atherosclerosis [3,5–8,88–91]. Thus, strategies aimed at reducing RAGE signaling may contribute to reduce the inflammatory response especially in chronic inflammatory settings, with potential therapeutic benefits [92,93]. On the other hand, at least neurons and skeletal muscle satellite cells appear to benefit from a low-intensity RAGE signaling in terms of resistance to apoptotic stimuli and activation of the differentiation program (neurons) [13,53], and of activation of the differentiation program and stimulation of apoptosis-mediated elimination of superfluous cells (myoblasts) [11,48,49,56]. Also, whereas RAGE signaling in carcinomas, mesotheliomas and gliomas sustains tumorigenesis and metastasis development [14,57–60], RAGE expression and/or activation in rhabdomyosarcoma cell lines results in reduced proliferation, migration, invasiveness and tumorigenesis [50], and RAGE expression and/or activation is reduced in certain lung and oral and esophageal tumors [94–96] and embryonal rhabdomyosarcoma [F. Riuzzi, G. Sorci, R.Sagheddu and R. Donato, manuscript in preparation]. As another example, whereas S100A4-dependent RAGE activation in chondrocytes results in the erosion of articular cartilage via upregulation and activation of matrix metalloproteinases [97], S100A4-dependent RAGE activation in cardiomyocytes may be protective [98]. Thus, the outcome of RAGE signaling is strongly cell type- and context-dependent, which may limit therapeutic strategies aimed at reducing RAGE signaling. Probably, the contradictory effects of RAGE signaling depend on the intensity and duration of RAGE signaling and on intrinsic properties RAGE-expressing cells.

8. RAGE promotes autophagy

RAGE ligation in several cell types promotes autophagy, a genetically programmed, evolutionarily conserved cell survival process, and inhibits apoptosis by a p53 transcription-independent pathway during the response to chemotherapeutic agents [99,100]. This RAGE activity may concur to tumorigenesis. Also, RAGE mediates β-amyloid-induced formation of autophagosomes in neuronal cells via CaMKKβ-AMPK signaling [101] with potential detrimental effects in Alzheimer's disease consequent to excess autophagy (Fig. 1). Yet, because authophagy is not detrimental per se [102–104], RAGE-dependent promotion of authophagy may be beneficial during the course of development and tissue regeneration, an as yet unexplored issue. On the other hand, RAGE signaling can promote apoptosis via enhanced ROS production in neuronal cells [17,53], myoblasts [48,49] and cardiomyocytes [105,106]. Thus, RAGE appears to play an important role in the delicate balance between cell survival (via stimulation of autophagy and inhibition of apoptosis) and cell death (via stimulation of apoptosis and excess authophagy) depending on the intensity and/or duration of its activity, which are largely dependent on the local concentrations of its ligands and the context.

9. RAGE in resolution of inflammation

There is consensus that RAGE signaling is not causative of inflammation; rather, RAGE signaling in monocytes/macrophages/microglia perpetuates inflammation by promoting phagocyte infiltration and the release of proinflammatory cytokines and chemokines. Indeed, interference with RAGE signaling in chronic inflammatory conditions results in amelioration of clinical and biochemical signs of inflammation [92,93]. However, recent evidence suggests that RAGE may be important for the attenuation and/or resolution of acute inflammation as well. Indeed, RAGE signaling limits the inflammatory and procoagulant response during *Escherichia coli* sepsis [107] and is protective during murine tuberculosis [108]. Also, S100B-activated RAGE signaling leads to resolution of inflammation in *Aspergillus fumigatus* infection in lung. Specifically, TLR-2 activation on bronchial epithelial cells by the fungus results in the upregulation and release of S100B, that paracrinally binds to RAGE on neutrophils and mediates its association with TLR-2 [109] (Fig. 2). By this mechanism, S100B-activated RAGE inhibits TLR-2 in neutrophils and restrains *A. fumigatus*-induced pulmonary inflammation [109]. However, when used at high doses S100B exacerbates *A. fumigatus*-induced pulmonary inflammation [109] likely via sustained stimulation of RAGE signaling. Also, in other lung pathological settings such as pneumococcal and influenza virus A pneumonia RAGE signaling is detrimental [110,111], which points to the different roles of RAGE in pathogen-induced inflammation perhaps depending on the identity and/or concentration of RAGE ligands, the intervening leukocyte population and the amount of expressed RAGE. In this regard, it is interesting that susceptibility to invasive aspergillosis in patients undergoing hematopoietic stem cell transplantation is significantly associated with *RAGE* (−374T/A) polymorphism resulting in RAGE overexpression in recipients, and with *S100B* (+427C/T) polymorphism resulting in S100B overexpression in donors [112]. Lastly, lack of RAGE results in lung fibrotic disease [113,114] pointing to an important role of RAGE in pulmonary tissue homeostasis. *RAGE* (*AGER*) is expressed in great abundance in type I alveolar epithelial cells [1,2], with a potential role in epithelium–extracellular matrix interactions given RAGE's ability to bind to heparan sulfate with a high affinity [41]. In humans, the *RAGE* variant rs2070600 has been associated with potential disturbances of RAGE structure and function in relation to host defense, inflammation, and tissue remodeling [115,116].

