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Understanding slippage: genetic variations and lumbar disc problems

Lower back pain will affect 70-80% of us at least once in our lives. When it strikes, it can cause unimaginable pain and steal strength, mobility, and youth. Thankfully, simple changes in lifestyle may prevent repeated or prolonged back pain. However, for unlucky individuals, like British Prime Minister Tony Blair, the pain is severe and current treatment provides little real hope. RIKEN researchers in the Laboratory for Bone and Joint Disease have found a genetic key that explains how bone tissue remains pliant. They are opening a new door to therapy for a huge number of back pain sufferers.

The intervertebral disc is a cartilaginous tissue between the vertebra that cushion them from impact and enable fluid movement. Its degeneration causes lumbar pain. In addition, the outer layer of these discs, the annulus fibrosus, may become brittle or thin over time, reducing spinal flexibility. When this disc degradation is severe, fissures may appear through which the inner layer of the disc, the nucleus pulposus, can seep out. A painful herniated disc results. Combined, degeneration and herniation make up lumbar disc degeneration, or LDD.

Although its causes are not known, the high prevalence of LDD among families strongly implicates genetic-based factors. More specifically, it points to genes that code for proteins involved in maintaining the extra-cellular matrix of the inner layer of the disc. Animal studies have shown that these proteins are important in developing the cartilage-like tissue of the nucleus pulposus, suggesting that abnormalities in these proteins contribute to the problems associated with disc degeneration. Therefore, the researchers in the laboratory examined all the genes that participate in extra-cellular matrix formation in search of LDD's etiology. They identified one small difference in the DNA (called a single nucleotide polymorphism or SNP) of one gene, CILP, which was associated with Japanese patients with LDD.
After confirming this association in a second screening and eliminating other explanations for the association, the researchers investigated the function of CILP and the damaging SNP in a series of cells studies. The results were enlightening. They found that CILP binds to TGF-β, a cardinal growth factor that maintains extracellular matrix proteins in the discs. This binding inhibits TGF-β activities on cartilage metabolism. This inhibition is stronger in the CILP variations (1184T -> C) and can prevent the growth factor from regenerating the matrix. Speculating on their findings, the researchers suggest that aberrations in CILP would upset the regulatory balance of TGF-β interaction and weaken the extra-cellular matrix. Disc degeneration and herniation often follow.

The importance of TGF-β goes beyond its contributions to vertebra tissue integrity. Most connecting tissue requires TGF-β activity so that they can remain supple. The researchers at RIKEN have found a genetic link for lumbar disc degeneration. Along the way they have also identified a possible etiology for the disease and opened up the possibility of developing a novel therapeutic treatment for an alarmingly common source of pain.

*Nature Genetics* published these results on-line in May 2005.

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