Metabolomics for the discovery of new therapeutic approach and personalized medicine: the case of exudative Age-related Macular Degeneration.

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1. Introduction

Age-related Macular Degeneration (AMD) is the leading cause of blindness among the elderly population in developed countries. 90% of all vision loss due to AMD result from the exudative form, which is characterized by choroidal neovascularization (CNV)[1]. Treatment is mainly based on regular intra-vitreal injection of anti-VEGF to stabilize CNV. Nevertheless, the comprehensive understanding of the pathogenesis and the evolution of this complex multi-factorial disease remain incomplete. Moreover, due to the long-term disease chronicity and to some resistance to treatment, a continuous follow-up of patients, a personalization of treatment and the discovery of new therapeutic approaches are mandatory.

2. Approach

Metabolomics provides a unique and direct vision of the functional outcome of organism's activities that could be correlated to pathologies and/or treatment administration. The links between metabolic changes, patient phenotypes, physiological and/or pathological status and treatment are now well established and have opened a new area for the application of metabolomics in target identification and in personalized medicine[2]. In order to study CNV occurrence and evolution and to get novel and innovative insights into AMD, we decided to apply a NMR-based metabolomics approach on both clinical and pre-clinical models (a murine laser-induced CNV model and patient's cohorts). Sera samples coming from 97 healthy volunteers and 95 exudative AMD patients have been collected during ophthalmic exams at the CHU of Liège. Patients were separated into bleeder AMD group (patients with AMD in bleeding phase) and non-bleeder AMD group (patients with non-bleeding AMD). The CNV mice model mimics the exudative phase of AMD and allows the dynamic study of CNV evolution.

3. Results

Metabolomics approach applied to the human cohorts led to a separation between healthy and non-healthy patients as well as between bleeder and non-bleeder groups. Few metabolites are linked to this discrimination. Among those, lactate and lipoproteins profile emerge as the main key metabolites. Higher lactate level was detected in patients during bleeding phase while low-density lipoproteins (LDL) and very low density lipoproteins (VLDL) levels seems to be increased in AMD patients.

In the mice model, metabolomics profiles varied according to CNV occurrence. In this case again, lactate and lipoproteins profile were related to this evolution.

Pharmacological normalization of lactate levels by blocking pyruvate deshydrogenase kinase (PDK) or by modulating LDH activity in the mice model, inhibits CNV formation, Moreover, CNV inhibition by anti-angiogenic drugs led also to a reduction of systemic lactate level.

4. Discussion

Mechanistically, we have demonstrated through a combination of NMR measurements (both 1D and 2D), pharmacological modulation and molecular biology approaches, that lactate, initially produced in the eyes then at the systemic level, plays a critical role in the onset of the inflammatory and angiogenic phases. Targeting lactate level by a modulation of PDK appears to be an alternative to intra-vitreal injection of anti-VEGF and a putative new therapeutic approach to reduce CNV progression.

Moreover, changes in lipoproteins profile could also be correlated with AMD and CNV progression and then could be a nice marker of the progression of the pathology.

A longitudinal patients follow-up during anti-VEGF treatment is currently running while MS-based targeted metabolomics and lipidomics studies are planned to validate and deepen our first findings.

Altogether, we demonstrated that metabolomics is a suitable tool to deep insight into pathologies and to identify some metabolites as functional, traceable and targetable molecules that open new perspectives for optimizing and personalizing treatment and patient follow-up.

References

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