INTRODUCTION

Dupuytren’s disease (DD) is a fibro-proliferative disorder characterized by progressive palmar fascia fibrosis with a variable prevalence among racial groups and an increased incidence in males of Northern European ancestry. Despite known risk factors, the pathogenesis of DD remains unclear.

Palmer fascia fibrosis in DD causes progressive fixed flexion contracture of the digits, resulting in functional impairment. Management options of DD include fasciectomy as the mainstay of treatment, and more recently, collagenase injections. Fasciectomy is associated with a risk of injury to the neurovascular bundle and recurrence rates of up to 70%.

Previous studies of DD have implicated an aberrant proliferation of myofibroblasts, the dominant cell type within DD. Myofibroblasts express types I and III collagen but are distinct from fibroblasts by their expression of α-SMA. It has been proposed that myofibroblasts normally differentiate from fibroblasts through a proto-myofibroblast intermediate, regulated by transforming growth factor-β (TGF-β) and platelet-derived growth factor. There is also increasing evidence supporting the role of stem cells in DD and other fibrotic conditions. This review examines the role of DD tissue-associated embryonic stem cells (ESCs) and mesenchymal stem cells (MSCs), and circulating fibrocytes and circulating MSCs, in the biology of DD. It is exciting to infer that dysfunction of an upstream ESC-like population within the affected tissue leads to the downstream development and proliferation of aberrant myofibroblasts through a putative MSC intermediate. This ESC-like population may be a potential novel therapeutic target through modulation of the renin-angiotensin system. Furthermore, circulating CD34+ fibrocytes and MSCs either derived from the bone marrow, peripheral blood cells, or DD-associated ESC-like population, may serve as potential additional extra-palmar reservoirs that undergo endothelial-to-mesenchymal transition, eventually giving rise to the aberrant myofibroblasts. Further studies examining the relative roles of these stem cells and the precise regulatory pathways that govern them may lead to novel therapy that targets these populations.

SUMMARY

The pathogenesis of Dupuytren’s disease (DD) remains unclear although there is increasing evidence supporting the role of stem cells in this and other fibrotic conditions. This review examines the role of DD tissue-associated embryonic stem cells (ESCs) and mesenchymal stem cells (MSCs), and circulating fibrocytes and circulating MSCs, in the biology of DD. It is exciting to infer that dysfunction of an upstream ESC-like population within the affected tissue leads to the downstream development and proliferation of aberrant myofibroblasts through a putative MSC intermediate. This ESC-like population may be a potential novel therapeutic target through modulation of the renin-angiotensin system. Furthermore, circulating CD34+ fibrocytes and MSCs either derived from the bone marrow, peripheral blood cells, or DD-associated ESC-like population, may serve as potential additional extra-palmar reservoirs that undergo endothelial-to-mesenchymal transition, eventually giving rise to the aberrant myofibroblasts. Further studies examining the relative roles of these stem cells and the precise regulatory pathways that govern them may lead to novel therapy that targets these populations.

MYOFIBROBLASTS

The development of nodules and cords in DD has been attributed to an aberrant proliferation of myofibroblasts, the dominant cell type within DD. Myofibroblasts express types I and III collagen but are distinct from fibroblasts by their expression of α-SMA. It has been proposed that myofibroblasts normally differentiate from fibroblasts through a proto-myofibroblast intermediate, regulated by transforming growth factor-β1 (TGF-β1) and platelet-derived growth factor. There is also increasing evidence supporting the role of stem cells in DD and other fibrotic conditions. This review examines the role of DD tissue-associated embryonic stem cells (ESCs) and mesenchymal stem cells (MSCs), and circulating fibrocytes and circulating MSCs, in the biology of DD. It is exciting to infer that dysfunction of an upstream ESC-like population within the affected tissue leads to the downstream development and proliferation of aberrant myofibroblasts through a putative MSC intermediate. This ESC-like population may be a potential novel therapeutic target through modulation of the renin-angiotensin system. Furthermore, circulating CD34+ fibrocytes and MSCs either derived from the bone marrow, peripheral blood cells, or DD-associated ESC-like population, may serve as potential additional extra-palmar reservoirs that undergo endothelial-to-mesenchymal transition, eventually giving rise to the aberrant myofibroblasts. Further studies examining the relative roles of these stem cells and the precise regulatory pathways that govern them may lead to novel therapy that targets these populations.

