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New insights in the development of Dupuytren's contracture: a review

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SUMMARY. Recent advances in the understanding of myofibroblast histology and function, the activity of fibrogenic cytokines, the role of the extracellular matrix and of free radicals are contributing to an understanding of the aetiology of Dupuytren's disease but not yet to its treatment. Surgical excision remains the best treatment.

Keywords: Dupuytren's contracture, myofibroblast, cytokines, extracellular matrix, free radicals.

Debate over the cause of Dupuytren's disease has been ongoing since its well-known description over 170 years ago.[1] However, many recent studies of the basic science of the disease are beginning to erase some of the enigma of its aetiology. Throughout the 1970s and 1980s, researchers established the myofibroblast as the hallmark of Dupuytren's disease by carefully studying and describing the appearance of these cells and their relation to the surrounding matrix. Many epidemiologic studies have suggested correlations with diabetes, epilepsy and behavioural patterns. More recently, efforts have focused on the factors controlling the (myo)fibroblasts such as free radicals and growth factors. Table 1 is a listing of implied aetiological factors. The expanding fields of cell biology, molecular biology, and research of other fibrotic diseases such as liver cirrhosis, lung fibrosis, atherosclerosis and glomerulonephritis[2,3] have, in particular, provided many new insights into the pathogenesis of Dupuytren's disease. This paper gives the clinician an integrated overview of the current understanding of Dupuytren's disease as related to recent advances in histology, cell biology (growth factors), free radicals, biochemistry and immunology. Until the accumulated efforts of these and additional investigations have solved this mysterious disease, there is no better treatment than surgical excision as advocated in the lecture that earned for Dupuytren this eponym.

Histology

The myofibroblast is a fibroblastic phenotypic variant first described in contracting experimental granulation tissue.[4,5] A year later, the myofibroblast was described in Dupuytren's tissue using electron microscopy,[6] and later confirmed by others.[7–9] Myofibroblasts have also been shown in many other tissues such as hypertrophic scar tissue,[10–12] frozen shoulder,[13] around mammary implants[14–16] and in desmoplastic stroma around neoplasms.[17–19] Presence in these different tissue types can be categorised in three groups: repair or inflammatory conditions, fibroproliferative conditions and in response to neoplasia.[19–21] Their role in these lesions is presumably of tissue contraction. In the case of Dupuytren's contracture for example, prostaglandins can cause contraction and relaxation of Dupuytren myofibroblasts in vitro, and are expressed in vivo in the affected fascia.[22,23]

The myofibroblast has features in common with both smooth muscle cells and fibroblasts, as they are characterised by a cytoplasmic microfilament system called α-smooth muscle actin (α-SM actin) reminiscent of a smooth muscle cell. Myofibroblasts connect with each other through gap-junctions, and to the surrounding stroma with extracellular fibronectin fibres.[19–21] In Dupuytren's fibroblasts, extracellular filaments containing fibronectin connect with intracellular actin through a transmembrane association called fibronexus[24,25] thus theoretically providing the myofibroblasts with a means to contract the matrix.

Since the initial description of the myofibroblast in Dupuytren's tissue, numerous other studies have contributed to a more detailed understanding of its histological appearance. Collectively, these studies describe how myofibroblasts dominate Dupuytren's tissue,[8,9,26–29] and seem to correlate with disease recurrence.[28,29] Some of the most current myofibroblast research is focused on understanding why the myofibroblast disappears in normal healing wounds but persists (longer) in desmoplasia and fibroproliferative diseases. The most likely explanation appears to be in the control of apoptosis or programmed cell death of the myofibroblasts,[30–32] suggesting that these cells are terminally differentiated.[31] The inducers of apoptosis are unclear, although certain genes such as *ced-3* and *c-Myc* have been suggested.[31] Other candidates for controlling apoptosis are growth factors such as transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF) and tumour necrosis factor (TNF).[31] Recently, it was shown that cells undergoing apoptosis in the late involutional stage in Dupuytren's tissue are myofibroblasts, and are associated with expression of TGF-β in the same areas.[33] Therefore it seems that there is not a complete loss, but rather a changed control of apoptosis in Dupuytren's tissue as compared to normal tissue.

