RAGE

RAGE, the Receptor for Advanced Glycation Endproducts is a 35kD transmembrane receptor of the immunoglobulin super family which was first characterized in 1992 by Neeper et al.

It is also called “AGER”. Its name comes from its ability to bind advanced glycation endproducts (AGE), which include chiefly glycoproteins, the glycans of which have been modified non-enzymatically through the Maillard reaction. In view of its inflammatory function in innate immunity and its ability to detect a class of ligands through a common motif, RAGE is often referred to as a pattern recognition receptor. RAGE also has at least one other agonistic ligand: high mobility group protein B1 (HMGB1).

Interaction of RAGE with its ligands can promote tumor progression, invasion and angiogenesis.

RAGE Inhibitor

Genetic ablation of RAGE significantly abrogated neuroinflammation and BBB disruption in the murine SBI model. The inflammatory responses to surgical brain injury (SBI) were associated with infiltration of S100A9-expressing myeloid-derived cells into the brain. Local release of pro-inflammatory S100A9 was confirmed in patients following tumor resection. RAGE and S100A9 inhibitors were as effective as dexamethasone in attenuating neuroinflammation. However, unlike dexamethasone and S100A9 inhibitor, RAGE inhibition did not diminish the efficacy of anti-PD-1 immunotherapy in glioma-bearing mice. These observations confirm the role of the RAGE axis in surgically induced neuroinflammation and provide an alternative therapeutic option to dexamethasone in managing postoperative brain edema [1].

Although blocking RAGE signaling has been proposed as a potential anti-cancer strategy, functional contributions of RAGE expression in the tumor microenvironment (TME) has not been investigated in detail.

Evaluation of the effect of genetic depletion of RAGE in TME on the growth of gliomas. In both invasive and non-invasive glioma models, animal survival was prolonged in RAGE knockout (Ager-/-) mice. However, the improvement in survival in Ager-/- mice was not due to changes in tumor growth rate but rather to a reduction in tumor-associated inflammation. Furthermore, RAGE ablation in the TME abrogated angiogenesis by downregulating the expression of pro-angiogenic factors which prevented normal vessel formation, thereby generating a leaky vasculature. These alterations were most prominent in non-invasive gliomas, where the expression of VEGF and pro-inflammatory cytokines were also lower in tumor-associated macrophages (TAM) in Ager-/- mice. Interestingly, reconstitution of Ager-/- TAM with wild-type microglia or macrophages normalized tumor vascularity. This results establish that RAGE signaling in glioma-associated microglia and TAM drives angiogenesis, underscoring the complex role of RAGE and its ligands in gliomagenesis [2].

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2)
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