Identification of Hypoxia-related Biomarkers in Dry age-related Macular Degeneration

Summary / Zusammenfassung

1. Background and rational

Dry age related macular degeneration (dry AMD) is characterized by loss of RPE (retinal pigment epithelium) and photoreceptor cells leading to severe visual impairment and eventually legal blindness in the elderly. Although dry AMD is highly prevalent with up to 25% of individuals being affected above the age of 80 years, a therapy for dry AMD is still an unmet medical need. During normal ageing, tissues at the posterior pole of the human eye undergo several changes including accumulation of autofluorescent material in RPE cells, formation and accumulation of Drusen deposits, thickening of Bruch’s membrane and reduction of choroidal blood flow. These changes reduce oxygen availability in RPE and photoreceptor cells, and may lead to mild but chronic tissue hypoxia imposing cellular stress. Since photoreceptors have an extraordinarily high energy demand, and maintenance of photoreceptor homeostasis and function requires sufficient tissue oxygenation, chronic hypoxia may lead to disease development when crossing critical threshold levels. Thus, hypoxia may be a major determinant of AMD.

This is supported by preliminary data showing that mice with chronically activated hypoxia-like response in rod photoreceptors develop a late onset, slowly progressing and age dependent retinal degeneration, leading to a reduction of the outer nuclear layer thickness by about 75% at one year of age. The chronic hypoxia-like response in the mouse retina was achieved by inactivation of the Vhl gene specifically in rod photoreceptors (VhlΔ-rod). VhlΔ-rod mice activated their hypoxia-inducible transcription factors (HIFs) and induced expression of hypoxia responsive genes such as vascular endothelial growth factor (Vegf) and others. Additional upregulation of several genes of the complement system may be of special significance since genetic variants of genes of the complement system and anomalous function of the complement pathway have been identified as key players in the development of AMD. Importantly, rod-specific inactivation of hypoxia-inducible transcription factor 1 alpha (Hif1α) in addition to Vhl not only prevented induction of complement genes and of many hypoxia responsive factors, but also protected against retinal degeneration and preserved tissue integrity. We hypothesize that reduced tissue oxygenation may be a major cause of photoreceptor cell loss in AMD and that retinal degeneration might be prevented by modulating hypoxic response in photoreceptors of affected patients.

2. Short outline of project

We propose to identify biomarkers associated with a hypoxic response in dry AMD in human eyes. In detail, we will first use a general proteomics approach to identify potential biomarkers in mice. The vitreous proteome of VhlΔ-rod mice will be compared to the vitreous proteome of control mice lacking Hif1α in addition to Vhl in rod photoreceptors. Identified candidate proteins will be tested individually for verification using appropriate antibodies.

In parallel, we will collect vitreous and anterior chamber biopsies from patients affected by ARM or established dry AMD, and respective control groups (see below). In a targeted approach, these biopsies will be tested for the presence of human orthologs of differentially regulated mouse proteins identified as described above. Biopsies will be collected from affected patients and control subjects after having obtained informed consent. Diagnosis of ARM or dry AMD will be established by medical retinal specialists. Inclusion and exclusion criteria are listed below.

If specific biomarkers are identified, they could be used to identify patients who may benefit from new treatment approaches specifically targeting retinal hypoxia. Such an approach is currently being developed in pre-clinical experiments. Due to the high prevalence of dry AMD, a rapid
translation to clinical studies is planned.
Weitere Informationen unter http://www.hochschulmedizin.uzh.ch/projekte/znz.html

Project Leadership and Contacts / Projektleitung und Kontakte
Lab Research: Prof. Dr. Christian Grimm, PhD (Project Leader) cgrimm@opht.uzh.ch
Clinical Research: Dr. Dr. Daniel Barthelmes, MD PhD (Project Leader) daniel.barthelmes@usz.ch

Other Links to external Webpages / Andere Links zu externen Webseiten
http://www.hochschulmedizin.uzh.ch/projekte/znz.html

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