Table 1 Aetiological factors implied in Dupuytren's disease.

Alcohol use
Cigarette smoking
Epilepsy
Diabetes mellitus
Hereditary
Growth factors (receptors)/cytokines: PDGF, bFGF, TGF-β, TNF-α, EGF, IL-1, γ-interferon
Immune system: HLA-DR3, CD-3, CD-68, HIV
Free radicals
Biochemistry: collagen type I and III, fibronectin (receptor)

Cell biology/growth factors/cytokines

The concept of cells producing and secreting polypeptide growth factors that subsequently bind to their own receptors resulting in a biologic response was introduced as autocrine growth control in the early 1980s.[34] Since then it has become common knowledge that cells exist in a balanced system of various growth factors and their receptors. These growth factors can function individually, or in conjunction with others. If tissue homeostasis is disturbed (e.g., following injury), adjustments in expression of growth factors and/or their receptors is part of the repair mechanisms needed to restore the balance. The hallmark of normal repair or growth mechanisms is that once the appropriate homeostasis is reached, the autocrine and/or paracrine loops adjust to their normal state. A classic example of this process is wound healing.[35]

Given that tumorigenesis somewhat resembles a repair mechanism gone awry, it is not surprising that many tumours have been shown to express an increased synthesis of certain growth factors and/or their receptors. Fibromatoses, including Dupuytren's disease, can be classified as benign fibroproliferative tumours,[36] and it has been shown that cultured fibroblasts from Dupuytren's contracture display features intermediate between those expressed by normal human fibroblasts and 'transformed' (neoplastic) fibroblasts.[37] As such, we can speculate on the possible autocrine and paracrine mechanisms, including the role of individual growth factors, underlying Dupuytren's contracture. Likely candidates should have a growth stimulatory effect on (myo)fibroblasts, possibly induce differentiation into myofibroblasts, stimulate production of extracellular matrix (ECM) and, once deposited, prevent the breakdown of ECM.

Considering these prerequisites, the most likely candidates are the so-called fibrogenic cytokines[3,38] PDGF,[39,40] TGF-β,[41,42] basic fibroblast growth factor (bFGF),[43] interleukin-1 (I1-1) and TNF-α.[44] In addition, most of these cytokines induce cell proliferation of endothelial cells, leading to another important feature of tissue growth (in repair as well as in neoplasia) called angiogenesis.

To my knowledge, only one study has screened Dupuytren's tissue for expression of a large panel of cytokines.[45] In contrast to this study of a broad group of cytokines, most other reports have focused on possible relations between one or two growth factors and Dupuytren's disease. Table 2 summarises the current data on growth factors and their implications in Dupuytren's contracture.[45–58]

In summary, of all the growth factors/cytokines having been studied so far for a possible role in the development of Dupuytren's contracture it seems that TGF-β is the most likely candidate, whereas other growth factors such as PDGF and bFGF probably play a minor role. Since the mitogenic effects of TGF-β on connective tissue cells are induced via a complex control of an autocrine PDGF loop,[59] increased expression of PDGF could be a normal response to an abnormal TGF-β expression.[53]

Of note is that recently, data have emerged in other fibrotic disease states suggesting a role for granulocyte macrophage-colony stimulating factor (GM-CSF). GM-CSF is mostly known for its stimulatory effect on cells of haematopoietic origin and its role in the inflammatory response.[60] However, it was recently shown to induce proliferation of mesenchymal cells[17] through the formation of granulation tissue containing many myofibroblasts rich in lung fibrosis model.[63] So far, GM-CSF and TGF-β are the only two cytokines that are able to induce α-SM actin rich myofibroblasts in the skin in vivo,[61–64] and thus should be considered the most likely candidates for inducing the myofibroblast phenotype in Dupuytren's disease. Currently, to my knowledge, there are no data on a possible relationship between GM-CSF and Dupuytren's disease.

