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The cell biology of Dupuytren's Disease

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Abstract

Dupuytren's Disease is a benign palmar fibromatosis characterised by progressive shortening of the palmar fascia, leading to significant deformity and impaired function of the hand. Having knowledge of the cellular biology is an essential part of understanding the disease, the treatment options and the high recurrence rate. Myofibroblasts are thought to play a key role in the pathogenesis of the disease though their origin is not clear. Progenitor stem cells originating from the skin overlying the nodule or perinodular fat have been identified as potential source of the myofibroblasts. Several key cytokines and growth factors that potentially play an important role in the development of the disease have been identified.

Introduction

Dupuytren's Disease is an ill-defined fibroproliferative disorder of the palmar fascia, which often causes significant contracture of the metacarpophalangeal and proximal interphalangeal joints. Patients experience striking deformity, loss of function and impaired quality of life as the disease progresses [1]. Throughout the course of the disease, patients characteristically develop nodules, cords and flexion contractures identifiable on clinical examination. The myofibroblast, with combined properties of smooth muscle cells and fibroblasts is thought to play a crucial role in the pathogenesis of the disease. These cells are thought to be responsible for the nodule formation and the subsequent contracture [2].

Much remains to be understood regarding the cellular biology, the aetiology and the pathogenesis of the disease [3]. Some studies have suggested a genetic basis to the disease and demonstrated an autosomal dominant pattern of inheritance [4], [5]. However, no single responsible gene has been identified and the disease also occurs sporadically in large number of cases [6]. Treatments are likely to improve as we further our understanding of the disease process in relation to cell biology and genetic basis of the disease.

Stages of Dupuytren's Disease

Dupuytren's Disease has been likened in several ways to the active process of connective tissue repair, based on histological and biochemical alterations [7]. Similarities between the two processes include: a large density of fibroblasts, increased extracellular matrix (ECM) protein deposition and the presence of myofibroblasts, cells which cause wound contraction.

Luck et al. initially described three distinct stages of the disease that can be differentiated both clinically and microscopically [7]. The proliferative (early) phase is characterised by an abundance of fibroblasts, in no particular arrangement. Most of the tissue, at this stage, is made up of fibroblasts and the nodules are thought to be vascular in nature. Compared with normal tissue, the fibroblasts in Dupuytren's Disease are the same but are importantly present at a much higher density [8]. The involutional (active) phase is where myofibroblasts predominate. Throughout this stage, fibroblasts become aligned in the direction of stress, most commonly on the ulnar side of the hand [9]. Over time, nodules gradually

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become smaller in size and eventually disappear. The residual (advanced) phase is characterised by cord formation. This is acellular and has a similar appearance to tendons. Shortening of cords and digital flexion contracture of the metacarpophalageal (MCP) or the proximal interphalangeal joints (PIPJ) may occur when skin overlying a nodule fuses with the fascia.

Large amounts of type III (compared to I) collagen are found in the active stage whilst more type I collagen are present in advanced disease. Generally patients progress through the stages at different rates, usually dependent upon their individual risk factors.

Structural and biochemical changes

Dupuytren's Disease progresses from a highly cellular nodule, early on in the disease, to a fibrous, tendon-like acellular cord. Important structural and biochemical changes have been characterised with this disease.

Compared with a normal palmar aponeurosis, collagen synthesis and turnover is rapid, with an increased total collagen content and ratio of type III to type I fibers. It has been postulated that this occurs due to an increased fibroblast density which inhibits the formation of type I collagen [10]. Though almost absent in a normal adult palmar fascia, collagen III is abundant in these patients [9]. Studies have shown that the proportion of type III collagen increases from normal fascia (2%) to nodules (15%), to cords (35%) [11], [12]. In addition, the unidirectional orientation of the collagen fibers differs from that found in a normal aponeurosis. Melling et al. noted that tissues affected by Dupuytren's Disease contained a greater proportion of irregularly arranged collagen fibers which were also of smaller average diameters than in normal tissue [13]. It is suggested that these alterations occur because of the increased proportion of type III collagen in the tissues and that the type III collagen content correlates with the clinical stage of contracture [8].

