

The Antioxidative Role of Cytoglobin in Podocytes: Implications for a Role in Chronic Kidney Disease

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Abstract

Aims: Cytoglobin (CYGB) is a member of the mammalian globin family of respiratory proteins. Despite extensive research efforts, its physiological role remains largely unknown, but potential functions include reactive oxygen species (ROS) detoxification and signaling. Accumulating evidence suggests that ROS play a crucial role in podocyte detachment and apoptosis during diabetic kidney disease. This study aimed to explore the potential antioxidative renal role of CYGB both *in vivo* and *in vitro*.

Results: Using a Cygb-deficient mouse model, we demonstrate a Cygb-dependent reduction in renal function, coinciding with a reduced number of podocytes. To specifically assess the putative antioxidative function of CYGB in podocytes, we first confirmed high endogenous CYGB expression levels in two human podocyte cell lines and subsequently generated short hairpin RNA-mediated stable CYGB knockdown podocyte models. CYGB-deficient podocytes displayed increased cell death and accumulation of ROS as assessed by 2'7'-dichlorodihydrofluorescein diacetate assays and the redox-sensitive probe roGFP2-Orp1. CYGB-deficient cells also exhibited an impaired cellular bioenergetic status. Consistently, analysis of the CYGB-dependent transcriptome identified dysregulation of multiple genes involved in redox balance, apoptosis, as well as in chronic kidney disease (CKD). Finally, genome-wide association studies and expression studies in nephropathy biopsies indicate an association of CYGB with CKD. **Innovation:** This study demonstrates a podocyte-related renal role of Cygb, confirms abundant CYGB expression in human podocyte cell lines, and describes for the first time an association between CYGB and CKD. **Conclusion:** Our results provide evidence for an antioxidative role of CYGB in podocytes.

Keywords: diabetic nephropathy; globin; oxidative stress; reactive oxygen species.