Dysregulated expression of imprinted genes is a common feature of palmar fascia fibrosis

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BACKGROUND: Fibrosis of the palmar fascia, also known as Dupuytren's disease (DD), affects 1% - 7% of the US population [1]. The pathogenesis of this benign fibroproliferative disease is not understood. In addition to exhibiting established fibrosis biomarkers, primary fibroblasts derived from fibrotic palmar fascia exhibit some biomarkers of malignant tumors. One of these is increased expression of *IGF2* [2], a gene that frequently exhibits loss of normal, parent-of-origin specific allelic expression (genomic imprinting) in tumors [3]. Therefore, we assessed the imprinted expression of *IGF2* in fibroblasts derived from patients with "informative" *IGF2* alleles (i.e., where paternally derived and maternally derived alleles can be readily distinguished) to determine if loss of imprinting (LOI) of *IGF2* was also evident in palmar fascia fibrosis.

METHODS: Primary fibroblasts ("DD cells") were derived from surgically resected, fibrotic palmar fascia of 8 informative patients, the adjacent, macroscopically uninvolved palmar fascia in these patients ("PF cells"), and normal palmar fascia from 3 informative patients undergoing hand surgeries for unrelated reasons ("CT cells") as normal controls. Mono or bi-allelic expression of *IGF2* was correlated with total *IGF2* transcript levels and with the expression levels of *H19* and *WT1*, syntenic genes with imprinted expression in normal fibroblasts, using restriction mapping and quantitative PCR.

RESULTS: 7 of 8 DD cells cultures exhibited bi-allelic *IGF2* expression, indicating LOI, whereas all 3 CT cell cultures exhibited normal mono-allelic (imprinted) *IGF2* expression. 6 of 8 PF cell cultures exhibited LOI of *IGF2*. LOI of *IGF2* was directly correlated with increased *IGF2* expression and inversely correlated with *H19* expression in DD cells, but not in PF cells. The detectable expression of *WT1* was consistently restricted to DD cells.

DISCUSSION: The majority of fibroblast cultures from informative patients with palmar fascia fibrosis exhibited LOI of *IGF2*, irrespective of whether cells were derived from fibrotic or macroscopically uninvolved palmar fascia. These findings imply links between palmar fascia fibrosis, LOI of *IGF2* and dysregulated expression of *IGF2*, *H19* and *WT1*, and are consistent with the pathogenesis of palmar fascia fibrosis and malignant tumors sharing similar molecular mechanisms.

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