A study by Brandes et al. demonstrated that external forces might lead to alterations in microfilaments, adherin junctions and connections with endothelial cells. A reorientation and reorganisation of tissue components by myofibroblasts is observed in these patients [14].

Regarding the process of contracture, it is not thought that contraction of the collagen bundles occurs but more that the active cellular process draws the extremities of the tissue together [15]. The changes in collagen and proteoglycans are similar to those occurring in connective tissue undergoing active connective tissue repair. The structural changes also bear a close resemblance to hypertrophic scar tissue, with a high turnover rate but failure to mature as in a normal scar [10].

Biochemical changes

Several studies have demonstrated increased glycosaminoglycans in the fascia of patients with Dupuytren's Disease. In particular, an accumulation of chondroitin sulphate and dermatan sulphate has been reported [16], [17]. This may occur secondary to abnormal growth factor expression and this has similarly been observed in hypertrophic scars. It is thought the increased content of these growth factors may affect collagen formation and the availability of growth factors in Dupuytren's Disease [17]. The concentration of glycosaminoglycans varies depending on the disease manifestation and levels increase gradually from normal fascia to fibrous band, nodule and cord.

Dupuytren's fascia has been demonstrated to have a raised hexosamine content and a greater number of reducible cross-links compared to normal fascia. In addition to this, the major reducible cross link, hydroxyl-lysino-hydroxy-norleucine, which is virtually absent from normal adult palmar fascia, has been reported [18]. Biochemical changes were also demonstrated in normal fascia of the same hand but to a much lesser extent [19]. However, no correlation has been made between the severity of symptoms and the degree of biochemical abnormality.

Proteoglycans and glycosaminoglycans

Studies have demonstrated significantly higher levels of glycosaminoglycans in patients with compared to those without Dupuytren's Disease. The concentration of glycosaminoglycans varies depending on the disease manifestation and levels increase gradually from normal fascia to fibrous band, nodule and cord. These changes are similar to those which occur in hypertrophic scar formation.

The architecture of the extracellular matrix differs depending on the levels of glycosaminoglycans.

Growth factors and cytokines

Experimental studies have demonstrated increased expression of several growth factors in tissue affected by Dupuytren's Disease. Though several of these cytokines are expressed in tissue undergoing repair, it is the inappropriate expression in the palmar aponeurosis, in the absence of any stimulus which is of importance in Dupuytren's Disease. The cytokines and their roles are outlines below [20], [21].

These include:

- Interleukin-1α and β (IL-1)
    - This cytokine causes fibroblast proliferation. Overexpression may account for the large number of fibroblasts found in the active stage of the disease.
- Basic fibroblast growth factor (bFGF)
    - This is has been shown to be mitogenic for the cells in Dupuytren's Disease.
    - Also stimulates fibroblast proliferation
- Platelet derived growth factor (PDGF)
    - Plays a role in the alteration of proliferating fibroblasts.
    - Also mitogenic for cells in Dupuytren's Disease.
- Transforming growth factor beta (TGF-β)
    - Potent stimulator of collagen synthesis
    - This growth factor increases fibroblast proliferation and acts as a fibroblast chemotactic agent.

Cellular biology of connective tissue – the myofibroblast

The nodules of Dupuytren's Disease contain mainly myofibroblasts, surrounded by a tight mesh of fine filaments (likely proteoglycans). Collagen fibrils, 40–60 nm thick and up to 100 nm in diameter, are intermingled between the cells and the mesh. Moving away from the cells, the collagen fibers become irregularly oriented and packed closer together [22].

The cords, in contrast, are composed of large, thick collagen bundles. These have an irregular contour and diameters varying from 50–350 nm. They are tightly packed together and oriented in many directions.

The contracture seen in Dupuytren's has been attributed to an active cellular process, which progressively draws together distal extremities of the affected tissue. Thus, a shorter, smaller tissue is created which still contains the same collagen, fibers and fibrils [15], [23].

