Mechanisms of retina degeneration: the role of rhodopsin synthesis in photoreceptor survival

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Rod photoreceptor degeneration is mostly studied in animal models in which the opsin protein has been ablated, overexpressed or mutated. Instead, we have generated a homozygous bovine rhodopsin knock-in mouse (KI/KI) that produces only 15% opsin compared to control mice. Although this expression level remains stable during the first four months, we observe a progressive photoreceptor loss which is almost complete at six months. This rate of photoreceptor degeneration is slower than that of homozygous rhodopsin knock-out mice (KO/KO), which is complete within three months. Cross-breeding generated a hemizygous KI/KO model in which the rate of photoreceptor cell degeneration is slower than in the null mutant, and degeneration is complete at approximately four months. EM analysis showed that, in contrast to the KO/KO mice, the KI/KI animals develop relatively normal outer segments at two weeks. We conclude that: (1) An opsin level of approximately 10% meets the requirements for outer segment formation of rod photoreceptors; (2) The rate of photoreceptor degeneration is inversely correlated to the expression level of opsin; (3) During the degeneration process the retina tries to compensate for the loss of photoreceptor cells by upregulating opsin expression in the remaining cells. The latter concept constitutes a hitherto unknown aspect of the retina degeneration process.

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