Beatrix Fuchs
Dr. sc. hum

Comparative study in various model organisms regarding the effect of the loss of glyoxalase 1

Fach/Einrichtung: Innere Medizin
Doktorvater: Prof. Dr. med. Dr. hc. Peter Paul Nawroth

The generation of methylglyoxal-derived advanced glycation end products plays an important role in the development of diabetes and late complications. Detoxification of methylglyoxal by glyoxalase 1 is therefore a key element in the context of dicarbonyl-induced damage in patients suffering from diabetes. This assumption was based on findings in simple organisms such as *S. cerevisiae* and *C. elegans*. Recent findings in *D. melanogaster*, zebrafish and murine cell lines indicate that glyoxalase 1 is less significant than in higher organisms. It has been shown that the loss of glyoxalase 1 is compensated by increased aldo-keto-reductase and aldehyde dehydrogenase activity. Therefore, the major aim of this study was to address potential differences in various organisms regarding their dependency on glyoxalase 1 and the determination of physiological consequences of the loss of glyoxalase 1. Glyoxalase 1-deficient *S. cerevisiae* and *C. elegans* accumulate more methylglyoxal, the proliferation rate and egg laying rate is decreased and they are sensitive to cellular stress induced by other toxins. In zebrafish, MG is mildly elevated, but interestingly they show a decreased sensitivity in part towards toxins compared to wild-type animals. Furthermore, in three glyoxalase 1-deficient murine cell lines, methylglyoxal is not elevated and they tolerate xenobiotics such as toxins or UV-C radiation in a cell and toxin-specific manner possibly through an up-regulation of compensatory enzymes. *In vivo* data reveal furthermore the up-regulation of antioxidant enzymes when glyoxalase is absent, subsequently correlating with an elevated natural survival in $GLO1^{-/-}$ mice. Complex organisms are less dependent on glyoxalase 1 and less prone to damage despite the loss of glyoxalase 1 than expected. In glyoxalase 1-deficient cells and mice, the phenotype even shows a protective character. Therefore, the data from this study suggests that the loss of glyoxalase 1 has less severe effects on complex organisms than expected and might even lead to an advantage on survival through the activation of antioxidant enzymes. The clinical relevance of glyoxalase 1 and possible compensatory pathways on the development of late complications in different organs has to be addressed in future studies.