Inhibition of RAGE signaling through the intracellular delivery of inhibitor peptides by PEI cationization

The receptor for advanced glycation end products (RAGE) is a multi-ligand cell surface receptor and a member of the immunoglobulin superfamily. RAGE is involved in a wide range of inflammatory, degenerative and hyper-proliferative disorders which span over different organs by engaging diverse ligands, including advanced glycation end products, S100 family proteins, high-mobility group protein B1 (HMGB1) and amyloid β. We previously demonstrated that the cytoplasmic domain of RAGE is phosphorylated upon the binding of ligands, enabling the recruitment of 2 distinct pairs of adaptor proteins, Toll-interleukin 1 receptor domain-containing adaptor protein (TIRAP) and myeloid differentiation protein 88 (MyD88). This engagement allows the activation of downstream effector molecules, and thereby mediates a wide variety of cellular processes, such as inflammatory responses, apoptotic cell death, migration and cell growth. Therefore, inhibition of the binding of TIRAP to RAGE may abrogate intracellular signaling from ligand-activated RAGE.

In the present study, we developed inhibitor peptides for RAGE signaling (RAGE-I) by mimicking the phosphorylatable cytosolic domain of RAGE. RAGE-I was efficiently delivered into the cells by polyethylenimine (PEI) cationization. We demonstrated that RAGE-I specifically bound to TIRAP and abrogated the activation of Cdc42 induced by ligand-activated RAGE. Furthermore, we were able to reduce neuronal cell death induced by an excess amount of S100B and to inhibit the migration and invasion of glioma cells in vitro. Our results indicate that RAGE-I provides a powerful tool for therapeutics to block RAGE-mediated multiple signaling.

論文審査結果の要旨

本研究ではreceptor for advanced glycation end product (RAGE)に対する阻害作用を持ったペプチド（RAGE-I）を開発し、そのRAGEに対する阻害効果を検討した。RAGEの抑制作用は細胞内領域に対する阻害作用であった。RAGE-Iの細胞内へのデリバリーファフレーム、細胞内での作用等について重要な知見を得たものとして価値のある業績であると認める。

よって、本研究者は博士（医学）の学位を得る資格があると認める。

審査概要：

RAGE-Iの臨床における応用法などについて今後の課題であることが指摘された。また、RAGEを抑制する方法として、RAGEに対する抗体などの開発も課題になる可能性があることが指摘された。