10. RAGE in tissue repair

In addition to its detrimental role in chronic inflammatory statuses, RAGE signaling counteracts the beneficial effects of MyD88 activity during liver regeneration [117]. However, an increasing body of evidence indicates that RAGE signaling has a beneficial role in tissue repair after acute injury which also calls for caution in anti-RAGE-based therapeutic procedures. For example, RAGE becomes expressed in

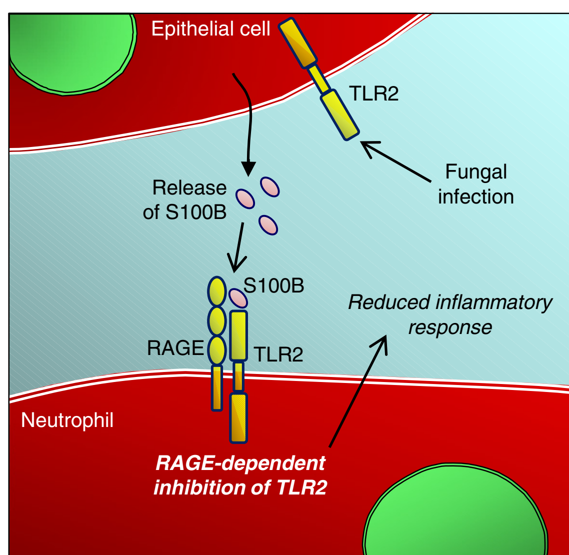

Fig. 2. RAGE promotes resolution of inflammation. TLR2 activation on bronchial epithelial cells by *Aspergillus* conidia results in the upregulation and release of S100B that paracrinally binds to RAGE on neutrophils, and mediates its association with TLR2 for subsequent inhibition. However, S100B, upon binding to nucleic acids in epithelial cells, also activates an intracellular TLR3/TLR9/TRIF/NF-κB-dependent pathway culminating in the transcriptional downregulation of S100B [109]. This latter mechanism provides the molecular basis for an evolving braking circuit in infection whereby the endogenous danger protects the host against pathogen-induced inflammation and a nucleic acid-sensing mechanism resolves danger-induced chronic inflammation.

axons and infiltrating mononuclear phagocytes upon peripheral nerve injury and reduction of RAGE activity in acutely injured peripheral nerves results in the suppression of anatomical regeneration and functional recovery [118,119], supporting a role of RAGE in neurite outgrowth in vivo (Fig. 3A). S100B and HMGB1 are RAGE ligands in macrophages stimulating RAGE signaling ultimately resulting in nerve repair. Also, S100B-activated RAGE promotes Schwann cell migration during the course of repair of injured peripheral nerves through the induction of the expression of thioredoxin interacting protein and the consequent activation of p38 MAPK, CREB and NF-κB [120]. Thus, RAGE signaling may intervene in peripheral nerve regeneration via stimulation of macrophage and Schwann cell migration to the site of damage (Fig. 3A): macrophages infiltrating the injured tissue exert beneficial effects by clearing cell debris and dead neutrophils and releasing trophic factors, whereas activated Schwann cells release cytokines and neurotrophic factors shown to be crucial for the repair of injured nerves. The ability of RAGE signaling, activated by either HMGB1 or S100B, to promote neurogenesis in the subventricular zone of the adult mouse brain [121] adds to the notion that RAGE transduces neurotrophic effects playing an important role in nervous system repair.

