Microglia-targeting nanocarriers reduce hypothalamic inflammation in cancer-related cachexia

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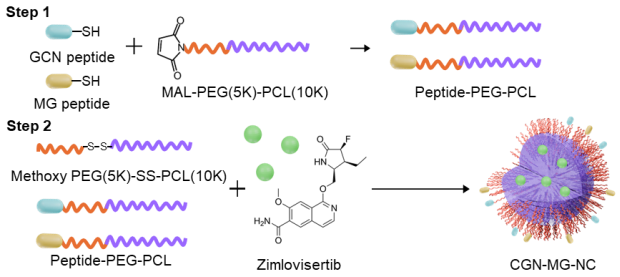
Introduction

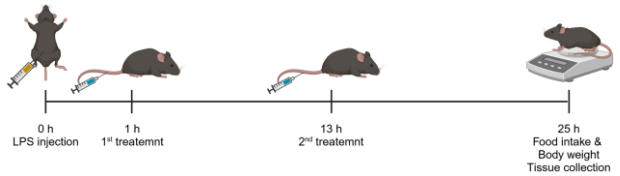
Hypothalamic inflammation plays a critical role in appetite dysregulation and metabolic dysfunction in cancer cachexia, a syndrome affecting up to 80% of advanced cancer patients. Pro-inflammatory cytokines, including TNF-α and IL-1β, activate microglia, exacerbating hypothalamic dysfunction. IRAK4 drives microglial activation, making it a promising therapeutic target. However, systemic delivery of IRAK4 inhibitors faces challenges due to the restrictive blood-brain barrier (BBB). This study presents polymeric nanocarriers engineered with dual-functional peptides: enhancing BBB penetration (CGN) and microglia targeting (MG). *In vivo* results demonstrate effective brain accumulation, targeted IRAK4 inhibitor delivery, and attenuation of hypothalamic inflammation, leading to improved appetite and weight maintenance in both LPS-induced acute neuroinflammation and cancer-related cachexia models.

Methods

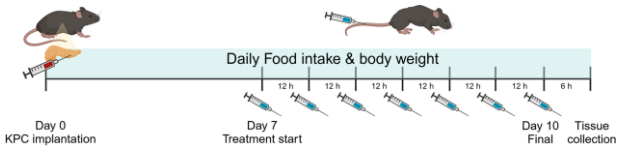
- ***Preparation of microglia-targeting nanocarrier (CGN-MG-NC)***



- ***LPS-induced acute neuroinflammation model***

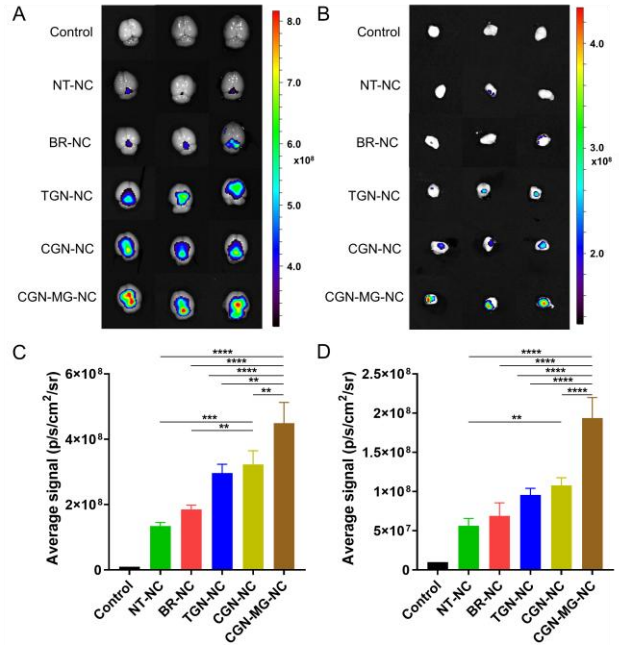


- ***Cancer-related cachexia model (orthotopic pancreatic cancer)***

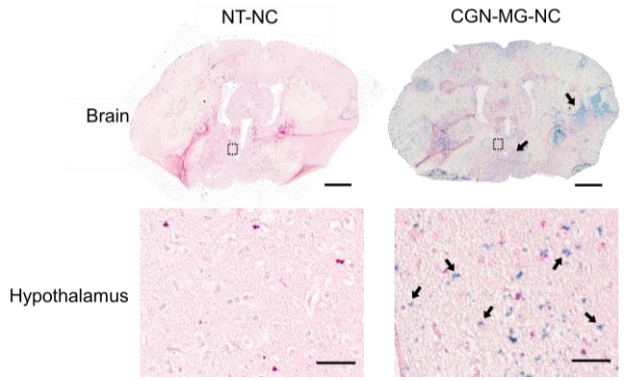


Results

- ***Brain and hypothalamus accumulation in LPS-induced acute neuroinflammation model***

