Glycomics and Lipidopics

Extended Abstract

Cord-Blood Lipidome in Progression to Islet Autoimmunity and Type 1 Diabetes

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Abstract:

Previous studies suggest that children who progress to type 1 diabetes (T1D) later in life already have an altered serum lipid molecular profile at birth. Here, we compared cord blood lipidome across the three study groups: children who progressed to T1D (PT1D; *n* = 30), children who developed at least one islet autoantibody but did not progress to T1D during the follow-up (P1Ab; *n* = 33), and their age-matched controls (CTR; *n* = 38). We found that phospholipids, specifically sphingomyelins, were lower in T1D progressors when compared to P1Ab and the CTR. Cholesterol esters remained higher in PT1D when compared to other groups. A signature comprising five lipids was predictive of the risk of progression to T1D, with an area under the receiver operating characteristic curve (AUROC) of 0.83. Our findings provide further evidence that the lipidomic profiles of newborn infants who progress to T1D later in life are different from lipidomic profiles in P1Ab and CTR. Type 1 diabetes (T1D) is an autoimmune disease, characterized by destruction of insulin-producing pancreatic islet β-cells that results in lifelong dependency on exogenous insulin [**1**]. The incidence of T1D is steadily increasing in children younger than 15 years of age and is projected to double in children under the age of five years by 2020. No effective T1D prevention strategies have so far been identified. Early detection of T1D risk has, consequently, become an important area of research, which may also inform about potential disease prevention strategies. The presence of predisposing human leukocyte antigen (HLA) alleles in the human genome is a major determinant of T1D susceptibility, but less than 10% of individuals with high-risk HLA alleles progress to the disease. Several lines of evidence suggest that environmental factors, such as viruses, diet, and gut microbes, may be associated with the initiation of islet autoimmunity and T1D progression . However, T1D is a heterogeneous and complex disease. It is thus unlikely that a single factor contributes towards autoimmunity initiation and overt disease. The identification of various endogenous and exogenous contributing factors and their interactions is essential for the early prediction and prevention of T1D. Type 1 diabetes is preceded by the appearance of autoantibodies against β-cell antigens . Increasing evidence also suggests that distinct metabolic signatures are associated with the development of T1D, already before the initiation of β-cell autoimmunity. Recent findings suggest that children who progress to T1D have a distinct lipidomic profile already present in their cord blood, which may be helpful in the early identification of at risk children at birth. However, more studies are needed in order to establish the link between the lipidome at birth and progression to islet autoimmunity and overt disease later in life. Here, we characterized the cord plasma lipidome in three study groups of newborn infants: (1) those who progressed to T1D (PT1D) during the follow-up, (2) those who developed at least a single islet autoantibody (Ab) during the follow-up but did not progress to T1D (P1Ab), and (3) controls (CTR) who remained autoantibody negative and healthy. Our findings have provided further evidence that T1D progressors have a characteristic lipidomic profile already present at birth. Phospholipids, specifically SMs, tended to be lower in T1D progressors than in P1Ab and the CTR. Previous studies have suggested that progression to T1D is associated with decreased concentrations of major phospholipids, including SMs and PCs in cord blood. These findings are also in line with prospective observations in children who later progressed to T1D, as well as in children with newly diagnosed T1D. The differences observed in the present study were not as pronounced as those observed in a previous study . However, in that study, the sample size allowed the PT1D group to be divided into early and late progressors (age of diagnosis below or above four years), and the distinct phospholipid signature was only identified among the early progressors. Sphingomyelins are one of the major choline-containing phospholipids in circulation. Choline is a precursor for the biosynthesis of PCs and SMs, which are essential constituents of cellular membranes . It is, however, challenging to identify the sources of the observed lipid changes in cord blood. There is evidence that cord

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blood lipid levels may partly reflect the maternal lipid profile during late pregnancy. During pregnancy, as well as in fetal development, there is high demand of choline, thus it is conceivable that insufficient maternal choline availability may have mediated the downregulation in phospholipid levels in the cord blood of T1D progressors. Low choline intake can also result in low levels of triacylglycerols (TGs). Intriguingly, we also observed lower levels of several TGs species among T1D progressors, and those TGs that remained downregulated were a component of the predictive models for T1D progression. A potential limitation of the study is that we could not investigate the association of maternal factors, such as lifestyle, diet, and body mass index (BMI), which could likely affect metabolome in both mothers and newborns. Future investigation in mother–offspring pairs will be needed to clarify the impact of the maternal factors that may lower cord blood phospholipid in relation to the progression of T1D. The evidence suggests that SMs, as well as TGs, are potent regulators of immunogenic processes and play a potent role in inflammatory disease. Based on our observations, we hypothesized that distinct cord blood phospholipids, as well as TGs, disturbed early immune developmental processes in T1D progressors. Further studies are clearly needed in order to elucidate the immune modulatory function of the observed lipid species during early T1D progression. Despite the current lack of mechanistic understanding of the observed lipid changes in T1D at birth, our findings suggest that lipid profiles of newborns may complement genetic testing and islet autoantibody determination for the identification of high-risk children for T1D. Clearly, further studies are needed to examine the complementary diagnostic value of these lipid signatures. The inclusion of mother–offspring pairs would also be a valuable comparison for future studies.

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