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Modulation of Metabolomics Profile by Protein Diets Lead to the Development of NAFLD in Glutaredoxin-1 Deficient Mice (#596)

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Introduction

NAFLD is the most common form of liver diseases in western countries (1). Indeed, high red and processed meat consumption is associated with insulin resistance (IR), type 2 diabetes, oxidative stress and chronic liver diseases (2, 3). Several studies have reported that excessive consumption of refined carbohydrates, fats, saturated fats in particular, and protein from meat can cause NAFLD (4, 5). However, the metabolic mechanisms involved in the complex pathophysiological processes and progression of NAFLD induced by meat protein diets remain unclear. In recent years, metabolome profiling has provided new insights into the molecular signature of diseases including NAFLD. However, there have been no previous metabolomic reports on the NAFLD induced by high fat meat proteins in Glrx1$^{-/-}$ mice. To assess the importance of Glrx1 in NAFLD, we generated a model of Glrx1 KO by deletion of Glrx1 gene using CRISPR cas9 technology, and studied its consequences on metabolism in pathophysiological parameters, potential metabolites and metabolic pathways responses induced by high fat meat proteins.

Methods

Glrx1 gene was deleted using CRISPR cas9 technology according to the protocols of Joung et al. (6). Twenty four Glrx1$^{-/-}$ male mice (6 weeks old) were kept in a controlled specific-pathogen-free animal center. After one week of acclimatization, mice were randomly assigned to four groups, and fed a normal diet with 12% Kcal from fat (Casein (Control)), a high fat diet with 60% Kcal (HFD) or a high fat fish with 60% Kcal (HFF) or a high fat mutton protein diets with 60% Kcal (HFM). After feeding period, the mice were sacrificed by cervical dislocation. Blood serum samples were collected and analyzed by LC–MS system (G2-XS QTof, Waters). Data acquisition was performed using MassLynx 4.1.

Results

As can be seen in figure 1, the HFM and HFF groups showed great interas well as intragroup to mutton and fish proteins in the diet ($P < 0.05$) from those to control and HFD. The top 15 VIP scores of component 1 were listed in Figure 1. The results showed that the mice fed with control group had the highest concentrations of Trihydroxycoprostane, (Monoglycerols (MG), (MG(22:6)), (Lysophosphatidylcholines (LysoPCs)) (LysoPC(22:6)) and MG (18: 1). We also found that the mutton protein group had higher levels of lysophospholipids, phosphatidylethanolamines, and bile acids (12-Ketodeoxycholic acid), (LysoPC(15:0), LysoPC(17:0), LysoPC(19:0), LysoPC(20:0), PC(20:1)), and LysoPE(16:0)), among diet groups ($P < 0.05$). One PLS component and one orthogonal component were calculated for all of the models. The OPLS plot showed that the overall profile of serum metabolites differed significantly. The responsible variables with top 15 VIP scores between the casein (Control) and the other three protein groups were shown in figure 2.

Conclusion

In summary, the present study identified several key metabolites in major metabolic pathways involved in the development of NAFLD. These metabolites could be considered as potential biomarkers for risk assessment of NAFLD. Moreover, these results provide comprehensive insights into the metabolic processes underlying the onset and progression of NAFLD induced by HFD meat proteins.

References

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Notes

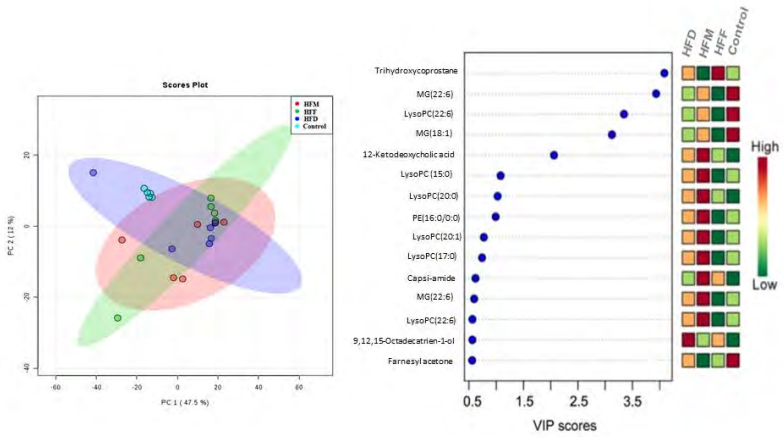

Figure 1
The PCA score plot of serum metabolites (15 VIP)

Notes

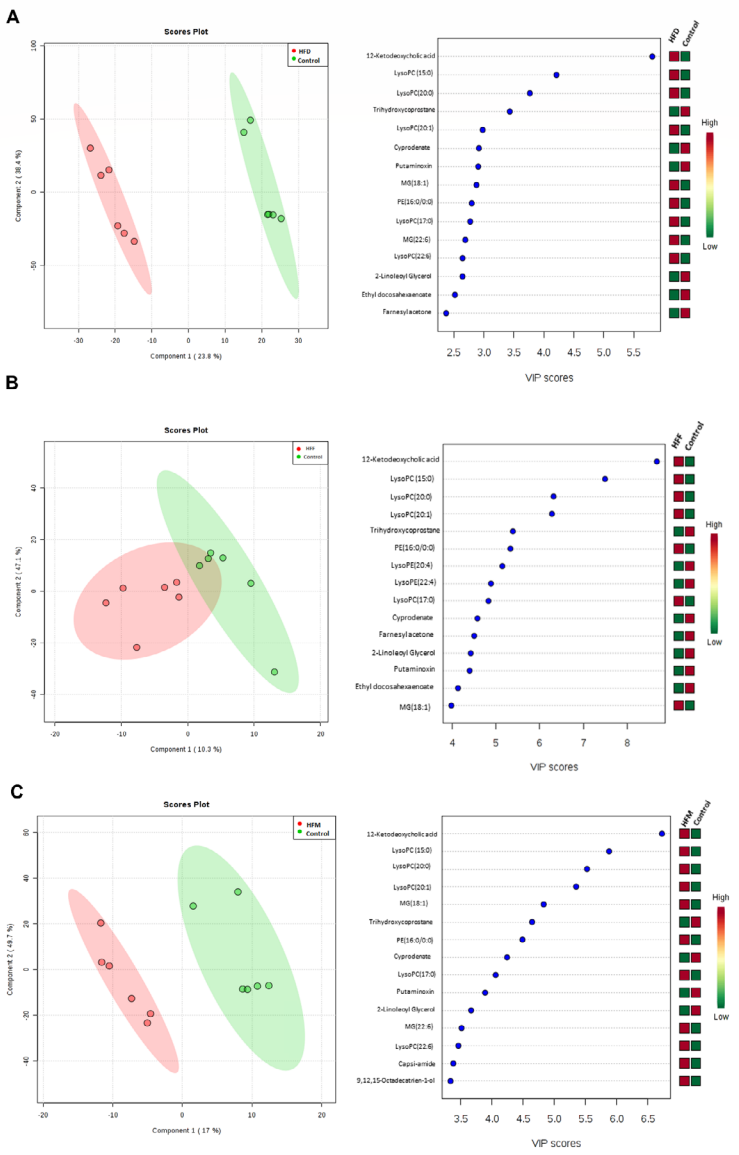

Figure 2
Pairwise comparisons between serum extract obtained from the high fat diet(HFD), high fat fish (HFF) and high fat mutton (HFM) protein groups using OPLS analysis

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