Free radicals

Murrell et al[65–68] introduced the free radical theory, which suggests a relation between localised ischaemia, superoxide free radicals (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radicals (OH^-) and Dupuytren's contracture. This was based on studies suggesting that microvessel narrowing secondary to age, smoking and other environmental factors leads to localised hypoxic conditions. Such conditions trigger increased levels of xanthine oxidase, which catalyses the conversion of hypoxanthine to xanthine to uric acid, and, ultimately, free radical generation. The free radicals subsequently would cause a proliferation of fibroblasts and deposition of collagen leading to tissue fibrosis and even lower local oxygen concentrations. The authors also speculated on a possible clinical/therapeutic role for allopurinol, which inhibits xanthine oxidase and thus prevents release of free radicals in the treatment and prevention of Dupuytren's disease.[69] However, the effect of allopurinol in Dupuytren's contracture was later found to be not significant.[70]

While the free radical theory seems to offer a unified approach to the morphological and epidemiological

Table 2 Growth factors implied in the aetiology of Dupuytren's disease: literature review

Growth factor	*Implied role in Dupuytren's contracture*	*Technique used*	*Reference*
Platelet-derived growth factor (PDGF)	PDGF bound to myofibroblasts cell membrane in DD (more in proliferative and involutional stage than in normal and residual phase)	Immunocytochemistry	46
	PDGF stimulates proliferation up to 100% in both cell types dose-dependently	In vitro proliferation assay	47
	PDGF increases stimulation of collagen production in DDC compared to normal fibroblasts Non-collagen stimulation stronger in normal cells	In vitro proline incorporation assay	
	PDGF-B and PDGF receptor genes expressed in DD	In situ hybridisation RT-PCR	48
	Elevated PDGF present in DD (not statistically significant)	RT-PCR	51
basic fibroblast growth factor (bFGF)	Higher expression of mRNA for bFGF and bFGF receptor in DD than in normal fascia	In situ hybridisation	49
	FGF and FGF receptor expression in DDC and normal fascia fairly equal	Immunohistochemistry	
	bFGF present in DD	Western blot	
	DDC proliferate in response to bFGF	In vitro proliferation assay	50
	bFGF mRNA present in DD	Northern blot	
	bFGF receptor present in DD	Cross linking receptor assay and Scatchard analysis	
	bFGF present in DD	Western blot	
	bFGF mRNA in fibroblast and myofibroblast in proliferative nodules	In situ hybridisation	51
	bFGF protein in proliferative areas of DD	Immunohistochemistry	
	bFGF stimulated normal fibroblast proliferation 200% bFGF stimulated DDC 50%	In vitro proliferation assay	47
	Collagen production elevated 20% in DDC Collagen production inhibited 30% in normal fascia Non-collagen synthesis stimulated 60% in normal fascia Non-collagen synthesis stimulated 15% in DDC	In vitro proline incorporation assay	
	bFGF expression significantly higher in DD than in normal tissue	RT-PCR	45
Transforming growth factor-β (TGF-β)	TGF-β produced by DDC	MvlLu assay	52,53
	DDC proliferation stimulated by TGF-β1 more than normal fibroblasts	In vitro proliferation assay	
	EGF and TGF-β synergistic proliferative effects in DDC, additive effects in normal cells	In vitro proliferation assay	
	TGF-β receptor profile different in DDC as compared to normal fibroblasts (ratio type II/I significantly higher)	Cross-linking receptor assay	
	TGF-β1 present in all 3 phases of DD and in normal fascia TGF-β2 present in proliferative and involutional but not residual phase of DD	Immunohistochemistry	54
	TGF-β1 and -β3 present in DD	Immunohistochemistry	51
	TGF-β1 and -β2 present in proliferative phase of DD	In situ hybridisation	
	TGF-β present in DD	In situ hybridisation	55
	No mitogenic effects of TGF-β on DDC	In vitro proliferation assay	47
	Collagen and non-collagen synthesis stimulated more by TGF-β in DD than in normal fascia	In vitro proline incorporation assay	
	TGF-β more abundant in DD than in normal fascia	RT-PCR	45
γ-interferon (γ-IFN)	Treatment of DDC with γ-IFN decreased α-SM protein and mRNA expression	Immunofluorescence and Northern blot	56
	γ-IFN decreases cell proliferation	In vitro proliferation assay	
	Intralesional injection of γ-IFN decreased α-SM actin expression	Immunohistochemistry	57
	Intralesional injection of γ-IFN decreased size of Dupuytren lesion	Clinical evaluation	
	γ-IFN decreased cellular proliferation and α-SM actin expression	In vitro proliferation assay and immunohistochemistry	
Interleukin-1 (Il-1)	Il-1 more abundant in DD	RT-PCR	45
Transforming growth factor-α (TGF-α or EGF)	High co-expression of TGF-α and EGF-receptors in the proliferative and involutional phase of DD as compared to residual phase and normal fascia	Immunohistochemistry and RT-PCR	58
	EGF not detectable in DD	Immunohistochemistry	55
	EGF and TGF-β1 synergistic proliferative effects in DDC, additive effects in normal cells	In vitro proliferation assay	52, 53
Tumour necrosis factor-α (TNF-α)	Equal expression in normal and DD	RT-PCR	45

