The potential roles of cell migration and extra-cellular matrix interactions in Dupuytren's disease progression and recurrence

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SUMMARY

Dupuytren's disease is a pathological condition of the palmar fascia characterized by the formation of contractile disease cords that result in permanent finger contracture. This condition is believed to progress from a myofibroblast-rich nodule in the early clinical stages of the disease to a contractile disease cord spanning a portion of the fascia, leading to contracture of one or more digits. The mechanism(s) by which this disease progresses from a nodule to a collagenous disease cord are poorly understood. Here, we discuss two possible models of disease progression. Firstly, disease progression might be mediated by the proliferation and outward migration of disease cells from within the nodule to populate the adjacent palmar fascia, resulting in a disease cord containing contractile cells derived from the nodule itself. Alternatively, nodular cells may secrete disease-associated factors into the surrounding extra-cellular matrix, thereby altering its composition and triggering quiescent, phenotypically normal cells in the adjacent palmar fascia to take on a proliferative and contractile phenotype. Based on the available evidence and the current state of knowledge of myofibroblast biology, we hypothesize that extra-cellular matrix interactions resulting in conversion of adjacent palmar fascia cells to a disease phenotype is more likely than cell migration from the nodule. Understanding the mechanisms of Dupuytren's disease progression will assist in the development of effective therapeutic interventions to address the high clinical recurrence rate of this condition.

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Conflict of interest statement

None declared.

Background

Dupuytren's disease (DD) is a pathological condition of the palmar fascia mostly affecting Caucasian men [1]. The disease is characterized by the formation of collagenous disease cords and permanent contracture of the affected finger(s) [2]. DD is most commonly treated by surgical resection; however, this procedure is associated with very high recurrence rates [3]. This disease has been previously hypothesized to progress through three stages: the proliferative, involutional, and residual stages [4]. In the proliferative stage, a nodule containing highly proliferative and contractile cells forms and with time, this nodule develops into a disease cord extending from the proximal palm into the finger [4]. The mechanism by which the disease progresses from a nodule to a collagenous disease cord is not understood. The hypothesis that residual cord formation is simply a mechanical consequence of contraction of the fascia mediated by the proliferative nodule, rather than a component of the disease process per se [4], is not supported by studies demonstrating marked changes in the gene expression profiles of cells in residual DD cord compared to phenotypically normal palmar fascia from patients with DD and to control palmar fascia derived from patients undergoing carpal tunnel release [5].

Hypothesis

We hypothesize that disease progression from nodule to cord formation is the result of cells within the nodule secreting disease-associated proteins into their extra-cellular matrix (ECM). This "primed" matrix induces quiescent cells in the adjacent palmar fascia to proliferate and take on a diseased cell phenotype. We compare this hypothesis to an alternative explanation, that cell migration from the nodule results in infiltration of the adjacent palmar fascia by disease cells and formation of a fascia populated by nodule-derived cells that give rise to a collagenous disease cord.

Evaluation of this hypothesis

If disease cord formation were driven by enhanced cell migration from nodule, we would expect that the nodule contain highly proliferative and motile cells. While the proliferative stage of DD is characterized by enhanced proliferation of nodule cells, both the proliferative and involutional stages are marked by increased numbers of myofibroblasts, i.e. fibroblast cells with smooth muscle properties [4]. Some studies have suggested that myofibroblasts have reduced motility relative to less differentiated fibroblasts [6,7]. Using a microgrooved surface migration assay that monitors cell migration in one dimension, Thampatty and Wang [6] found that once human fibroblasts differentiated into myofibroblasts they were less motile than the undifferentiated controls. This reduction in migration may be associated with the incorporation of α -smooth muscle actin in stress fibres, a widely accepted marker of myofibroblast formation, and the development of supermature focal adhesions which exerts greater stress compared to other focal adhesions [8,9]. Together, these properties may contribute to increased cell adhesion, thereby limiting cell motility. Studies have demonstrated that the inhibition of α -smooth muscle actin production by myofibroblasts leads to a decrease in their cell adhesion [8], and an increase in cell motility [7]. Thus, while cell migration of proliferative but relatively non-contractile fibroblasts may contribute to

disease cord formation, it seems less likely that migration of contractile, α -smooth muscle actin expressing myofibroblasts is the driving force responsible for disease progression.