Disclosure: T.I. and S.T.T. are inventors of a provisional patent application Treatment of Fibrotic Conditions (PCT/ NZ2016/050187). The authors are otherwise not aware of any commercial associations or financial relationships that might pose or create a conflict of interest with information presented in any submitted manuscript. The Article Processing Charge was paid for by the Gillies McIndoe Research Institute’s internal fund.
Evidence showing MSCs as the potential origin of aberrant myofibroblasts observed in DD.

**Mesenchymal Stem Cells**

Mesenchymal stem cells (MSCs) are fibroblast-like cells that are multipotent and express mesenchymal markers CD73, CD90, and CD105. These MSCs are devoid of hematopoietic stem cell markers CD45, CD34, or CD19 and are derived from the bone marrow, adipose tissue, and peripheral or umbilical cord blood. The multipotency of MSCs is defined by their ability to differentiate into multiple cell lineages such as adipocytes, osteocytes, chondrocytes, and fibroblasts.

A recent study has demonstrated the presence of a MSC population that expresses surface markers CD73, CD90, CD105, but not CD34, within DD tissue. These MSCs are localized to the surrounding skin and are proposed to be a potential source of aberrant myofibroblasts observed in DD (Fig. 1). The proposed role of this MSC population within the surrounding tissue in DD is further supported by reduced recurrence rates following dermofasciectomy in which the skin overlying the cords and nodules is also excised.

The terminology proposed by the International Society for Cellular Therapy does not differentiate MSCs from fibroblasts. Fibroblasts, like MSCs, also express cell markers CD73 and CD105, and whether these 2 populations are homogenous or distinct cell populations, remains to be investigated in DD.

**Embryonic Stem Cell–Like Cells**

We have demonstrated an ESC-like population localized to the endothelium of the microvessels in DD cords and nodules that express ESC markers NANOG, pSTAT3, SALL4, and OCT4.

NANOG is a homeoprotein linked to self-renewal and pluripotency. Intrinsic to the function of ESCs, the absence of NANOG leads to a loss in pluripotency and results in differentiation. STAT3 is a transcription factor and plays a role in cellular regulation pathways. Unlike NANOG, STAT3 is an independent mediator of pluripotency in stem cells. SALL4 is a regulator of NANOG and is also required for maintaining stem cell pluripotency. The transcription factor SALL4 binds to the NANOG gene and upregulates NANOG expression. In addition, SALL4 regulates OCT4, a Pou transcription factor required for the maintenance of the pluripotent potential in ESCs.

Through the process of endothelial-to-mesenchymal transition (EndoMT) the primitive population on the endothelium of the microvessels in DD that expresses ESC markers are proposed to give rise to an MSC intermediate, which in turn, gives rise to the downstream myofibroblasts (Fig. 1). Additionally, these ESC-like cells express components of the RAS, namely pro-renin receptor, ACE, and ATIIR1 and ATIIR2, implicating RAS dysfunction in the ultimate development of aberrant myofibroblasts. This is supported by similar findings in keloid scar. Although a causal relationship has yet to be established, the improvement of fibrotic conditions such as keloid scar following administration of low-dose enalapril, an ACE inhibitor, supports a role for the RAS in this condition.

**Circulating Fibrocytes and Circulating MSCs**

The role of circulating cancer stem cells (CSCs) in cancer has also recently been reported. These circulating CSCs express the surface marker CD34 and undergo an epithelial to mesenchymal transition, attributed to the ability of cancer to metastasize. Circulating CSCs, like hematopoietic stem cells, are found in the peripheral blood, and they have the ability to migrate to target organs.

The role of circulating fibrocytes in fibrosis has also been reported recently. Circulating fibrocytes are fibroblast progenitors that migrate to distant tissue sites where they contribute to inflammation and fibrosis. The origin of these circulating fibrocytes remains unclear and may include the bone marrow or peripheral blood cells. It is exciting to speculate that these circulating fibrocytes express CD34, migrate from the peripheral circulation to target organs, leading to fibroblast proliferation and fibrosis in DD. These CD34+ circulating fibrocytes have also been implicated in tissue repair, wound healing, and contributes to keloid scar and hypertrophic scar. The ability of these circulating fibrocytes to differentiate into myofibroblasts, further supports their role in fibrosis in DD.

Circulating MSCs have also been reported to play a potential role in fibrosis. Circulating MSCs, are a subset of MSCs, that exist in the peripheral circulation, and like circulating fibrocytes, they increase in number and migrate to target organs during tissue injury and inflammation. The similarity in function and structure between the circulating CD34+ fibrocytes and the circulating MSCs suggests that these cell types may act as additional reservoirs that give rise to the aberrant myofibroblasts observed in DD. Whether these circulating fibrocytes and circulating MSCs are the same population, potentially originating from the DD-associated primitive endothelium and/or from other sites, such as the bone marrow through an EndoMT process, and subsequently migrate to the site of DD (Fig. 1), remains the topic of future research.