DDC: Dupuytren derived cells; DD: Dupuytren disease; RT-PCR: reverse transcriptase-polymerase chain reaction.

findings in Dupuytren's tissue, little work has been done to push our understanding significantly forward.

Biochemistry

Extensive literature exists with respect to the biochemical aspects of Dupuytren's disease, primarily on the components of the extracellular matrix (ECM). The ECM is made of collagens, fibronectin, and proteoglycans, which form a matrix to which cells attach by means of their surface receptors called integrins. The ECM is a dynamic structure, constantly being broken down and rebuilt.

An elevated level of total collagen in Dupuytren's tissue is considered to be typical.[71,72] The ratio of different collagen types and their potential roles in diseased versus normal tissue, however, has not been fully worked out. For example, whereas Brickley-Parsons et al[71] said that the ratio of type III to type I collagen was related to the degree of disease severity, Gelberman et al[28] could not confirm these results. Two other studies[72,73] showed that there is increased expression of type III in clinically 'normal' fascia of patients with established Dupuytren's disease, suggesting that the disease is widespread throughout the fascia. Murrell et al[74,75] dispute the causative role of the increased collagen III/I ratio in Dupuytren's disease, citing the fact that increased cell proliferation leads to decreased type I production, but the total of type III collagen produced per cell is unchanged.

One of the other constituents of the ECM is fibronectin,[76] which has been shown to play a role in cell migration, adhesion, cell morphology and differentiation. Fibronectin was shown to be upregulated by TGF-β about 2–3 fold in fibroblasts in vitro.[76–78] In Dupuytren's tissue, fibronectin expression has been documented using indirect immunofluorescence showing an 'embryonic pattern' of so-called oncofetal fibronectin (ED-A and ED-B) suggesting the relation of Dupuytren's disease to normal processes such as healing and granulation with production of immature tissue.[79–80]

Immune system

Neumuller et al[81] studied the presence of HLA-DR3 in patients with Dupuytren's disease, and calculated an increased relative risk of 2.94 for people who express HLA-DR3 to develop Dupuytren's disease. Baird et al[82] showed increased presence of HLA-DR and CD-3 positive lymphocytes in Dupuytren tissue as compared to normal fascia. Other isolated reports speculate on a link between dermal dendrocytes and Dupuytren's disease based on immunohistochemical detection of factor XIIIa (marker for dermal dendrocytes) in Dupuytren's tissue,[83] and presence of HLA-DR as well as CD-68 positive cells, which have an immunologic function, being of macrophage lineage. The importance of this finding is that macrophages are known to secrete cytokines including TGF-β and GM-CSF, which have a role in tissue fibrosis as discussed above.

