Hüpotermia poolt reguleeritud transkriptsiooni faktorite tuvastamine

Terapeutiline hüpotermia (32C) on üks lootustandvamaid akuutse isheemilise insuldi ravimeetodeid, kuid hüpotermia kaitsva efekti taga olevad molekulaarsed mehhanismid ei ole veel teada. Seni on kehatemperatuuri langetamist vaadeldud kui tegurit, mis vähendab metabolismi ja hapnikutarbimist (Erecinska et al., 2003; Yenari ja Han, 2012). Eskla et al 2018 näitab, et hüpotermia mõjutab enam kui 3000 geeni ekspressiooni. Samas kui hüpoksia (madal hapniku kontsentratsioon) mõjutab vähem kui 1000 geeni ekspressiooni. Hüpoksia efekt on vahendatud HIF1 (*hypoxia indicible factor* 1) transkriptsiooni faktori poolt (Semenza ja Wang, 1992; Forsythe et al., 1996). Meie viimased tulemused viitavad sellele, et eksisteerivad hüpotermia spetsiifilised transkriptsiooni faktorid (HRFs), mis on seotud hüpotermiale iseloomuliku vastusega. Projekti eesmärk ongi tuvastada hüpotermia poolt reguleeritud transkriptsiooni faktorid. Saadud tulemused võimaldavad paremini ennustada ravimimärklaud kandidaate ja võivad viia täiesti uudse lähenemisviisini isheemia reperfusiooni kahjustuse ravis.

Transcriptional factors of hypothermia response

Over the past 15 years, therapeutic hypothermia (32C) has emerged as one of the most promising neuroprotective interventions. Previous studies have shown that lowering body temperature (therapeutic hypothermia) can have remarkable effects on protecting the brain from ischaemia reperfusion injury. The mechanisms that underlie the protective effects of cooling are only partially understood. To date, the protective effects of hypothermia have been associated with its suppressive effect (Erecinska et al., 2003; Yenari ja Han, 2012). However, basic research by our group suggests that hypothermia affects the expression of thousands of genes. More than 3000 genes are differentially expressed in response to hypothermia versus less than 1000 in response to hypoxia (Eskla et al., 2018). The effects of hypoxia are mediated by HIF1 (hypoxia inducible factor) signalling cascade (Semenza and Wang, 1992; Forsythe et al., 1996). However, there remains a fundamental knowledge gap regarding the regulatory factors that mediate hypothermia response, which prevents the development of novel agents against ischemia reperfusion injury. We have evidence that there exists hypothermia responsive factors (HRFs), coordinating cellular response to hypothermia. The current project aims to identify those HRFs. This in turn will allow better prediction of drug target candidates and may lead to new approaches for the treatment of ischemia reperfusion injury.

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