

Haptoglobin as an early serum biomarker of virus-induced type 1 diabetes in genetically susceptible rats

Type 1 diabetes (T1D), formerly known as juvenile diabetes, is a multifactorial disease of complex etiology characterized by the autoimmune destruction of pancreatic beta-cells. In addition to genetic susceptibility, it is generally accepted that environmental factors play important roles in triggering the disease, with virus infection having perhaps the strongest association. Multiple viral infections including cytomegalovirus, mumps, rubella, enteroviruses and parvovirus have all been associated with human T1D. Indeed, the effects of diverse viruses in triggering T1D may explain the heterogeneous nature of disease onset and kinetics in the general population.

The recent availability of novel immunomodulatory therapies that may preserve residual beta-cell mass in new onset diabetics has generated a demand for non-invasive testable biomarkers that can identify the development of the autoreactive process before it becomes clinically apparent. In the work published on page 1328 of this issue of *Experimental Biology and Medicine*, Kruger and co-workers have utilized several well-established rat models of virus-induced T1D to search for serum biomarkers that occur early in disease development. Annie Kruger, working together with Rita Bortell and other colleagues at the University of Massachusetts Medical School, carried out the work. Dr Kruger, a recent MD/PhD graduate, investigated the viral induction of autoimmune diabetes as part of her PhD thesis.

In a proteomics study of serum from rats treated with diabetogenic virus, the research team utilized two-dimensional gel analysis and mass spectrometry and found increased levels of serum haptoglobin very early in the time course

of diabetes induction. This result was confirmed by Western blot and enzyme-linked immunosorbent assay analyses, and sustained elevations of serum haptoglobin were generally predictive of ensuing diabetes. 'Intriguingly,' Dr Bortell stated, 'mutations in the human haptoglobin gene are associated with increased risk of diabetic complications such as retinopathy, nephropathy and cardiovascular disease. In our rat studies, however, haptoglobin was identified very early following virus infection, well prior to the development of diabetes or its complications, and thus may represent a biomarker for the *pathogenesis* of autoimmune diabetes as well.'

To the researchers' knowledge, this is the first study that investigates T1D serum biomarkers found specifically in response to virus infection. Dr Bortell said 'As virus infections have historically been associated with the development of T1D in children, these rat models have particular relevance to the human disease. Reliably identifying children in the earliest phases of diabetes (pre-diabetes) would provide clinicians with a window of opportunity when pharmacotherapy could be most effective in slowing or halting the disease.'

Steven R Goodman, Editor-in-Chief of *Experimental Biology and Medicine*, said 'Kruger *et al.* have identified haptoglobin as an early serum biomarker predictive of virus-induced T1D utilizing well-known rat models. This discovery, in conjunction with established markers of genetic susceptibility, should prove useful in identifying those children at risk for T1D.'

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