Applications of Lipidomics in Studies of Autoimmune Diseases

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BACKGROUND

The risk determinants of type 1 diabetes (T1D), initiators of autoimmune response, mechanisms regulating progress toward beta cell failure and factors determining time of presentation of clinical diabetes are poorly understood. We investigated changes in serum metabolome prospectively in children who later progressed to type 1 diabetes as well as in the non-obese diabetic (NOD) mouse.

METHODS

HLA-associated diabetes risk was screened in 104,111 consecutive newborns over 11.5 years. Children with moderate or high risk were enrolled in follow-up, with blood samples drawn at 3- to 12-month intervals from birth to clinical diabetes. Serum metabolite profiles were compared between sample series drawn from 56 children who progressed to type 1 diabetes and 73 controls who remained non-diabetic and permanently autoantibody negative. The controls were matched for time and site of birth, gender and genetic risk. Additionally, serum samples were collected every week from 80 (35 female, 35 male) NOD mice starting at 3 weeks of age.

RESULTS AND DISCUSSION

Individuals who developed diabetes had reduced serum levels of succinic acid (P=0.04) and phosphatidylcholine (P=0.004) at birth, reduced levels of triglycerides (P=0.005) and antioxidant ether phospholipids (P<0.001) throughout the follow-up and increased levels of proinflammatory lysophosphatidylcholines several months prior to seroconversion to autoantibody positivity (P=0.005) (1). The lipid changes were not attributable to HLA-associated genetic risk. The appearance of insulin and GAD autoantibodies was preceded by diminished ketoleucine (P=0.009) and elevated glutamic acid (P=0.03). The metabolic profile was partially normalized following the seroconversion. Phospholipid changes observed prospectively in progressors to type 1 diabetes were also observed in female NOD mice who later progressed to T1D. Similarly as observed in children, lysophospahtidylcholines were elevated in insulin autoantibody (IAA) negative mice that later progressed to T1D, but were at normal levels in IAA positive mice in the same group. Autoimmunity may therefore be a relatively late response to the early metabolic disturbances. Recognition of these pre-autoimmune alterations may aid in studies of disease pathogenesis as well as open a time window for novel type 1 diabetes prevention strategies.

REFERENCES

1. M. Orešič et al., Dysregulation of lipid and amino acid metabolism precedes islet autoimmunity in children who later progress to type 1 diabetes, J Exp Med 2008;205:2975-2984.