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Tumor necrosis factor-alpha mediates hyperthermia-induced glioma invasiveness decreases☆

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Abstract

Background: Thermotherapy has already been proved effective for the treatment of various tumors, including glioma. This study was performed to determine whether tumor necrosis factor-alpha was involved in the regulation of this biological process. **Methods:** RT-PCR and immunocytochemistry were used to investigate the levels of tumor necrosis factor-alpha mRNA and heat shock factor-1 protein, respectively, in glioma cells. Radioimmunoassay was used to dynamically monitor contents of TNF-α in nutrient fluid for C6 cells after hyperthermia treatment. Crystal violet staining method was used to detect glioma invasiveness. **Results:** The most obvious increase of heat shock factor-1 protein and tumor necrosis factor -alpha mRNA in C6 cells were observed at 30 min and 60 min after hyperthermia, respectively. In addition, the radioactivity of tumor necrosis factor-alpha in C6 cells' culture fluid also reached peak at 120 min of hyperthermia. The glioma invasiveness decreases and the concentration of tumor necrosis factor-alpha reached the maximum at 120 min of hyperthermia. **Conclusion:** Our results showed that the hyperthermia-mediated glioma invasiveness decreases was due to accelerated release of tumor necrosis factor-alpha,

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which could cause the decreases of glioma invasiveness by promoting the release heat shock factor-1 from neurospongioma cells.

Keywords: Tumor necrosis factor-α; Heat shock factor-1; Thermotherapy; Glioma invasiveness

1. Introduction

Gliomas are characterized by an intense local invasiveness that limits surgical resection [1-2]. A new method for treating malignant glioma by thermotherapy has proven to be effective in patients with malignant glioma [3]. As one of the comprehensive treatment methods, thermotherapy has been gradually recognized and employed by clinicians. Accumulating evidence has revealed that it has an effective response and no side effects [4-7].

However, the detailed mechanisms of the thermotherapy have not yet been clarified. Thus, the pathophysiological mechanisms of thermotherapy-mediated action on the glioma need further investigation.

Our previous study has shown that thermotherapy might decrease the invasiveness of malignant glioma via tumor necrosis factor -alpha (TNF-α) pathway [8]. However, thermotherapy could decrease the glioma invasiveness markedly independent of thermotherapy pretreatment. The mechanism remains unknown.

The thermotherapy has the property of inducing the HSP70 expression in most cell types [9]. Heat shock factor-1 (HSF1) combines with the heat shock element (HSE) in the promoters of the gene encoding HSP70 to promote the HSP70 transcription and expression [10]. And the TNF-α gene near the promoter region has many incomplete HSE sequences [11]. Previous study demonstrated that TNF-α and thermotherapy could decrease the invasiveness of glioma [12]. Consequently, we hypothesize that activated HSF1 could affect the transcription of both TNF-α and HSP70 through combining with the HSE sequence of HSP70 and TNF-α, and finally decrease the glioma invasiveness.

In order to test this hypothesis, in present study, we investigated whether thermotherapy could induce the expression of TNF-α and HSF1 in glioma cells with Western blotting and RT-PCR methods. In addition, we also studied the effect of TNF-α on the glioma invasiveness.

2. Materials and methods

2.1. Cell culture and TNF-α radioactivity

Rat C6 glioma cells were cultured to reach 80%