TGF β Collagen-Keloid and the abnormal collagen hypothesis

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Leiomyoma (uterine fibroids) are a prevalent disorder of the reproductive tract that affects millions of women leading to: bleeding, pelvic pain, infertility, pre-term birth, and pregnancy loss. There are significant differences in the prevalence of disease among women of African-American background. Despite their considerable impact upon women, understanding of the condition is limited and the cause of these common benign growths remains unknown. In order to gain understanding into the genetic features that might contribute to fibroid growth, our group has used global gene expression [1,2] profiling to study uterine leiomyoma (fibroids) and ask the question: what are the genetic features that characterize the leiomyoma cell? To address this question we compared surgically-obtained tissue from normal myometrium with fibroid tumors using Affymetrix™ U133 A&B chips, which contain transcripts from up to 33,000 genes. Differences in gene expression were confirmed using RT-PCR, real-time PCR, immunohistochemistry, or other approaches. Overall, results revealed that approximately 1% of genes differed greater than two-fold between normal myometrium and tissues harvested from uterine fibroids. An unexpected observation was that there were rather marked differences between arrays from different core facilities using different Affymetrix™ platforms. We interpret the differences to variation in procedure, but concluded it was essential to confirm results using additional experimental approaches.[3] A second unexpected result was that genes involved in sex steroid action were not featured as differentially expressed genes. Instead, genes involved in formation of collagen, and proteins comprising the extracellular matrix (ECM) were differentially expressed. The remarkable changes in expression of genes encoding collagen were accompanied by ultrastructural studies that revealed that collagen fibrils were loosely packed and arrayed in a non-parallel manner in leiomyoma, compared to tight bundles in normal myometrium. Analysis of mature collagen fibrils in myometrium using electron microscopy suggested an ordered, barbed structure at 64,000-x magnification. In contrast, collagen fibrils in leiomyoma lacked this barbed structure.[4]

Furthermore, when our list of differentially expressed genes was compared with published lists obtained using a similar methodology, six transcripts were consistently identified.[5] One transcript encoded dermatopontin, a 22kd extracellular protein known to bind the collagen-binding protein decorin, as well as TGF-beta. Reverse-transcriptase real-time PCR, RT-PCR, and immunohistochemical experiments confirmed the reduction in dermatopontin in fibroids.[2] Of note, reductions in dermatopontin were previously recognized in hypertrophic scar and keloid, two disorders of tissue remodeling in skin also with an increased prevalence in African-American women. Next, we compared our list of genes with a recently reported list for keloid tissues where a similar approach had been used.[6] Although not identical, there were striking similarities in gene expression among the two conditions. These observations raise the possibility that disordered tissue remodeling may result in part from an abnormal extracellular matrix in this condition and contribute to leiomyoma growth. These findings support and extend earlier studies of TGF signaling in leiomyoma[7,8] and bring to question whether anti-fibrotic therapies may hold promise as non-surgical treatment for leiomyoma.

In summary, gene profiling experiments suggest the possibility that leiomyoma may arise from normal uterine cells that undergo alteration in response to disordered extracellular signals. We are now examining the hypothesis that abnormal tissue repair may contribute to leiomyoma development.

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