Lastly, from an epidemiologic standpoint, the reported findings of a high prevalence of Dupuytren's contracture in immunocompromised HIV patients (36%)[84] have been disputed by others.[85]

Discussion

Fibrotic disorders affecting organs such as kidney, lung, heart and bone marrow provide a major cost to healthcare. Whereas fibrosis of the palmar fascia known as Dupuytren's disease is not a major health hazard, its pathogenesis is likely to be fairly similar to these other fibrotic disorders. It has recently become clear that progressive fibrosis is a complex process involving a cascade of molecular and cellular events, with TGF-β playing a pivotal role in the final common pathway.[2,86]

Although Dupuytren's is not regarded as an inflammatory disease, it seems that in most related fibrotic diseases the presence of GM-CSF and macrophages is related to the production of cytokines, including TGF-β. This results in chemotaxis, cell proliferation, collagen production, myofibroblast differentiation (α-SM actin induction), fibronectin (receptor) production and cell transformation.[76–78] The reported co-localisation of myofibroblasts, growth factors and fibronectin isoforms substantiates this theory.[51] Once this process is started, a positive feedback loop ensues, with autoinduction of TGF-β.[87] Additionally, increased fibrosis leads to local hypoxia, which is known to induce TGF-β in an additional amplification step.[88] Other described mechanisms such as the production of free radicals[66–68] may well be part of this complex mechanism.

Descriptive findings such as those on the absence or presence of myofibroblasts, the type III/I collagen ratio, and epidemiologic data such as the relation to race, smoking, diabetes and epilepsy are historically important, but are unlikely to help us find the cause or a non-surgical cure for Dupuytren's contracture. The answer will undoubtedly come from cell biological or molecular biological advances. Each step is slowly being elucidated but many questions still remain. What starts the cascade that leads to excessive fibroblast proliferation and ECM production similar to wound healing, and why does it not shut itself off as a normal repair process? Is it similar to other fibrotic diseases and are GM-CSF and TGF-β the key players? Can we modulate the mechanism of apoptosis on the myofibroblast once the diagnosis of Dupuytren's disease is established? It seems that investigation of GM-CSF expression in Dupuytren's tissue would be worthwhile.

Once all the steps of the cascade are elucidated on a cellular level, it will be interesting to see if this leads us back to the (historic) epidemiological data. Does Dupuytren's contracture start with local hypoxia, as seen in smokers and diabetics[89–90] or with repeated microtrauma resulting in an inflammatory response with macrophages and/or platelets releasing specific fibrogenic cytokines, or is a genetic defect (apoptotic control) at the core of the disease?

Although a number of important questions remain unanswered, work has begun to identify possible

non-surgical treatments for Dupuytren's and related diseases, such as keloids and hypertrophic scars, based on the scientific evidence currently available. The most prevalent ideas for treatment include alteration in the growth factor expression by local gene therapy, local application of growth factor antibodies and blocking of receptor binding and/or post-receptor signalling. Experimental studies attempting to decrease scarring and fibrosis have been targeted at modulating the expression of TGF-β isoforms,[72] for example, and preliminary clinical reports are encouraging. Local application of antibodies to TGF-β resulted in decreased scarring in an experimental dermal healing study in rats, and histological evaluation of those tissues revealed fewer macrophages, blood vessels, lower collagen and fibronectin content.[91] These findings are in line with a later report in which binding of TGF-β by decorin protected against scarring in an experimental glomerulonephritis syndrome without detectable side-effects.[92] Other treatments could involve down-regulation of α-SM actin expression with γ-interferon, which has recently been shown in clinical studies of Dupuytren's disease[57] and keloids.[93]

At the end of his lecture in Hotel Dieu on the contraction of the palmar fascia, Guillaume Dupuytren expressed the hope that 'these hints may become useful to science and humanity, in multiplying observations on the cause, symptoms, and treatment of this disease'.[1] Now, more than 170 years later, although there is a much better understanding of Dupuytren's contracture, surgical excision of the diseased fascia remains the best treatment available. Advances in the basic sciences of the disease, however, will ultimately provide us with better options.

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