It is thought that fibroblasts undergo a process of modulation in order to form myofibroblasts [24]. These cells have unique properties that allow them to create cell-to-cell and cell-to-stroma connections. The myofibroblasts also have a distinctive contractile mechanism which when connected to surrounding myofibroblasts and stroma may provide significant contractile force to explain the severe contractures occurring with Dupuytren's. The biomechanical forces created by the myofibroblasts contribute to the mechanism of contraction. Unlike in normal fascia, the collagen in Dupuytren's has helical configurations and a wave pattern, of shorter wavelength than normal. Some studies have found correlation between myofibroblast activity with clinical severity of Dupuytren's Disease, with greater

myofibroblast ATPase activity found in more severe cases [25], [26]. Though much is understood about the contractile mechanisms, the source of the myofibroblasts in the disease remains unknown. Hindocha et al. postulated that mesenchymal (MSC) and haematopoietic stem cells (HSC) may be involved in Dupuytren's Disease. They compared stem cells in the cord, nodule, perinodular fat and skin of patients with Dupuytren's and compared this with controls. Progenitor cells were identified in the skin overlying the nodule and peronodular fat in Dupuytren's patients. This implied that the palmar fat in these patients may be abnormal and a potential cause for the disease and its recurrence. In addition to these findings, there was greater expression of MSC markers including CD13 and CD29 in the fat surrounding the nodule in Dupuytren's patients compared with controls. The origin, of the myofibroblasts as such may be the skin overlying the nodule or the perinodular fat [2], [27], [28].

Theories of Dupuytren's Disease

Intrinsic theory – Mc Farlane et al. 1974

- Pathological changes in the normal fascia lead to the formation of diseased cords [29].
- Cords occur along routes determined by the normal fascial anatomy and arise from fascial precursors.
- However this does not explain the commonly observed central cord which may occur in Dupuytren's Disease.

Extrinsic theory – Hueston 1985

- The process of fibrosis begins with nodule formation. Nodules arise *de novo* from the metaplasia of fibrofatty tissue [30].
- Nodules then develop into cords which lie superficial to the palmar aponeurosis and eventually spread to form cords which lie superficial to the palmar aponeurosis.
- This theory provides a rational explanation for the presence of nodules. It also explains why recurrence occurs following fascial excision and why rates of recurrence are lower after dermofasciectomy.

Synthesis theory – Gosset's 1985

- This theory states that both cords and nodules are different forms of the same disease process [31].
- Nodules are thought to arise de novo and cords from the palmar fascia.
- Studies by Strickland and Leibovic support this theory.

Murrell's free radical hypothesis – Murrell 1992

- This theory centres of the hypothesis of local ischaemia leading to free radical generation [8].
- Narrowed microvessels and a thickened basal lamina, similar to in patients with diabetes, were reported in patients with Dupuytren's Disease.
- The release of free radicals is thought to be a stimulus for excessive fibroblast proliferation, as occurs in Dupuytren's Disease.

Macrophage hypothesis – Andrew 1991

- This hypothesis states that macrophages present at the initial stages of the disease release growth factors that leads to endothelial proliferation as well as local proliferation of fibroblasts [32]. Proliferation of fibroblasts is thought to lead to microvascular occlusion, hypoxia, free-radical release and fibroblast proliferation as described by Murrell.

Conclusion

Myofibroblasts play an important role in the pathophysiology of Dupuytren's Disease and may potentially arise from stem cells in the skin and fat surrounding the nodule. Significant differences in stem cell expression has been shown in Dupuytren's compared to normal tissue. Several other important biological changes have been identified in Dupuytren's Disease. In particular, alterations in collagen (with greater proportions of type III/type I) biochemical changes and cellular changes have all been characterised. Cytokines are known to play an important role in this process and myofibroblasts, in the same way as in wound repair, lead to contraction of the fascia and eventual contracture of the digits. The trigger stimulating this overzealous response is unknown. Despite the extensive research and theories that have been postulated, the condition remains elusive is many ways. Understanding of the cell biology is essential so that we can understand the disease and offer patients the best treatment.

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