**Neuroprotective effects of gold nanoclusters by manipulating microglial phenotypes**

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Introduction.

Neuroinflammation is one of the most significant features in a variety of central nervous system (CNS) disorders such as traumatic brain injury, stroke and many neurodegenerative diseases. Microglia are the resident macrophages in the CNS. The resting microglia can be activated by external stimuli and polarize towards either a neuron-destructive pro-inflammatory M1 phenotype or a neuron-regenerative M2 phenotype (1). M1 microglia can induce neuroinflammation and trigger astrocyte infiltration. Thus, modulating microglial polarization from M1 to M2 phenotype is a novel therapeutic approach for CNS repair and regeneration. Gold nanoclusters (AuNCs) have been intensively studied in bioimaging and drug delivery due to their biocompatibility and excellent optical properties. AuNCs of ultrasmall size (less than 3 nm) are able to penetrate the blood-brain barrier and accumulate in the brain in vivo. It has been reported that AuNCs can improve Parkinson’s disease treatment (2). However, the effects of AuNCs on microglia polarization and neuronal regeneration have not been fully understood.

Methods.

Ultrasmall gold nanoclusters were prepared and their physicochemical properties were characterized using UV-Vis, DLS and fluorescent detector. Their effect on microglia polarization, neuroinflammation, astrogliosis, and neurogenesis was examined using in vitro and ex vivo stroke models.

Results and discussion.

AuNCs synthesized showed good biocompatibility without affecting cellular metabolic activity. AuNCs were able to effectively suppress inflammation in the microglial cell line BV2 in vitro by inducing polarization towards the M2 phenotype. The mechanism includes reduced reactive oxygen species and reduced NF-kB signaling, and an improvement in cell survival coupled with enhanced autophagy and reduced apoptosis. In addition, we collected conditioned medium from AuNC-treated BV2 cells and found they can enhance neuronal differentiation in both the neuronal cell line N2a in vitro and in an ex vivo brain slice stroke model. We then treated the ex vivo stroke model with AuNCs and results showed reduced astrocyte activation and improved neurogenesis.

Conclusion.

Our data suggest AuNCs effectively inhibit the microglial inflammatory response by inducing M2 polarization phenotype. The change in polarization benefits neurogenesis while discouraging astrogliosis. We believe AuNCs may provide a promising treatment for neuroinflammation in CNS disorders.

**References**

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