The cytoprotective effect of biglycan core protein involves TLR4 signaling in primary cardiomyocytes

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Native biglycan consisting of a core protein and two glycosaminoglycan (GAG) chains has been shown to protect cardiomyocytes against simulated ischemia/reperfusion injury (SI/R) however, the mechanism of action is not clearly understood. In this study, we investigated which structural component of biglycan (core protein or GAG chains) is responsible for its cytoprotective effect and further explored molecular mechanisms responsible for this protection.

Primary neonatal cardiomyocytes isolated from Wistar rats were treated with glycanated biglycan, recombinant human biglycan core protein (rhBGNc), and the GAG components dermatan sulfate and chondroitin sulfate, and were subjected to SI/R followed by viability measurement. Glycanated biglycan and rhBGNc reduced dose-dependently SI/R-induced cell death, however, the GAG chains did not show protection. We have also demonstrated that pharmacological blockade of Toll-like receptor 4 (TLR4) signaling or its downstream mediators (IRAK1/4, JNK and p38 MAP kinases) abolished the cytoprotective effect of rhBGNc against SI/R injury. Pretreatment of cardiomyocytes with rhBGNc increased Akt phosphorylation and NO production without having a significant effect on phosphorylation of ERK1/2, STAT3, and production of superoxide. Blockade of NO synthesis abolished the cytoprotective effect of rhBGNc.

We conclude that the core protein of biglycan is able to protect cardiomyocytes from SI/R injury via TLR4-dependent signal mechanisms involving activation of JNK and p38 MAP kinases and increased NO production.