As another example, deletion of *Rage* results in delayed regeneration of acutely injured skeletal muscles [11]. RAGE is not expressed in adult skeletal muscle tissue in normal physiological conditions and becomes expressed in muscle satellite cells early after acute injury in a ROS/NF-κB-dependent manner with further expression in myocytes (i.e., differentiated myoblasts) being sustained by the muscle-specific transcription factor, myogenin [11]. RAGE activity in myoblasts is sequentially stimulated by S100B and HMGB1 which are released from injured myofibers with distinct kinetics thus contributing to the expansion of the myoblast population and myogenic differentiation, respectively [11,56] (Fig. 3B). Besides, deletion of *Rage* results in delayed infiltration of injured muscle tissue with macrophages [11] (Fig. 3B), known to contribute to muscle regeneration. Thus, the absence of RAGE is detrimental twice to muscle regeneration due to delayed macrophage infiltration of injured tissue and delayed differentiation of activated satellite cells. However, a delayed, strong macrophage infiltration occurs in *Rage*$^{-/-}$ injured muscles likely in relation to delayed efferocytosis with potential exacerbation of detrimental effects of inflammation [11]. Lastly, compared with control muscles uninjured *Rage*$^{-/-}$ muscles exhibit elevated satellite cell numbers which further increase following injury as a result of elevated asymmetric division [11], which points to an important role of RAGE in muscle satellite cell homeostasis.

Interestingly, muscle satellite cells isolated from aged (>72-years old) human subjects show defective differentiation into fusion-competent myocytes and defective expression of RAGE, and transient transfection with *RAGE* restores their differentiation potential in part [122]. Also, at odds with the accepted tumorigenic role of RAGE signaling in most tumors, embryonal rhabdomyosarcomas show absent or reduced RAGE expression and no myogenic potential, and ectopic *RAGE* expression in embryonal rhabdomyosarcoma cell lines results in reduced tumor formation in vivo and a partial restoration of their myogenic potential in vitro [50]. Thus, it is possible that absent or reduced RAGE signaling in activated muscle satellite cells may concur to progression of embryonal rhabdomyosarcomas given that these latter originate from activated, proliferating satellite cells [123] and *Rage*$^{-/-}$ myoblasts exhibit a high proliferation rate, migration and invasiveness, and defective myogenic potential [11].

Moreover, HMGB1-induced RAGE signaling in cardiac fibroblasts results in the release of a number of factors responsible for cardiomyocyte migration and proliferation potentially leading to cardiac muscle regeneration [124]. Lastly, a role for RAGE in keratinocyte proliferation and migration and wound closure has been proposed [125].

11. Conclusions and unanswered questions

The pathogenic role of RAGE in chronic inflammation and epithelial cancer is undisputed. However, increasing evidence suggests that RAGE signaling is not restricted to these disease states. Also, the widespread expression of RAGE during development, in contrast to the repression of RAGE expression in the vast majority of cell types upon completion of development, points to an important, albeit as yet undisclosed role of this receptor during embryonic and early postnatal life. The fact that *Rage*$^{-/-}$ mice develop normally and show no overt phenotype does not exclude that RAGE signaling may play a regulatory role in developing tissues: absence of RAGE signaling in *Rage*$^{-/-}$ animal models might well be compensated by the activity of other receptors belonging to the same superfamily. Aside from the potential importance of RAGE during development, evidence begins to be offered that RAGE signaling participates in the resolution of inflammation and in tissue regeneration, especially in acutely injured tissues where re-expression of RAGE occurs. Also, absent or reduced RAGE signaling in activated muscle satellite cells may concur to rhabdomyosarcomagenesis, and absent or altered RAGE signaling results in lung fibrosis. Thus, RAGE is likely to represent one main factor intervening in the fine regulation of the balance between injury and repair: short-term (i.e., up to a few days) RAGE signaling triggered by low concentrations of its ligands may support tissue homeostasis and concur to tissue repair by promoting cell proliferation and differentiation, whereas long-term (i.e., weeks to months) RAGE signaling triggered by high concentrations of its ligands may be deleterious by amplifying and perpetuating the inflammatory response, excessively stimulating cell survival, proliferation and migration or causing a lethal accumulation of ROS. In this scenario, the ability of RAGE ligands to upregulate RAGE expression appears to play a fundamental role in the friend or foe behavior of this receptor in that the higher their local concentration in case of tissue injury the greater the number of expressed RAGE molecules and the probability of RAGE's foe behavior. Cell type identity (i.e., cell intrinsic properties) and the local environment also appear to condition the outcome of RAGE signaling. The

