
Controversy: The Contracture in Dupuytren Disease Is an Active Process

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10.1 Introduction

All cellular processes involve energy expenditure and hence can be considered to be active. These include cell migration, proliferation, matrix deposition and remodelling. In Dupuytren Disease the key cells are the myofibroblasts, which are responsible for matrix deposition and shortening.

10.2 Myofibroblast

10.2.1 The Cell

The hallmark of all fibrotic disorders is the presence of activated myofibroblasts. A myofibroblast is characterised by the presence of α -smooth muscle actin (α -SMA), the contractile element seen in smooth muscle cells, pericytes and myoepithelial cells. However, only myofibroblasts assemble their α -SMA into stress fibres that form the contractile apparatus of the cell. This mechanism is, for example, different from smooth muscle cells, which express the myosin heavy chain (Hinz 2015b), whereas myofibroblasts express non-muscle myosin II (Southern et al 2016). Unlike the relatively short-lived contraction of striated and smooth muscle, myofibroblast contractions tend to be sustained. Some of the earliest work that identified myofibroblasts in granulation tissue characterised their sustained contraction of tissue (Majno et al. 1971).

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10.2.2 Coordinated Activities

Myofibroblasts are also characterised by the presence of specialised junctions that connect them to the matrix and to adjacent myofibroblasts (Follonier Castella et al. 2010; Hinz and Gabbiani 2003). The former are termed fibronexi (Singer et al. 1984; Yannas 1998), and the latter include adherens junctions, mechanosensitive junctions and gap junctions. Adherens junctions are composed of cadherins that extend through the plasma membrane and mediate calcium-dependent intercellular adhesion through homophilic association of their ectodomains (Yap et al. 1997; Follonier Castella et al. 2010). The cadherin receptors associate intracellularly with several structural and signalling proteins, most notably β -catenin, as well as the α -SMA cytoskeleton (Yap et al. 1997). OB cadherin or cadherin 11 predominates in myofibroblasts (Hinz et al. 2004; Verhoekx et al. 2013). Mechanosensitive ion channels open when force is transmitted by an adjacent cell via adherens junctions, allowing an influx of cations such as calcium. Adjacent cells can also communicate directly via gap junctions. Gap junctions are composed of six connexin 43 molecules. Hexamers in adjoining cells make direct contact to allow passage of molecules of up to 1 kDa between cells via hydrophilic channels. We showed that Dupuytren myofibroblasts function as a coordinated cellular syncytium via the 3 types of intercellular junctions (Verhoekx et al. 2013). Inhibition of the intercellular junctions reduced the contractile effect on the matrix by approximately 50%, and disassembly of the cellular cytoskeleton abolished the remaining 50%, suggesting the residual activity was due to tension exerted by the individual cells on the matrix via the focal adhesions (Verhoekx et al. 2013).

10.3 Matrix

10.3.1 Deposition, Degradation and Remodelling

Activated myofibroblasts play a prominent role in the secretion of the matrix that accumulates in fibrotic disorders. This includes the collagens as

well as a proteoglycans, fibronectins, fibrillins, tenascins and various growth factors and cytokines (Klingberg et al. 2013). Furthermore, the myofibroblasts are highly active in remodelling the matrix, and multiple studies have highlighted aberrations in matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs) in Dupuytren Disease at the mRNA and protein level (Ulrich et al. 2003, 2009; Augoff et al. 2006; Johnston et al. 2007; Ratajczak-Wielgomas et al. 2012). Overall, these data suggest a high turnover state of the matrix, with increased expression of MMP1, MMP2, MMP12, MMP14 (MT1-MMP), TIMPs 1 and 2 and ADAMTS-14. The deposition, degradation and remodelling of the matrix are all processes that require cellular activity.

10.3.2 Contraction by Myofibroblasts

Tomasek et al. (2002) proposed an elegant model of how fibrotic contractures develop as opposed to short-lived muscle contractions. They proposed that myofibroblasts contract the local matrix. The cells then add new matrix components to the shortened framework. The process is repeated by multiple cells such that localised matrix remodelling around multiple groups of cells results in tissue contracture (Fig. 10.1). This process was subsequently likened to a lockstep or ratchet mechanism (Follonier et al. 2008).

10.3.3 Vicious Cycle

A prominent pro-fibrotic cytokine is TGF- β 1. It is secreted and resides in the matrix as an inactive form. Traction on the matrix by myofibroblasts liberates active TGF- β 1, which can then bind to the cell surface receptors to upregulate transcription of genes associated with fibrosis (Hinz 2015a).

Conclusion

Fibrotic contractures only develop in living tissues, and, as for all other fibrotic contractures (Tomasek et al. 2002), the contracture in Dupuytren Disease that results in flexion

