Integrated miRNomic and lipidomic analysis in mice for the identification of novel miRNAs involved in lipid metabolism

Alice Colombo[1], Stefano Manzini[1], Elsa Franchi[1], Giada Poletti[1], Reijo Laaksonen[2], Marco Busnelli[1], Giulia Chiesa[1]

[1] *Department of Pharmacological and Biomolecular Sciences Rodolfo Paoletti, Università degli Studi di Milano, Milan, Italy*
[2] *Finnish Cardiovascular Research Center, University of Tampere, Tampere, Finland*

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Alice Colombo: alicecolombo10@gmail.com

Background and Aims: The miRNomic and lipidomic profiles of mice with specific genotypes/phenotypes were integrated with a novel approach, with the aim of increasing our knowledge on the mutual interplay between miRNAs and lipids, and thus to discover previously uncharacterized miRNAs, potentially playing a role in lipid metabolism.

Methods: miRNomic and lipidomic analyses were performed in wild-type, Pcsk9 and Ldlr knockout mice fed normal laboratory diet or Western diet. Small RNA was extracted from liver, brain, duodenum, jejunum, ileum and abdominal white adipose tissue and quantified by RNAseq. Lipid species were quantified by high-throughput mass-spectrometry in liver, aorta and plasma. miRNA expression levels were tested for correlations with each lipid measurement in different samples. Highly correlated, uncharacterized miRNAs were subjected to testing *in vitro* in murine hepatoma Hepa1-6 cells. For each miRNA to be tested, cells were transfected with the miRNA mimic, the miRNA inhibitor and a non-target control. After 24-hours incubation, the cellular content of cholesterol and triglycerides was measured. For each miRNA, at least three independent experiments were carried out.

Results: Correlation analyses between miRNA expression levels and lipid concentrations in the different experimental conditions led to the selection of miRNAs potentially playing a major role in the regulation of lipid levels. Correlations mainly clustered in liver. Among selected miRNAs, some were already known to be related to lipid metabolism (miR-33, miR-210 and miR-21a) whereas others, including miR-431-5p, miR-434-3p, miR-434-5p and miR-677-5p had never been associated to lipid changes before. *In vitro* experiments allowed to highlight a potential role of miR-431-5p and-miR-677-5p in the modulation of total cholesterol and triglyceride concentrations.

Conclusions: This study, bridging miRNomic and lipidomic data in well characterized mouse models, allowed to identify novel miRNAs potentially playing a role in the modulation of lipid levels.

Survivors of acute lymphoblastic leukemia show an increased cardio-immune-metabolic risk

Marta Iaia[1], Alessandro Cattoni[2], Santo Di Marco[2], Giovanni Vingiani[1], Elena Olmastroni[1], Annalisa Moregola[1], Adriana Balduzzi[2], Giuseppe Danilo Norata[1], Fabrizia Bonacina[1]

[1] *Department of Pharmacological and Biomolecular Sciences, University of Milan, Italy*
[2] *Pediatrics, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy*

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Marta Iaia: marta.iaia@unimi.it

Background and aims: Acute lymphoblastic leukaemia (ALL) is the most common haematological cancer in children. In high-risk cases, treatment involves chemotherapy, radiation and stem cell transplantation. Despite high survival rates (up to 90%), increased cardiovascular and metabolic risk has been observed in survivors. This project aims to study post-transplant metabolic and inflammatory changes and their impact on mature immune cells derived from stem cells.

Methods: 14 ALL survivors who underwent transplantation (11 males, 3 females) and 14 matched sibling donors (3 males, 11 females) were selected according to defined criteria. Each recipient-donor couple were profiled for medical anamnesis and clinical assessment and were subjected to a blood collection, for immunophenotyping, transcriptomic analysis and telomere length measurement. An ultrasound examination of the supra-aortic trunks was also performed to assess intima-media thickness (IMT).

Results: No differences have been detected in anthropometric characteristics, however, signs of dyslipidaemia were observed in recipients (cholesterol: 157.5 SE±9.194 vs 171.9 SE±10.43; triglycerides 65.57 SE±5.216 vs 105.0 SE±11.31; hyperinsulinemia 8.457 SE±1.870 vs 15.23 SE±2.945 and an increase in the HOMA index (1.587 SE±0.3653 vs 2.981 SE±0.6225). Metabolic syndrome was diagnosed in 14.3% of recipients. Carotid IMT analysis showed accelerated thickening (0.0083 vs 0.0034). Plasma proteomic analysis revealed increased levels of pro-inflammatory proteins (CRP, SAAP) and proteins related to dyslipidaemia (APOB, APOC4-APOC2).

This metabolic and inflammatory phenotype is associated with accelerated telomere shortening in circulating immune cells (slope -0.009 vs -0.0008), a reduction in CD34+ and an increase in circulating CD19+. RNA-seq confirmed inflammation and B-cell dysfunction. Plasma IgM immunoglobulins were decreased in recipients compared to donors (58.62 SE±4.062 vs 49.23 SE±3.188), while IgG levels were comparable (350.6 SE±14.49 vs 329.7 SE±16.43).

Conclusions: These data suggest that TBI conditioning negatively impact on the immunometabolic profile of cALL survivors, contributing to an increased risk of long-term cardiovascular complications. Together this evidence suggests the need to optimize the clinical follow-up strategies to mitigate the increased cardiometabolic risk in cALL survivors.