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Effects of Unfolded Protein Accumulation on the Redox State of the Endoplasmic Reticulum

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Abstract. Alpha1-antitrypsine (AAT) is a serum protein synthesized by the liver cells. 4% of the humans is carrying its folding deficient mutant, the Z form (or PiZ). This protein can neither be folded, nor degraded by the proteasome although it is partially transported back to the cytoplasm. Only 15% of PiZ is released into the bloodstream. The remaining proteins accumulate mainly in the endoplasmic reticulum forming insoluble aggregates inside the lumen. Protein aggregates are also present in the cytoplasm. The resulting AAT deficiency is a well-characterized disease causing emphysema, hepatic injury, liver cirrhosis and a higher risk for hepatocellular carcinoma in human patients.

Our animal model, the PiZ transgenic mouse is expressing the Z form of AAT protein in its liver, having similar symptoms than human patients have. The only difference of the animal model is that transgenic mice do not develop emphysema, because they have the normal, mouse AAT gene also.

In the hepatic endoplasmic reticulum of AAT mice we found an elevated level of protein thiols, and an elevation in both the GSH/GSSG ratio and total GSH. There were no significant changes in the levels of the most important lumenal stress proteins, like Grp94, Grp78, PDI or calnexin. In contrast, the cytoplasm did not show any marked change in the redox state, but we found a marked induction of Hsp70 as well as Hsp90. The higher lipid peroxidation found in red blood cells suggests a higher oxidative damage regarding the whole organism.

Our results are reminiscent to the redox changes after the onset of diabetes in STZ-mice showing a gross disturbance of folding homeostasis in the endoplasmic reticulum. Retrograde transport of unfolded proteins and their accumulation in the cytoplasm may explain the induction of major heat shock proteins in this cellular compartment. Mutant AAT, which can neither be folded nor degraded may remain bound to the chaperones causing a chaperone overload and a relative shortage of chaperones. These phenomena may lead to a general defect in protein folding of the affected livers, and may be a clue to the higher rate of hepatic tumors in PiZ mice.

Introduction

Links between redox changes and protein folding defects in various diseases receive a revived attention in these days. In diabetes the common change toward a more oxidizing state regarding the whole organism is accompanied with a shift toward a reducing state in the lumen of the endoplasmic reticulum [1]. It is known that oxidative stress is one of the reasons of the pathogenesis in Parkinson's disease, since oxidized alpha-synuclein is more prone for aggregation than the unmodified one [2]. Several pieces of evidence show that in Alzheimer's disease the neurotoxicity of the _-amyloid is related to the oxidative state of a methionine [3]. Although we have a plenty of data about the oxidative stress as a consequence of various pathological states, the changes of redox protein folding are not