

## Pharmacological inhibition of the Hsf1 pathway as a potential strategy for treating glioblastoma

To overcome stress-induced protein imbalance, cells have evolved a protective mechanism called the heat shock response (HSR). In mammals, this response is primarily regulated by heat shock transcription factor 1 (Hsf1). Under stress conditions, Hsf1 activates genes involved in various cellular processes, including protein folding and degradation, membrane organisation, chromatin regulation, signalling pathways, and apoptosis control, all of which enhance cell survival. Beyond its role in the HSR, Hsf1 is also associated with ageing and various pathophysiological conditions, including cancer, where it is often found overactivated. Importantly, Hsf1 remains minimally active in healthy cells under normal conditions, suggesting that selective Hsf1 inhibitors could potentially target cancer cells while sparing healthy tissues.

Glioblastoma represents an aggressive brain tumour with a particularly poor prognosis. It is responsible for the majority of brain tumour-related deaths among children and adults. Low survival rate classifies glioblastoma as a lethal disease. The current standard treatment, unchanged for nearly 20 years, consists of surgery followed by radiotherapy and temozolomide (TMZ) chemotherapy. First-line therapy only postpones the progression of glioblastoma, with a median progression-free survival of 7 to 10 months. Given these poor outcomes, there is an urgent medical need to develop novel therapeutic approaches for glioblastoma treatment. In our work, we explore the efficacy of existing Hsf1 pathway inhibitors as both monotherapy and combination therapy (with TMZ and/or radiation) using adult glioblastoma cell culture models. Our findings reveal that Hsf1 inhibition significantly reduces proliferation in adult glioblastoma cell lines, including those resistant to TMZ. Notably, the combination of Hsf1 pathway inhibition and TMZ treatment exhibits an additive effect, potentially enhancing therapeutic impact.

References: Kmiecik SW et al. 2020, 2022; Le Rhun E et al. 2019; Omuro A et al. 2013; Ou A 2020; Dai C et al. 2007; Im CN et al. 2017.

### Research type

Translational research

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