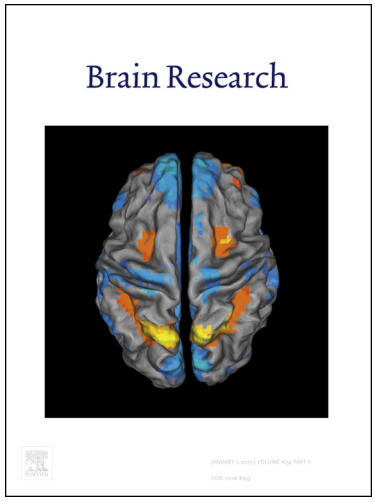

Research report

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Neuronal complement cascade drives bone cancer pain via C3R mediated microglial activation

Xiaoxia Huang [1#] Jinyuan Li [2#] Jin Xie[3] Yang Li [3] Yan Gao[3] Xiaohui Li[3] Xueqin Xu [3] Ruoshi Shi [3] Wanjun Yao [3] Changbin Ke [3*]

[1] Department of Nephrology, Taihe Hospital, Hubei University of Medicine, Shiyan City, 442000, Hubei Province, China.

[2] Department of Emergency, Taihe Hospital, Hubei University of Medicine, Shiyan City, 442000, Hubei Province, China.

[3] Institute of Anesthesiology & pain (IAP), PET-CT, Department of Anesthesiology, Taihe Hospital, Hubei University of Medicine, Shiyan City, 442000, Hubei Province, China.

*Correspondence to: Changbin Ke, Institute of Anesthesiology & pain (IAP), PET-CT, Department of Anesthesiology, Taihe Hospital, Hubei University of Medicine, Shiyan City, 442000, Hubei Province, China.

Tel: +86-719-8876616

E-mail address: changbinke-iap@taihehospital.com

[#] These authors contributed equally to this work.

Abstract

Activation of spinal cord microglia is crucial for the development of bone cancer pain (BCP). The essential signal between neuronal excitability and microglial activation is not fully understood. In the present study, carcinoma implantation into tibia was used to induce BCP and RNAi-lentivirus was injected into spinal cord to knock down C1, C2 or C3 of complement cascade. We showed that C1, C2 and C3 co-localized in the same neurons and increased in cancer-bearing rats along with microglial activation. Knocked down of C1, C2 or C3 inhibited microglial activation and prevented the development of cancer-induced bone pain. Intrathecal administration of either minocycline (an inhibitor of microglial activity) to inhibit the activation of microglia or compstatin (a C3-targeted complement inhibitor) to block the complement cascade reversed cancer induced bone pain. Further study indicated that neuronal complement promoted the activation of microglia via complement 3 receptor (C3R). In the in vitro experiments, the proliferation of microglia was enhanced by the activation product of C3 (iC3b), but was inhibited by compstatin. These results indicated that neuronal complement pathway promoted the activation of microglia via C3R and contributed to the development of BCP.

Keywords: bone cancer pain; complement pathway; microglia; complement receptor

Introduction

The majority of patients with metastatic bone cancer will experience moderate to severe pain. Bone pain is one of the most common types of chronic pain in these patients (Luger et al., 2001). Bone cancer pain (BCP) is usually progressive as the disease advances, and is particularly difficult to treat (Mundy and Others, 2002). The underlying mechanisms of cancer induced bone pain are poorly understood.

Microglia represent 5-10% of glia and constitute the resident macrophage population in the central nervous system (CNS). Under normal conditions, microglia are ramified and act as sensors for a range of stimuli that threaten physiological homeostasis. Once activated, microglia show a stereotypic, progressive series of changes in morphology, gene expression and function (Graeber, 2010). Multiple evidences indicate that activation of microglia is a key event in the pathogenesis