NMR-based metabolomics study of Age-related Macular Degeneration (AMD): patient follow-up and new target discovery

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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 of this pathology, which is characterized by choroidal neovascularization (CNV). Currently, diagnosis of AMD relies on ophthalmologic exams and treatments of the exudative form are based on the use of anti-angiogenic drug targeting vascular endothelial growth factors (VEGF). Despite these advances, several clinical challenges have to be overcome, among these the choice of adapted therapeutic treatments and the identification of biomarkers as indicator of patient stratification, disease progression and treatment responses are essential.

2. Approach

In this study, we decide to apply a NMR-based metabolomics approach on a cohort of AMD patients and on a laser-induced murine choroidal neovascularization experimental (CNV) model that mimics the development of the angiogenesis phase of the pathology(1).

Sera from controls and exudative AMD patients (in active and non active phases of the pathology) and from induced and non-induced mice have been collected and submitted to a metabolomics study, using a multivariate approach.

3. Results and discussion

Metabolomics approach does not allow a complete differentiation between control and AMD patients after PCA, PLS-DA and O-PLS_DA analysis. This is probably due to the high variability in patients in terms of AMD stages and phases, treatments and fasting status. However, when we focused on AMD patient, a separation between active and non-active phases could be highlighted.

In the most controlled mice model, a separation occurs between laser-induced and control mice 5 to 7 days after induction, concomitantly with CNV formation (Figure 1). Moreover, an interesting point is that the discriminating spectral zones are the same in the human study and in the mice model, leading to the emergence of different putative biomarkers of the active phase of exudative AMD. Among those, lactate and lipoprotein profile are of particular interest to better understand the development of CNV. These results were confirmed by a quantification of lactate and by an evaluation of lipoproteins profiles.

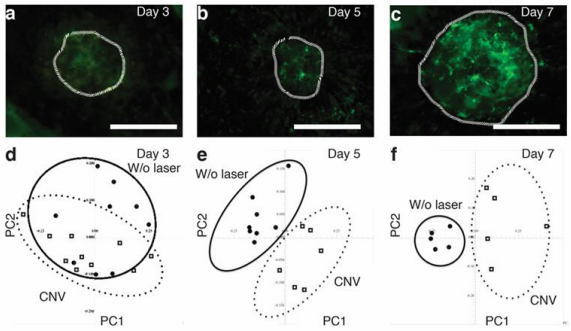

Figure 1. FITC-dextran–labeled flat-mounted choroid observed at day 3 (a), 5 (b) or 7 (c) after laser induction. (d-f) Score plot resulting PCA of NMR data collected.

Mechanistically, we demonstrated that lactate, produced locally and by inflammatory cells, plays a critical role in the onset of the inflammatory and angiogenic phases and could be correlated with the CNV development. Modulation of blood lactate level trough the inhibition of pyruvate dehydrogenase kinase (PDK) led to a reduction of CNV (as efficient as anti-VEGF treatment) and then this receptor appears as a putative target to control exudative AMD.

On the other hand, lipoprotein profile is of particular interest for patient follow-up. Indeed, this profile is clearly modified according to the active or non-active status of the patient and to the induced or non-induced status of the mice.

4. Conclusion

This study demonstrates that metabolomics approach applied to AMD could lead to relevant outcomes for AMD patient follow-up and potential new treatment strategies.

5. Reference

1. Lambert V, et al. Nat Protoc. 2013;8(11):2197–211.