COMMON GENETIC VARIATION IN NATURAL KILLER CELL RECEPTOR PROTEIN G2D DOES NOT MODIFY SUSCEPTIBILITY TO SPORADIC CHOLANGIOCARCINOMA

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In this latest study from Imperial College, Dr Chris Wadsworth and colleagues investigate whether or not specific genes involved in tumour immunity are associated with the development of sporadic cholangiocarcinoma.

Previously it has been shown that people who suffer from the bile duct autoimmune disease primary sclerosing cholangitis who subsequently develop cholangiocarcinoma were more likely to have particular variants of an individual immune cell gene than people with sclerosing cholangitis who do not develop cholangiocarcinoma. The gene, called NKG2D, is a receptor protein expressed on the surface of white blood cells called natural killer (NK) cells. It is proposed that NK cells use a variety of surface receptors including NKG2D to look for changes in body cells associated with infection or tumours. When such changes are recognised, NK cells are activated and initiate an immune response against the offending cell, causing its destruction. It is proposed that mutations in NKG2D renders NK cells less able to see the changes associated with cholangiocarcinoma, thus less able to control the growth of cancerous cells and the development of the tumour. However, to date these genetic changes have not been looked for in cases of cholangiocarcinoma not associated with primary sclerosing cholangitis.

Many cases of cholangiocarcinoma have no known risk factors and are therefore known as sporadic cholangiocarcinoma. This study was designed to investigate if the same NKG2D mutation was found more frequently in people with sporadic cholangiocarcinoma compared to a very similar group of people from the general population without cholangiocarcinoma. DNA was taken from 172 patients with sporadic cholangiocarcinoma and 256 healthy controls and sequenced to determine the genetic code in each case. The DNA sequence encodes the protein sequence and therefore differences in the DNA code indicated differences in the protein sequence. Using computer programs the amount and type of variation in this DNA code at 7 specific locations (known as single nucleotide polymorphisms or SNPs) was compared between the two groups of patients.

Comparison of the genetic differences in the NKG2D gene between patients with and without cholangiocarcinoma found no significant difference in the genetic code for this protein between the two patient groups. Therefore this study found no increased risk of sporadic cholangiocarcinoma arising from a particular genetic variation in the NK cell receptor protein NKG2D. This is unlike primary sclerosing cholangitis associated cholangiocarcinoma, and may reflect different mechanisms of tumour development between primary sclerosing cholangitis associated and sporadic cholangiocarcinoma. Dr Wadsworth and colleagues suggest that a wider study assessing the differences in many genes between people with and without cholangiocarcinoma may reveal genetic risk factors for the development of this cancer.

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