We hypothesize that cells in the nodule secrete disease-associated molecules into the surrounding ECM microenvironment affecting nearby cells of the palmar fascia. Analyses of surgically-resected DD tissues have identified a number of dysregulated ECM proteins, including proteoglycan [10], Platelet Derived Growth Factor (PDGF) [11], periostin [12], and A Disintegrin and Metalloprotease (ADAM)-12 [13]. In other systems, these molecules have been shown to affect key processes previously identified in DD, such as cell proliferation and myofibroblast formation. Normal human dermal fibroblast have been shown to express different integrins in response to PDGF treatment depending on whether the cells were cultured in collagen, fibronectin-rich, or fibrin-rich ECM [14]. Moreover, in vitro studies have shown that cells derived from unaffected palmar fascia of DD patients are sensitive to disease-associated ECM [15,16]. Cells derived from unaffected palmar fascia of DD patients were shown to have enhanced contraction of collagen lattices in the presence of Transforming Growth Factor- β 2, similar to DD cellular responses to this cytokine [16]. Furthermore, the addition of cyclic strain on cells from the unaffected palmar fascia of DD patients responded similarly to DD cells, displaying elevated levels of PDGF-A, while cyclic strain did not affect PDGF-A levels in cells derived from normal palmar fascia [15]. Cells from diseased and non-diseased palmar fascia from DD patients responded to the exogenous addition of 5-fluorouracil, a treatment used to reduce scarring, displaying decreased proliferation and myofibroblast differentiation while having negligible effects on cells derived from normal palmar fascia [17]. Cumulatively, these data suggest that cells derived from adjacent, phenotypically unaffected palmar fascia cells of DD patients are not truly normal, displaying behaviours that are similar to DD cells rather than normal palmar fascia cells, and that they may be hypersensitive to disease-associated ECM molecules relative to palmar fascia cells derived from patients without DD.

Finally, in clinical studies, there is some evidence to suggest that full thickness skin grafts during DD surgical resection attenuate disease recurrence [18]. This observation may suggest that perhaps the residual ECM post-surgery can stimulate the transition of phenotypically normal cells of the remaining palmar fascia towards a disease-like phenotype, thereby promoting disease recurrence. Replacing the dermis with skin grafts, which would theoretically remove the disease ECM, essentially reduces the potential for contamination of the unaffected palmar fascia by disease promoting molecules.

Testing these hypotheses

Unfortunately there are no animal models of DD, making any hypothesis of DD progression difficult to test. If ECM interactions are primary mediators of DD progression, it should be possible to identify ECM-associated molecules that can induce primary cells derived from adjacent, phenotypically normal palmar fascia from patients undergoing surgical resection of DD cord to take on the proliferative and contractile characteristics of primary DD cells. Conversely, studies assessing the relative invasive potential of primary cells derived from adjacent, phenotypically normal palmar fascia and DD on engineered palmar fascia substrates could determine which cell type has the greater invasive potential.

Consequences of this hypothesis

We hypothesize that it is more likely that DD progression and recurrence after surgery is associated with cell-ECM interactions than with the cell migration model of disease progression. This hypothesis would predict that primary cells derived from surgically-resected DD cord samples are not derived directly from the nodule but are instead the result of the nodule regulating the proliferation and differentiation of cells in the adjacent fascia of patients with a predisposition to develop DD. If this proves to be correct, therapies targeting the molecules shown to be secreted by nodules and to induce the proliferation and/or myofibroblast differentiation of adjacent palmar fascia cells derived from patients with DD, rather than cells derived from normal palmar fascia taken from patients without DD, may result in identification of novel therapeutic targets. Such therapies could be targeted to the phenotypically unaffected fascia of patients after DD cord resection with the aim of inhibiting disease recurrence. Interventions designed to alter the fate of phenotypically normal cells of the palmar fascia adjacent to the disease environment may also yield a greater understanding of the pathogenesis of this debilitating disease.

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