Editorial Commentary: Bad For Your Cuff. Smoking Causes Alterations in Gene Expression Resulting in Inflammation, Fatty Degeneration, and Fibrosis. Or Maybe Not?

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Abstract: Gene expression is the transcription from DNA to RNA and then translation into proteins or other mediators. Smoking causes alterations in gene expression and can result in inflammatory changes, fatty degeneration, and fibrosis in patients with rotator cuff disease. Whether the smoking-related upregulation of inflammatory mediators such as interleukin 6 and C-reactive protein is one of the responsible factors for rotator cuff tears and also influences healing after surgery is currently not known. The current evidence is inconclusive and controversial.

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Gene expression is the process when the instructions in our DNA are transcribed into RNA or messenger RNA, which is then translated into a functional product such as a protein. Increased gene expression means that more proteins are made, either in volume or over time.[1] This is a critical process for any species to adapt and evolve and is an important component in the primary evolutionary force.[1] So gene expression is everywhere. Healthier diet is associated with gene expression and gene regulation and potentially makes you live longer.[2] Smoking upregulates inflammatory mediators such as interleukin 6 and C-reactive protein levels, possibly causing tissue damage.[3,4] Interestingly, gene expression levels remain elevated even up to 30 years after smoking cessation.[3,4] Not surprisingly, tendon tissue and the rotator cuff are also affected. Plachel et al.[5] have demonstrated that changes in RNA expression profiles were correlated with chronic rotator cuff disorders but most strongly with age and severity of the rotator cuff pathology. Obviously, factors other than smoking also play an important role. Or maybe simply aging, with its associated degenerative changes, causes alterations in gene expression, which are then modulated through smoking? Smoking habit associations were also investigated by Plachel et al.[5] but did not play a role.

In their article in this issue, "Influence of Smoking on the Expression of Genes and Proteins Related to Fat Infiltration, Inflammation, and Fibrosis in the Rotator Cuff Muscles of Patients With Chronic Rotator Cuff Tears: A Pilot Study," Lee, Kim, Ki, and Chung[6] have investigated alterations in gene expression and proteins that are associated with myogenesis, inflammation, adipogenesis, and muscle fibrosis and compared medium-sized rotator cuff tears in heavy smokers to non-smokers. What were the results? In simple words, some of the marker genes were upregulated in smokers; no differences were observed in other genes that regulate similar pathways. Adipogenetic genes were upregulated in smokers, and there was no difference in gene expression for myogenetic and fibrotic gene expression between smokers and non-smokers.[6] For the inflammatory mediators, specifically for interleukin 6, no differences between the groups were observed. This is in contrast to the findings of a previous meta-analysis[3] and makes you wonder whether the results of Lee et al.[6] are valid or whether the sample size was simply too low to observe any meaningful between-group differences. The *P* levels (.02-.05) may mislead us into believing that there really is a difference. The recent discussions about

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fragility index suggest that only a very small number of events may change the study significance.[7] Thankfully, the authors have acknowledged that their study is insufficiently powered to detect meaningful differences.[6] Nevertheless, this means that the results must be viewed with extreme caution. One of the difficulties with gene expression is that it may not be a single mediator but rather a combination of events triggering a specific response. For example, interleukin 6 can be either a good or a bad guy, contributing to tissue damage, promoting carcinogenesis, or regulating tissue healing and regeneration.[3,4,8]

But we have to accept this study for what it is: a pilot project. Let us congratulate the authors for taking on such a difficult and laborious project and hope they will use the experience and existing data to expand and enroll sufficient numbers with the follow-up study. I suspect that smoking may not only kill you but also cause fatty degeneration, fibrosis, and chronic inflammation in smokers and that smoking is a major risk factor for rotator cuff tears. There clearly is as yet an unknown relationship between genes, gene expression, and environmental factors, but we still need to establish which of these factors contribute to rotator cuff disease.

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