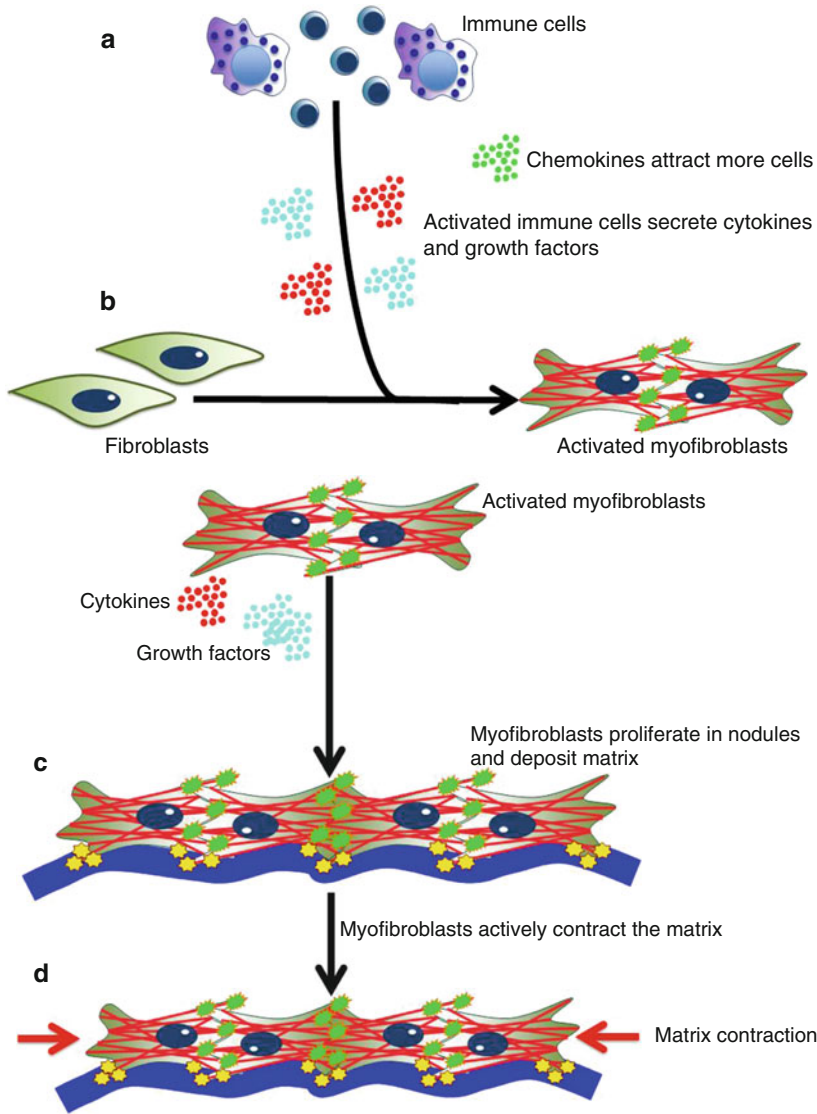
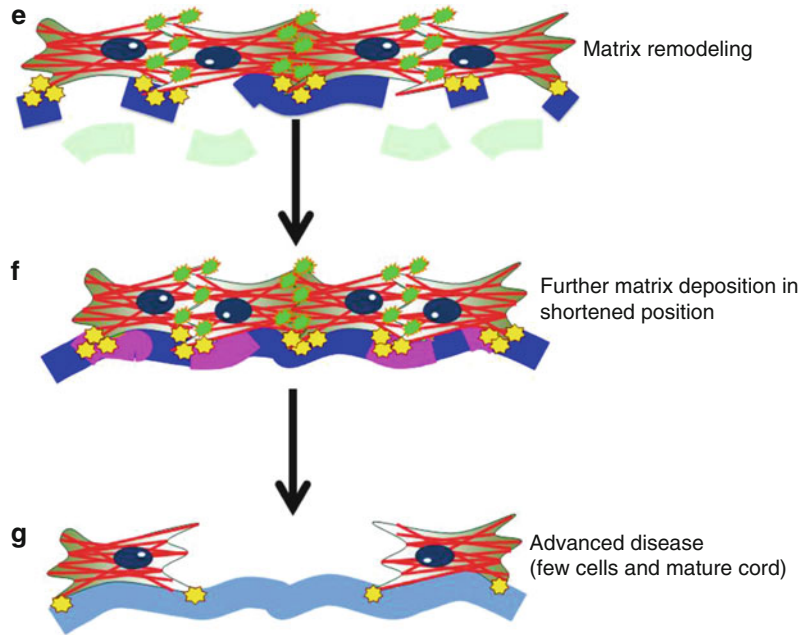


Fig. 10.1 Schematic showing the development of contractures in Dupuytren patients through a series of active processes, involving cell recruitment, cell differentiation, metabolism, cell and matrix contraction, secretion and phagocytosis. **(a)** Resident immune cells in the fascia of genetically susceptible individuals are activated, and more immune cells from the circulation are attracted to the site by locally secreted chemokines. **(b)** The cytokines and growth factors convert the precursor cells into myofibroblasts. **(c)** In the presence of growth factors and cytokines, the myofibroblasts proliferate and secrete matrix compo-

ments that make up Dupuytren cords. The myofibroblasts communicate with each other through intercellular junctions (*shown in green*) and attach to the matrix via specialist adhesions (*shown in yellow*). **(d)** Through their coordinated actions, groups of myofibroblasts contract the matrix. **(e)** The myofibroblasts remodel the matrix through the action of matrix-degrading enzymes. **(f)** The myofibroblasts secrete further components to augment the shortened matrix. **(g)** Eventually the myofibroblasts disappear and the patient presents with relatively acellular contracted cords of advanced disease

Fig. 10.1 (continued)

deformities of the digits is an active process. All of the following components of the process require cell activity and energy expenditure:

1. Inflammation, which precedes all forms of fibrosis (Wick et al. 2013)
2. Generation of activated myofibroblasts
3. Secretion of matrix components, growth factors and cytokines by the myofibroblasts
4. Contraction of the matrix by the coordinated activity of myofibroblasts
5. Further matrix deposition and remodelling by myofibroblasts

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