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Pathology Elsewhere

Expression of genes involved in hepatic morphogenesis and fibrogenesis are altered in biliary atresia

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Biliary atresia (BA) is the most common cause of cholestatic liver disease in infants. BA of the postnatal type, which accounts for 65–90% of cases, manifests as a progressive obliteration of the hepatobiliary system. Early surgical intervention to restore the biliary flow by porto-enterostomy is not successful in approximately one-third of the patients and the disease progresses relentlessly toward cirrhosis. Although cirrhosis from BA is the most common indication for liver transplantation in early childhood, little is known about the cause and pathogenesis of BA. Racial, gender, viral and environmental contributions to the development of BA, as well as genetic factors, have been considered, but their roles remain inconclusive.

In an effort to identify the possible pathogenetic mechanisms involved in BA, **Chen *et al***[1] used a new approach by performing comprehensive genome-wide gene expression analysis using complementary DNA (cDNA) microarray analysis on RNA isolated from livers of patients with BA, from normal livers and from diseased controls. Messenger RNA expression levels of approximately 18 000 genes were compared in these three groups; reverse-transcription–polymerase chain reaction (RT–PCR) and Northern blot analysis confirmed the changes in gene expression. Cluster and principal component analysis showed that all BA samples clustered together, forming a distinct group well separated from normal and diseased controls. They further identified 35 genes with transcription specifically affected in the BA cases as compared to normal and diseased controls. The genes identified belong to the functional classes of morphogenesis, fibrogenesis, tissue remodeling, transcription regulation and cell signaling. Fibrogenesis and matrix remodeling seem to be the major groups represented. The overexpression of these latter genes may be related to aberrant hepatic fibrogenesis, potentially influenced by the fact that the specimens tested were all of end-stage cirrhotic livers as the authors critically admitted.

This study provides an opportunity to elucidate the mechanisms involved in BA, by providing a platform for understanding the complex interplay between inflammation, morphogenesis and fibrogenesis in this important disease of childhood.

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References

1 Chen L, Goryachev A, Sun J, *et al*. Altered expression of genes involved in hepatic morphogenesis and fibrogenesis are identified by cDNA microarray analysis in biliary atresia. *Hepatology* 2003;38:567–576.

Is there a chance for another Lyme disease vaccine?

Lyme disease is the most common tick-borne disease in North America and Europe. *Borrelia burgdorferi*, the spirochetal agent of Lyme disease, is transmitted when infected *Ixodes* ticks feed on susceptible hosts. The efficacy of its Outer surface protein A (OspA)-based vaccine, which was recently taken off the market, was questionable and required frequent booster immunizations to maintain antibody levels above the threshold required for protection.

A newly published study in Microbes and Infection showed that immunization with plasmid DNA encoding the outer surface protein C (OspC) was able to induce protective immune responses against Lyme disease. Lyme disease patients as well as naturally or experimentally infected mice mainly produce antibodies specific for OspC rather than OspA. OspC is expressed early in the infection in mammals and upregulated during tick feeding. Mice that were immunized in this study showed elevated OspC-specific IgG titers and were improved by further immunizations, regardless of the vaccination methods (intradermal injection or gene-gun application of plasmid DNA). There was a difference, however, in T-helper-type response between these two vaccination methods; that is, both showed elevated amounts of interferon gamma, but interleukin 4 levels were reduced in the intradermally injected mice, supporting the notion that different T-helper types are induced via different plasmid immunization methods. Nevertheless, both intradermal injection and gene-gun application of plasmid DNA were able to induce a reliable humoral response with high antibody titers, antigen-specific cellular responses and, most importantly, provided effective protection. A protection rate of 80–100% was achieved after challenging the mice with virulent *B. burgdorferi* strain for 4 weeks.

'It is evident that a successful vaccine against borreliosis is not restricted to a certain method or the induction of a certain T-helper cell type of immune response' commented Sandra Scheiblhofer, a researcher of this study.[1] The result of this study demonstrated that a DNA vaccine encoding OspC of *B. burgdorferi* is suitable for inducing protection against Lyme disease.

References

1 Scheiblhofer S, Weiss R, Durnberger H, *et al*. A DNA vaccine encoding the outer surface protein C from Borrelia burgdorferi is able to induce protective immune responses. *Microbes Infect* 2003;5:939–946.

Increased erythrocyte adhesion in hereditary spherocytosis and elliptocytosis.

Hereditary spherocytosis (HS) and hereditary elliptocytosis (HE) are two major forms of hereditary hemolytic anemia.[1] Defects in the red blood cell (RBC) cytoskeleton, which normally provides the RBC with mechanical strength and deformability, are the main pathology in these forms of anemia. The severity of HS and HE in humans is variable, usually mild, but thrombosis and stroke have been documented in a small number of cases. Mice with deficiencies in erythroid α-spectrin (*sph/sph*) develop severe hemolytic anemia within hours of birth and have the highest incidences of thrombosis and stroke. It is interesting to note that there is increased exposure of aminophospholipid phosphatidylserine (PS) on the outer leaflet of the RBC membrane in humans and mice with HS and HE. This phenomenon, which correlates with increased activity of the coagulation cascade as well as increased RBC adhesion, is well recognized in both humans and mice with sickle cell disease. **Wandersee *et al***[1] tested whether murine and human HS/HE RBCs aberrantly adhered to components of the subendothelial matrix under controlled flow conditions, and explored the potential relationships between RBC adhesion and pathologic cerebral infarction. Adhesions of mouse and human RBCs to immobilized human thrombospodin (TSP) and laminin (LM) were measured under controlled flow conditions.

They found that mutant RBCs had $\geq$10-fold higher adhesion to TSP and had significant increased adhesion to LM compared to normal RBCs. Similar to human sickle RBCs, adhesion of RBCs from patients with HS to TSP and LM varied from patient to patient. RBC adhesion was independent of PS exposure and the degree of reticulocytosis. Mutant RBCs from young *sph/sph* mice exhibited enhanced adhesion to TSP immediately prior to and during a high-risk period for initiation of cerebral infarction.

The data presented in this study indicated that *sph/sph* RBCs have enhanced adhesion to TSP immediately prior to and during a high-risk period for stroke development in these animals; therefore, they speculated that changes in the adhesive characteristics of the RBC membrane might contribute to the pathology of cerebral infarction in HS and HE.

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References

1 Wandersee NJ, Olson SC, Holzhauer SL, *et al*. Increased erythrocyte adhesion in mice and humans with hereditary spherocytosis and hereditary elliptocytosis. *Blood* 2003; prepublished online August 28 2003; DOI 10-1182/blood-2003-02-0492.