Research Update

Pinpointing the genes at work in osteoarthritis and cardiovascular disease

Several diseases thought of as age- or lifestyle-related have strong genetic components, according to research in progress presented at the Human Genome Meeting held in Vancouver in April. Dr. Elina Slagboom of the TNO-PG Gaubius Laboratory in Lieden, The Netherlands, presented her findings from genetic research into osteoarthritis and cardiovascular disease.

As a late-onset disease, osteoarthritis (OA) has a strong genetic component, says Slagboom. But is the genetic influence detectable, and which genes are involved? One of the difficulties in determining the genetic factors influencing OA is that risk factors for the disease also have genetic components of their own.

In her recent work, Slagboom looked at radiographic evidence of OA in subjects enrolled in the "Rotterdam" study, which included 1000 subjects aged between 55 and 65. Only 18% of the subjects, however, had OA changes on radiographs.

Slagboom's next step was to look for candidate genes in cartilage damage and repair. The presence of the type II collagen (*COL2AI-5*) gene has been shown to correlate with a fivefold increase in the risk of OA. The angiotensinogen (*AGN*) gene has been associated with OA in both hands. However, the search for genes "could go on forever," says Slagboom, who then turned her attention to autosomal dominant families with generalized early-onset OA. She is now trying to find a gene associated with early-onset OA and more common OA phenotypes, using sibling pairs with OA demonstrated on radiographs. She will look for associations between these pairs and the subjects in the Rotterdam study.

In her work on cardiovascular disease (CVD), Slagboom is looking at 500 twin pairs to find the heritability of risk factors. Forty genes are associated with arteriosclerosis, and she is trying to discover if any 1 gene is linked to the risk of death from CVD. In a study of 650 patients over age 85, Slagboom examined the hypothesis that mutations in the methylenetetrahydrofolate reductase (*MTHFR*) gene contributed directly to death. The patients were followed for 10 years; 89% of them died during that decade, 38% from cardiovascular disease. The male gene carriers had 4 times the risk of dying from cancer than from cardiovascular disease, which Slagboom concluded was due to their high rate of smoking — 50% smoked, compared with 4% of the women in the study.

Slagboom is currently replicating the study with a second sample of subjects aged 85 and older, whom she will test for the *MTHFR* gene. In another study of 900 men aged 65 to 85, preliminary results show no significant relation between the presence of the gene and risk of death, but almost twice the risk of CVD and cancer among gene carriers. — *Heather Kent*, Vancouver

Turning T cells to the task of fighting cancer

In addition to their essential role in fighting infection, T lymphocytes are proving their use in eliminating cancer cells. This ability is at the heart of recent research into immunotherapy for cancer. Now researchers at the Memorial Sloan-Kettering Cancer Center in New York have developed stable, artificial cells that stimulate T cells to fight cancer (*Nat Biotechnol* 2000;18:405-9).

"There are cells in the body that are specialized in the function of presenting antigens to T cells," says lead researcher Dr. Michel Sadelain. "These cells, termed 'antigen-presenting cells,' naturally express a cohort of molecules that render them effective in this task. However, the generation of such cells for the purpose of inducing specific T cells is labour-intensive and time-consuming. We therefore examined what are the minimal components needed to make genetically engineered cells that are potent activators of T cells that are able to recognize and destroy tumour cells."

Sadelain and his colleagues used mouse cells to stimulate the expansion of human tumour-reactive T cells in the laboratory. They found that introducing just 6 genes was enough to create a cell that efficiently stimulates and amplifies human cytotoxic T lymphocytes that break down melanoma cells in vitro. Three genes are used to generate the peptide complex that directly engages the T cell receptor. The other 3 genes enhance T cell activation by engaging other receptors expressed by the responding T cell.

"To our surprise, these artificial antigen-presenting cells worked at least as well as dendritic cells, the most potent naturally occurring antigen-presenting cells, under the experimental conditions used so far," says Dr. Sadelain.

The next step, he adds, is to confirm that artificial antigen-presenting cells can be generally applied to induce tumour-specific T cells in the laboratory. "We will initially focus on antigens found in lymphomas, leukemias and prostate cancer. We also plan to assess the efficacy of these T cells in animal studies. We intend to develop a system that could also permit stimulation of T cells against more than 1 antigen at a time." — *Donalee Moulton*, Halifax