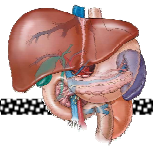

# Introductions

Mammals protect themselves against exogenous pathogens (viruses, bacteria, fungi, parasites, and toxins) and endogenous danger (malignancy) with a complex, interacting set of defence mechanisms. These include primordial "identify and destroy" strategies (innate immunity) as well as sophisticated detection and targeted killing processes that display exquisite specificity, multiple layers of regulation, and memory (adaptive immunity). ***(O`Farrely C, 2009)***. The liver is an important contributer to and prominent victim of the immunological reactivities of the body .

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease of unknown etiology characterized by high-titer serum antimitochondrial autoantibodies (AMAs) and an autoimmune-mediated destruction of the small and medium-sized intrahepatic bile ducts. It affects women more frequently than men, with a female-to-male ratio of 9 to 1, and the average age at diagnosis is within the fifth and sixth decades of life, with exceptional cases described in pediatric ages. The diagnosis of PBC is made when two of three criteria are fulfilled, i.e., presence of serum AMAs, increased enzymes indicating cholestasis (i.e., alkaline phosphatase) for longer than 6 mo, and a compatible or diagnostic liver histology. Clinical symptoms include fatigue, pruritus, and jaundice. The progression of PBC varies widely for unknown reasons, as represented by certain patients remaining asymptomatic and others reaching liver failure at young ages. Several clinical and experimental findings strongly imply an autoimmune pathogenesis for PBC, whereas

the disease onset recognizes two necessary components in a permissive genetic background and an environmental trigger.***(Selmi .C.et al,2009).***

Primary sclerosing cholangitis comprises a spectrum of chronic cholestatic disease of the hepatobiliary system characterized by hepatic inflammation, biliary strictures, and fibrosis. The best studied form is primary sclerosing cholangitis (PSC), which is a slowly progressive disorder eventually resulting in concentric obliterative fibrosis of the bile ducts, biliary cirrhosis, and, in approximately 30% of patients, cholangiocarcinoma. There is a strong association between PSC and inflammatory bowel disease (IBD), with between 75 and 80% of PSC patients of northern European origin having underlying IBD ***(Aadland E et al1987).*** Ulcerative colitis is the most common form of IBD associated with PSC, and, interestingly, when considering the pathogenesis of the disease, those PSC patients who have Crohn's disease almost invariably have disease predominantly affecting the colon. ***(Gossard AA et al2005).***

Autoimmune hepatitis (AIH) is an inflammatory liver disease with a strong female preponderance, characterized by elevated levels of transaminases and immunoglobulin G (IgG), seropositivity for organ and non-organ-specific autoantibodies, and a histological picture of interface hepatitis. The major pathogenic mechanism is believed to be immune reaction against host liver antigens. AIH responds well to immuno-suppressive treatment. The diagnosis should be made as soon as possible because symptomatic AIH, if left untreated, progresses to liver failure requiring transplantation. The development of a panel of" marker autoantibodies has allowed the subdivision of AIH in distinct types, type 1 (AIH-1) being positive for antinuclear (ANA) and/or anti-smooth

muscle antibodies (SMA) and type 2 (AIH-2) being positive for anti-liver-kidney microsomal antibody type 1 (anti-LKM-1).***(Vergani.D.et al,2009)***

Autoimmune liver diseases are not classical Mendelian autosomal or sex-linked genetic traits. However, there is con- siderable evidence that our genes play a significant role in determining individual sceptibility to (and progression of) these diseases. In the absence of a "simple" pattern of inheritance; attributable to a single gene locus, autoimmune liver diseases are classified as "genetically complex." Variation at a gene locus gives rise to a number of alleles. When alleles are- rare within a population (less than one percent), they are referred to as mutations. When alleles are common, they are referred to as polymorphisms. To the geneticist, "complex traits'" are those in which one or more genes (alleles) acting alone or in concert increase or reduce the risk of a disease or syndrome ***(Haines and Pericak-Vance, 1998)***. This finding suggests that inheritance of a specific allele or group of alleles is neither necessary nor sufficient for disease genesis but will simply increase (or reduce) the likelihood (risk) of disease ***(Donalson,2009)***.

Even so, when it comes to candidate selection in autoimmune liver disease, the most frequently examined genes have been those involved in antigen presentation, especially the MHC-encoded human leukocyte antigens (HLAs) on chromosome 6p21.3. Although historically it has always been convenient to study HLA and rather difficult to study other IR genes, it is also important to remember that HLA molecules have critical roles in both innate and adaptive immunity, and this makes them "prime candidates" in autoimmune disease. More recently, studies of

autoimmune diseases have concentrated on non-MHC immunoregulatory genes including genes encoding accessory molecules, which provide second signals in antigen presentation; genes encoding the cytokines and chemokines that regulate the inflammatory mileau; genes encoding proteins involved in wound healing and repair; and genes whose expressed products are important in redressing the immunological balance and restoring immune homeostasis ***(Donalson,2009)***.