**Endothelial-to-Mesenchymal Transition**

Endothelial-mesenchymal transition is characterized by the loss of expression of endothelial surface markers CD31 and VE-cadherin, and the expression of mesenchymal components α-SMA and type I collagen. In early human development, the cardiac valves and septum have been proposed to arise from endoMT, whereby the surrounding endothelium gives rise to endocardial cushions through a mesenchymal intermediate. Similar findings have also been shown in the development of hematopoietic cells from a hemogenic endothelial phenotype.
In addition to its aforementioned role in embryological development, endoMT has also been shown to contribute to the development of pulmonary, cardiac, and renal fibrosis.

EndoMT is initiated by cytokines such as TGF-β. Although the exact mechanism is yet to be elicited, TGF-β has been shown to upregulate transcription factors Snail, Slug, and Twist, which leads to the downstream regression of endothelial cell surface markers, and the expression of mesenchymal markers.

We postulate that cytokines, such as TGF-β, expressed by the tissues surrounding the putative primitive phenotypic endothelium, induces differentiation of the ESC-like cells to form a MSC intermediate via an endoMT, which ultimately give rise to aberrant myofibroblasts (Fig. 1). Currently, there remains no consensus on whether MSCs and fibroblasts are phenotypically distinguishable populations within DD. Furthermore, the mechanism by which MSCs differentiate into myofibroblasts in DD remains unclear, and may result from direct differentiation of MSCs into myofibroblasts, or via a fibroblast intermediate.

**DISCUSSION**

There is increasing evidence supporting the role of DD tissue-associated ESC-like cells and MSCs, and circulating fibroblasts, and circulating MSCs, in DD. We have described the characteristics and potential source and the role of each of these cell populations and how they may relate to one another. We propose that dysfunction of the ESC-like cells on the endothelium of the microvessels gives rise to the downstream aberrant myofibroblasts, through an MSC intermediate. This ESC-like population expresses components of the RAS, and therefore may be a novel therapeutic target through modulation of the RAS using existing medications. We also propose that circulating CD34+ fibrocytes and circulating MSCs may serve as additional extra-palmar reservoirs that migrate to target sites.
Increasing evidence suggesting that in addition to fibroblasts, myofibroblasts may also putatively arise from MSCs and give rise to aberrant myofibroblasts in Dupuytren's disease either by directly differentiating into myofibroblasts or indirectly through a fibroblast intermediate.

MSCs Putatively arise from ESC-like cells on the endothelium of the microvessels in the fat and skin surrounding Dupuytren cords and nodules

Circulating fibrocytes Through an endothelial-to-mesenchymal transition process, differentiate into MSCs, which in turn give rise to fibroblasts or indirectly through a fibroblast intermediate

Myofibroblasts Normally derived from fibroblasts through a proto-myofibroblast intermediate regulated by TGF-β1 and PDGF

Myofibroblast proliferation leads to tissue fibrosis

Increasing evidence suggesting that in addition to fibroblasts, myofibroblasts may also putatively arise from MSCs in Dupuytren’s disease

Table 1. Stem Cells that Putatively Give Rise to Myofibroblasts in Dupuytren’s Disease

| Cells Types                  | Characteristics                                                                 |
|------------------------------|---------------------------------------------------------------------------------|
| Embryonic stem cells (ESC)-like cells | Localized to the endothelium of the microvessels in Dupuytren nodules and cords Regulated by the renin-angiotensin system Through an endothelial-to-mesenchymal transition process, differentiate into MSCs, which in turn give rise to myofibroblasts |
| Circulating fibrocytes and MSCs | Derived from bone marrow and peripheral blood and migrate to target organs via the peripheral circulation |
| MSCs                          | Putatively arise from ESC-like cells on the endothelium of the microvessels in the fat and skin surrounding Dupuytren cords and nodules Express similar cell markers as fibroblasts Proposed to give rise to aberrant myofibroblasts in Dupuytren’s disease either by directly differentiating into myofibroblasts or indirectly through a fibroblast intermediate |
| Myofibroblasts               | Normally derived from fibroblasts through a proto-myofibroblast intermediate regulated by TGF-β1 and PDGF |

PDGF, platelet-derived growth factor.

organ and differentiate into aberrant myofibroblasts through EndoMT.

The key cell types in DD and their characteristics are presented in Table 1. A better understanding of the role of stem cells in DD may potentially lead to the development of targeted therapy for this enigmatic condition.

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