Antiviral diabetes susceptibility gene

Summary and Comment:
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Summary

The authors previously showed that an A/G splicing site single nucleotide polymorphism in the *OAS1* gene is strongly correlated to the basal activity of the antiviral oligoadenylate synthetase (OAS). Basal activity was highest in individuals with the GG genotype and lowest in those with the AA genotype.

In the present study, *OAS1* GG and GA genotypes were increased in type 1 diabetic individuals compared with their healthy siblings ($p = 0.0023$). The strength of association was similar to that at *IDDM2,* where the variable number of tandem repeats (VNTR) class I (C/C) genotype was increased in diabetic compared with healthy siblings ($p = 0.0025$). Since OAS enzyme activity reflects an antiviral response under the control of interferon-α, the authors concluded that the host genetic response to viral infection could influence susceptibility to type 1 diabetes.

Comment

A number of genes determining susceptibility (or resistance) to type 1 diabetes have been identified, most of which encode important factors for the development of the autoimmune response to islet β-cells [1]. The class II major histocompatibility complex (MHC) genes on chromosome 6 account for approximately 50% of the risk and correspond to the machinery responsible for autoantigen presentation. The non-MHC VNTR at the *INS/IGF2* locus (*IDDM2*) represents another important locus involved in the expression of the major autoantigen related to type 1 diabetes. Until now, there has been no association between susceptibility to type 1 diabetes and genetic loci more specifically linked to the host response to viral infection. However, children from the general population with the susceptible MHC genotype have a lower than 10% risk of developing type 1 diabetes, and more than 50% of monozygotic twins of type 1 diabetic individuals are discordant for the disease. These facts clearly underline the influence of the environment in the pathogenesis of type 1 diabetes, in particular viral infections such as congenital rubella and enterovirus infections.

In their elegant study, Field et al. reported that, compared with their healthy siblings, type 1 diabetic patients have a very significantly increased frequency of the single nucleotide polymorphism genotypes associated with high OAS activity. This result is consistent with that of a previous paper from the same group showing persistent activation of the antiviral response in human type 1 diabetes [2]. As discussed by the authors, it is unclear why such antiviral enzyme activity would predispose to the disease, but two explanations are proposed: first, the increased enzyme activity during viral infection could directly damage sensitive β-cells through a death-promoting process following degradation of cellular RNA by latent RNase activity known to be stimulated by OAS; second, the less susceptible AA genotype — associated with the production of a proapoptotic isoform of OAS — may induce a rapid apoptosis of virus-infected islet β-cells, whereas GG and GA individuals would be less competent or incompetent at mounting such antiviral protection. Another point to be discussed is the evidence for another discordance between human type 1 diabetes and a classical animal model of the disease, the non-obese diabetic (NOD) mouse. Indeed, a previous interesting study evidenced that the development of autoimmune diabetes following coxsackie B4 (CVB4) infection of NOD mice depends on the β-cell antiviral response to the CVB4 infection. The anti-CVB4 response, mounted by the β-cells in response to interferons, resulted in a reduced permissiveness to CVB4 infection and an efficient antiviral protection by natural killer cells [3].

> *This study demonstrates a strong linkage between the development of type 1 diabetes and a host genetic determinant of the antiviral response*

In summary, this study demonstrates for the first time a strong linkage between the development of type 1 diabetes and a host genetic determinant of the antiviral response. This linkage has since been confirmed by another independent research group [4]. Further work, how-

ever, remains to be performed in order to decipher the full meaning and explanation underlying this association.

References

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The DPP and cardiovascular protection

Original articles:
Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the Diabetes Prevention Program. Ratner R, Goldberg R, Haffner S, Marcovina S, Orchard T, Fowler S, Temprosa M, for the Diabetes Prevention Program Research Group. *Diabetes Care* 2005; 28(4): 888–94.

Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes. Eddy DM, Schlessinger L, Kahn R. *Ann Intern Med* 2005; 143(4): 251–64.

Summary and Comment:
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Summary

Although no data are yet available on the impact of diabetes prevention interventions on hard clinical outcomes, two recent papers have addressed this question by examining surrogate cardiovascular risk factors and by modelling.

The first of these papers, from the Diabetes Prevention Program (DPP) Research Group, reports on the changes in blood pressure and lipids over 3 years in each of three study arms (placebo, metformin and intensive lifestyle). The levels of risk factors were well matched at baseline and the most impressive differences after 3 years were in blood pressure. At baseline, 17% of participants were on antihypertensive therapy. At 3 years this had risen to 31% and 32% in the placebo and metformin groups, respectively, but to only 23% in the lifestyle group. Furthermore, the blood pressure had fallen by a mean of 3/2
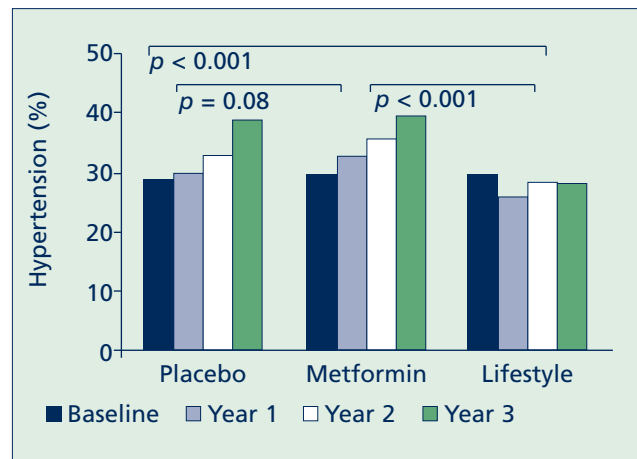

Fig. 1: *Changes in hypertension over time by treatment assignment (p represents the pairwise comparison from generalized estimating equation models).*

mmHg more in the lifestyle group than in the other groups. There were no differences between the groups in total or LDL cholesterol, but lifestyle intervention led to a reduction in the numbers of participants with small, dense, atherogenic LDL particles, and improved triglycerides by 0.28 mmol/l and HDL by 0.025 mmol/l compared with the other groups. Of 89 cardiovascular disease (CVD) events occurring in the trial, there was a non-significant excess among the lifestyle group. Metformin showed no benefits compared with placebo, except for an improvement in LDL particle size and a non-significant reduction in CVD events.

Over a 30-year time frame, the DPP lifestyle intervention was estimated to reduce the likelihood of developing a serious diabetes complication from 38% to 30%

Eddy et al. used a sophisticated modelling program (Archimedes), which, like a flight simulator, undertakes a whole set of calculations on disease parameters and physiological functions to estimate outcomes on theoretical populations. Archimedes' estimates of outcomes have been impressively close to actual findings in a number of clinical trials relevant to diabetes. Over a 30-year time frame, the DPP lifestyle intervention was estimated to reduce the chances of adults who would have been eligible for the DPP of developing diabetes from 72% to 61%, the likelihood of developing a serious diabetes complication from 38% to 30%, and the likelihood of a diabetes death from 13.5% to 11.2%. The cost/quality-adjusted life-year of lifestyle intervention over 30 years was US $143,000 from a