A susceptibility gene to the most common form of human arthritis

A susceptibility gene to osteoarthritis, a painful degenerative joint disease, has been identified by researchers led by Shiro Ikegawa, in Laboratory for Bone and Joint Diseases at the RIKEN Institute in Tokyo. This discovery would open up a new route to treatment for osteoarthritis. They found in the asporin gene (ASPN), a polymorphism (D14) occurs more commonly in patients with osteoarthritis. Asporin suppresses TGF-β expression in chondrogenesis (cartilage generative and regenerative processes) in vitro, which is necessary to maintain healthy cartilage in joints. The D14 allele presents the strongest inhibitory effect among all alleles of asporin, preventing or impairing chondrogenesis.

Over 5% of the global population, including more than 7 million people in Japan, are diagnosed with osteoarthritis, which is characterized as the gradual decline of cartilage until bone grates against bone. When the cartilage cushioning the bones breaks down, the pain can often lead to immobility, restricting activity and impacting an individual's the quality of life. The aetiology is unclear but it is considered a polygenetic disease where a combination of genetic and environmental factors contributes to its onset and progression. Osteoarthritis still lacks reliable treatments that alleviate symptoms or halt progression.

Articular cartilage is a slick layer of proteins that lubricate and cushion the bone against abrasion in the joint. This viscoelasticity is maintained by the extracellular matrix (ECM) that builds and rebuilds the articular cartilage. Degeneration of the cartilage may result from impairment in this matrix, processes involved, or in gene transcription.

Asporin, a member of the SLRP (small leucine rich protein) protein family, contributes to ECM formation as a negative regulator of chondrocyte differentiation and binds to TGF-β a growth factor for cartilage. Therefore, the researchers in the Bone and Joint Disease
laboratory suspected that naturally occurring variations in *APSN*, might affect individual susceptibility to osteoarthritis.

**RESEARCH RESULTS**

After locating *APSN* and sequencing all its variations, Ikagawa's team identified 21 polymorphisms, 16 of which were newly discovered in 48 patients with osteoarthritis. Two independent analyses using separate populations showed a positive association between one of the D (asparatic acid)-repeat polymorphisms, the D14 allele, and subjects with knee or hip osteoarthritis.

To understand how changes in the D-repeat region of asporin contribute to cartilage loss, the researchers first examined the role of asporin for the proteins involved in cartilage formation. TGF-β (transforming growth factor-beta) is an important peptide in chondrogenesis that regulates the differentiation and proliferation of chondrocytes. Overexpressing either D13 or D14 alleles in cells suppressed this TGF-β activity, indicating that asporin negatively regulates TGF-β activity and prevents cartilage matrix production. Variations in the D-repeat had different effects on TGF-β signalling, with D14 having the strongest influence.

The next research step will be to flush out the functional relationships of asporin and the effects of the various D-repeats on those relationships. Understanding how asporin contributes to osteoarthritis requires first understanding how the protein interacts with other extracellular matrix proteins and TGF-β activity. With this knowledge, new therapeutic treatments might become possible, and the current study is opening the new pavement for the future dream.

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