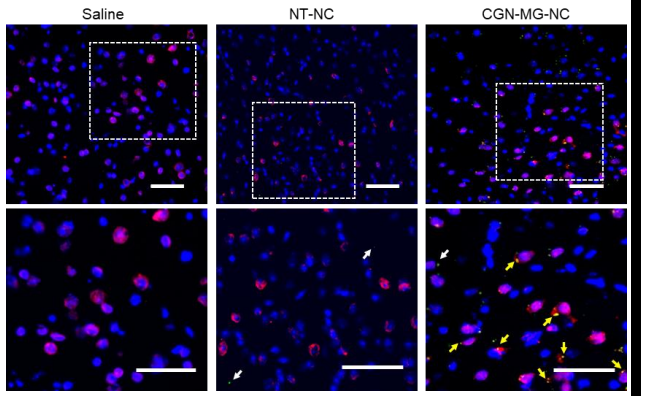


Brain (A,C) and hypothalamus (B,D) accumulation efficiency of DiR-loaded nanocarriers functionalized with different brain-targeting peptides in an LPS-induced neuroinflammation model.



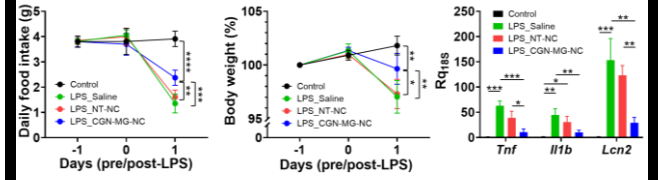
Prussian blue-stained histological sections of the whole brain and hypothalamus from mice injected with non-targeted nanocarriers (NT-NC) or nanocarriers functionalized with MG and CGN peptides (CGN-MG-NC), both loaded with iron oxide nanoparticles, were prepared to validate the fluorescence imaging results and address potential artifacts such as autofluorescence, which can lead to false positive signals.

- ***Interaction between CGN-MG-NC and microglia***



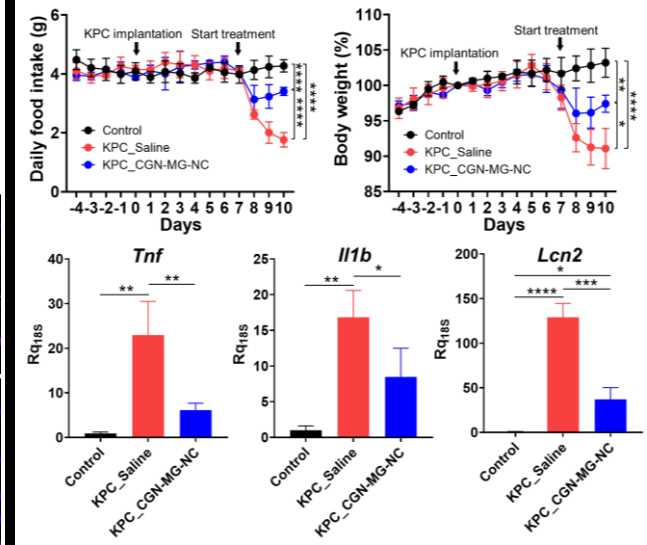
Representative fluorescence micrographs of hypothalamus cryosections from LPS-treated mice 6 h post-intravenous administration of saline, Coumarin 6-loaded NT-NC, or Coumarin 6-loaded CGN-MG-NC. Microglia were visualized using an anti-IBA1 antibody (red), nanocarriers were detected by Coumarin 6 fluorescence (green), and nuclei were stained with DAPI (blue).

- ***Therapeutic effect of ZLV-loaded CGN-MG-NC in LPS-induced acute neuroinflammation model***



Daily food intake and body weight of control mice and LPS-injected mice treated with saline (LPS_Saline), NT-NC (LPS_NT-NC), or CGN-MG-NC (LPS_CGN-MG-NC). Relative qRT-PCR quantification in hypothalami of pro-inflammatory cytokines (*Tnf*, *Il1b*, *Lcn2*) from each experimental group.

- ***Therapeutic efficacy of ZLV-loaded CGN-MG-NC in a Murine Model of Cancer-associated Cachexia***



Daily food intake and C) body weight of cancer-free mice injected with saline (control) and KPC mice treated with saline (KPC_Saline), or CGN-MG-NC (KPC_CGN-MG-NC). Relative qRT-PCR quantification of *Tnf*, *Il1b*, and *Lcn2* expression in the hypothalamus of each group.

Conclusions

This study presents a dual-targeting nanocarrier system (CGN-MG-NC) that effectively crosses the BBB and targets microglia, addressing key challenges in treating hypothalamic inflammation. This system achieves efficient delivery of ZLV to the hypothalamus through the combination of a BBB-penetrating peptide (CGN) and a microglia-targeting peptide (MG). The CGN-MG-NC system demonstrated superior targeting efficiency both *in vitro* and *in vivo* offering new possibilities for treating hypothalamic inflammation and provides a foundation for developing targeted therapies for neurological disorders.

Acknowledgements

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