ID 07.3

Role of Phosphatase and Tensin homolog (Pten) in Insulin mediated DNA damage

Ezgi Eyluel Bankoglu[1], Geema Kodandaraman[1], Andreas Geier[2] and Helga Stopper[1]

[1] Institute of Pharmacology and Toxicology, University of Wuerzburg, V ersbacher Str. [9], Wuerzburg, Germany
[2] Division of Hepatology, Department of Medicine II, University Hospital of Wuerzburg, Wuerzburg, Germany
**stopper@toxi.uni-wuerzburg.de*

Endogenous substances such as hormones may cause DNA damage when present at pathophysiological levels. For example, hyperinsulinemia is a characteristic of early type 2 diabetes mellitus, resulting from the oversecretion of insulin. The association between elevated insulin levels and cancer is well-known, however, the precise role of insulin in cancer development is far from clear. In this study, our focus was the role of Phosphate and Tensin homolog (Pten), a tumor suppressor dual phosphatase that negatively regulates PI3K/AKT signaling downstream after insulin activation. For further elucidation Phosphatase and Tensin homolog (Pten), a tumor suppressor phosphatase that plays a role in insulin signaling by negative regulation of PI3K/AKT and its downstream targets, was investigated here.

We used dihydroethidium staining to measure reactive oxygen species (ROS) formation and analyzed DNA damage using comet assay, micronucleus test, and an antibody staining against phosphorylated H2Ax. Our findings showed an increase in insulin-mediated ROS formation and as a result, elevated DNA damage by using a pharmacological Pten inhibitor in a liver cell line. Furthermore, the knockdown of Pten in a mouse model increased oxidative stress and yielded increased DNA double-strand breaks in the liver tissue.

We conclude that Pten is involved in oxidative stress and genomic damage induction in vitro and that this may also explain the in vivo observations. This further supports the hypothesis that the PI3K/AKT pathway is responsible for the damaging effects of high levels of insulin.

Keywords:
Insulin, DNA damage, oxidative stress, Pten, insulin signalling.