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Dexamethasone Treatment Deregulates Proteoglycans Expression in Normal Brain Tissue

Authors : A. Y. Tsidulko, T. M. Pankova, E. V. Grigorieva

Abstract : High-grade gliomas are the most frequent and most aggressive brain tumors which are characterized by active invasion of tumor cells into the surrounding brain tissue, where the extracellular matrix (ECM) plays a crucial role. Disruption of ECM can be involved in anticancer drugs effectiveness, side-effects and also in tumor relapses. The anti-inflammatory agent dexamethasone is a common drug used during high-grade glioma treatment for alleviating cerebral edema. Although dexamethasone is widely used in the clinic, its effects on normal brain tissue ECM remain poorly investigated. It is known that proteoglycans (PGs) are a major component of the extracellular matrix in the central nervous system. In our work, we studied the effects of dexamethasone on the ECM proteoglycans (syndecan-1, glypican-1, perlecan, versican, brevican, NG2, decorin, biglican, lumican) using RT-PCR in the experimental animal model. It was shown that proteoglycans in rat brain have age-specific expression patterns. In early post-natal rat brain (8 days old rat pups) overall PGs expression was quite high and mainly expressed PGs were biglycan, decorin, and syndecan-1. The overall transcriptional activity of PGs in adult rat brain is 1.5-fold decreased compared to post-natal brain. The expression pattern was changed as well with biglycan, decorin, syndecan-1, glypican-1 and brevican becoming almost equally expressed. PGs expression patterns create a specific tissue microenvironment that differs in developing and adult brain. Dexamethasone regimen close to the one used in the clinic during high-grade glioma treatment significantly affects proteoglycans expression. It was shown that overall PGs transcription activity is 1.5-2-folds increased after dexamethasone treatment. The most up-regulated PGs were biglycan, decorin, and lumican. The PGs expression pattern in adult brain changed after treatment becoming quite close to the expression pattern in developing brain. It is known that microenvironment in developing tissues promotes cells proliferation while in adult tissues proliferation is usually suppressed. The changes occurring in the adult brain after dexamethasone treatment may lead to re-activation of cell proliferation due to signals from changed microenvironment. Taken together obtained data show that dexamethasone treatment significantly affects the normal brain ECM, creating the appropriate microenvironment for tumor cells proliferation and thus can reduce the effectiveness of anticancer treatment and promote tumor relapses. This work has been supported by a Russian Science Foundation (RSF Grant 16-15-10243)

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