Asporin Inhibits Collagen Matrix-Mediated Intercellular Mechanocommunications Between Fibroblasts During Keloid Progression

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Background:
Keloids are fibrotic lesions that grow unceasingly and invasively and are driven by local mechanical stimuli. Unlike other fibrotic diseases and normal wound healing, keloids exhibit little transformation of dermal fibroblasts into α–SMA$^+$myofibroblasts.

Methods and Results:
Differential gene expression in the keloid–leading edge relative to surrounding healthy skin showed that asporin is the most strongly expressed gene in keloids and its gene–ontology terms relate strongly to ECM metabolism/organization. Experiments with human dermal cells (HDFs) showed that asporin overexpression/treatment abrogated the HDF ability to adopt a perpendicular orientation when subjected to stretching tension. It also induced calcification of the surrounding 3D collagen matrix. Asporin overexpression/treatment also prevented the HDFs from remodeling the surrounding 3D collagen matrix, leading to a disorganized network of thick, wavy collagen fibers that resembled keloid collagen architecture. This in turn impaired the ability of the HDFs to contract the collagen matrix. Asporin treatment also made the fibroblasts impervious to the fibrous collagen contraction of α–SMA$^+$myofibroblasts, which normally activates fibroblasts. Thus, by calcifying collagen, asporin prevents fibroblasts from linearly rearranging the surrounding collagen; this reduces both their mechanosensitivity and mechanosignaling to each other through the collagen network. This blocks fibroblast activation and differentiation into the mature myofibroblasts that efficiently remodel the extracellular matrix. Consequently, the fibroblasts remain immature, highly proliferative, and continue laying down abundant extracellular matrix, causing keloid growth and invasion. Notably, dermal injection of asporin–overexpressing HDFs into murine wounds recapitulated keloid collagen histopathological characteristics.

Conclusion:

This study shows that ASPN–mediated inhibition of mechanocommunications between fibroblasts promotes keloid growth. It also suggests that ASPN is a potential diagnostic biomarker and therapeutic target for keloids.