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Superoxide Dismutase 1 and Cataract

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Superoxide Dismutase 1 and Cataract

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Abstract

Light and oxygen generate harmful reactive oxygen species (ROS) in the lens, causing biochemical changes that gradually disarrange the lens fibres resulting in light scattering and loss of transparency. In the healthy eye, this chronic exposure to oxidative stress may lead to age-related cataract. However, there are also some conditions that accelerate cataract formation, such as diabetes mellitus, in which increased glucose levels may contribute to increased generation of ROS.

The superoxide dismutases (SOD) participate in the defence against ROS by catalysing the dismutation of superoxide radicals. The main SOD isoenzyme in the lens is copper-zinc superoxide dismutase (SOD1). The aim of this thesis was to explore if this antioxidant enzyme is important for the protection against age-related and diabetes-induced cataract development.

Lenses from wild-type mice and mice lacking SOD1 were incubated in high levels of glucose *in vitro* and their transparency and damage evaluated daily. Also, the impact of nitric oxide was studied by adding a nitric oxide synthase inhibitor. Furthermore, *in vivo* cataract formation in relation to the oxidative status of the lens was evaluated in streptozotocin-induced diabetic mice as well as in non-diabetic mice of both genotypes. Finally, the spontaneous age-related cataract development was studied in both genotypes.

In vitro, the SOD1 null lenses showed increased levels of superoxide radicals and developed dense nuclear lens opacities upon exposure to high levels of glucose. They also showed increased lens leakage of lactate dehydrogenase, reduced transport function across cell membranes, and increased water contents. However, the lens damage and cataract formation were eliminated when the synthesis of nitric oxide was inhibited. This indicates that both superoxide and nitric oxide have important roles in glucose-induced cataract development possibly through their reaction with each other which generates the highly reactive peroxynitrite.

In vivo, both the SOD1 null and the wild-type mice showed cortical cataract changes after 8 weeks of diabetes, although the SOD1 null mice showed a more pronounced cataract formation than the wild-type mice in relation to the level of hyperglycaemia. As cataract formation was accentuated the lenses showed diminishing levels of glutathione but increasing amounts of protein carbonyls, suggesting a reduced lens antioxidant capacity as well as increased lens protein oxidation. Non-diabetic young (18 weeks of age) SOD1 null mice did not show any signs of cataract. At 1 year of age they had developed some cortical lens obscurity as compared to the wild-type mice which did not show equivalent changes until 2 years of age.

The results presented in this thesis show that SOD1 null mice are more prone to develop diabetes-induced and age-related cataract than wild-type mice. The findings thus further endorse the importance of oxidative stress as a contributor to cataract development and indicate that both superoxide and nitric oxide may be damaging to the lens. I therefore conclude that the antioxidant enzyme SOD1 is important for the protection against cataract.

Keywords: cataract, diabetes mellitus, nitric oxide, SOD1 null mice, superoxide, superoxide dismutase

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