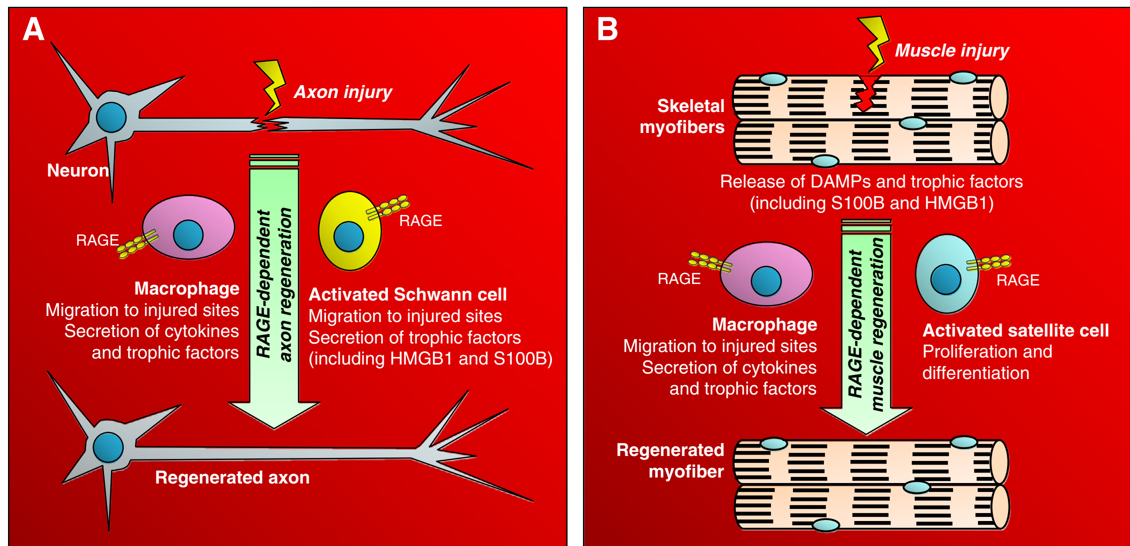

Fig. 3. RAGE promotes regeneration of acutely injured tissue. (A) Upon acute injury of peripheral nerves RAGE becomes expressed in activated Schwann cells and in infiltrating mononuclear phagocytes [118–120]. S100B and HMGB1 attract macrophages and promote Schwann cell migration to the damage site RAGE-dependently and stimulate both, macrophages and Schwann cells, which concur to nerve repair. (B) Upon acute skeletal muscle injury, RAGE engagement in activated satellite cells results in their proliferation and differentiation ultimately leading to regeneration. Under the action of S100B, which is sharply and abundantly released from myofibers on day 1 post-injury [56], RAGE signaling in satellite cells promotes proliferation via ERK1/2 and simultaneously activates the myogenic program via p38 MAPK [56]. Once sufficient amounts of the muscle-specific transcription factor, myogenin, have accumulated under the action of p38 MAPK (activated by HMGB1, which is released in high abundance from injured myofibers beginning at day 3 post-injury [56]), activated satellite cells stop proliferating and differentiate into fusion-competent myocytes that build up new myofibers and/or repair damaged myofibers [11]. Released S100B also attracts macrophages to the damage site RAGE-dependently (unpublished results); infiltrating macrophages concur to muscle regeneration.

complex nature of RAGE signaling calls for caution in the effort to block RAGE signaling for therapeutic purposes.

From the side of RAGE biology future work should address the following questions:

1. Do RAGE ligands compete with each other for RAGE binding?
2. Are there adaptor proteins other than diaphanous-1, TIRAP and MyD88 mediating RAGE signaling?
3. What is the role of RAGE in tissue development?
4. Does RAGE play a widespread role in tissue regeneration/repair?
5. Is RAGE expressed in embryonic and/or adult stem cells? Or is it expressed in activated stem cells only, perhaps in a tissue-specific manner?
6. Is RAGE-dependent promotion of authophagy beneficial during development and tissue regeneration?
7. Which transcription factors in addition to NF-κB, myogenin and PAX7 regulate RAGE expression?
8. Is a low-intensity RAGE signaling beneficial to cells?

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