Journal of Hand Surgery Global Online 5 (2023) 682–688

Contents lists available at ScienceDirect

Journal of Hand Surgery Global Online

journal homepage: www.JHSGO.org

Review Article

Let's Focus on the Fibrosis in Dupuytren Disease: Cell Communication Network Factor 2 as a Novel Target

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ARTICLE INFO

Article history:
Received for publication June 21, 2023
Accepted in revised form June 24, 2023
Available online August 1, 2023

Key words:
CCN2 protein
Connective tissue growth factor
Dupuytren contracture
Fibrosis
TGF-beta

Dupuytren disease is a progressive, benign fibroproliferative disorder of the hands that can lead to debilitating hand contractures. Once symptomatic, treatment involves either surgical intervention, specifically fasciectomy or percutaneous needle aponeurotomy, or enzymatic degradation with clostridial collagenase. Currently, collagenase is the only pharmacotherapy that has been approved for the treatment of Dupuytren contracture. There is a need for a pharmacotherapeutic that can be administered to limit disease progression and prevent recurrence after treatment. Targeting the underlying fibrotic pathophysiology is critical. We propose a novel target to be considered in Dupuytren disease—cell communication network factor 2/connective tissue growth factor—an established mediator of musculoskeletal tissue fibrosis.

Research into fibroproliferative disorders continues to expand our knowledge of the underlying mechanisms behind disorders such as idiopathic pulmonary fibrosis, Dupuytren disease (DD), scleroderma, and Peyronie disease. As a result, potential therapeutics for targeting these diseases are being identified. Although newer pharmacotherapies are being developed, there has also been interest in repurposing medications already approved by the US Food and Drug Administration for the treatment of fibrotic disorders.[1–3] Despite these efforts, the mainstay of treatment for symptomatic Dupuytren contracture is largely surgical.

The most common nonsurgical treatment is local collagenase injection for enzymatic degradation. To date, collagenase treatment is the only Food and Drug Administration–approved pharmacotherapy in DD. There is a need for additional pharmacotherapeutic options that target the underlying fibrotic response, thereby halting early disease progression, reversing fibrosis once the disease has progressed, and, in doing so, potentially avoiding the risks of invasive treatments.

Pathophysiology and Disease Progression

The fibroproliferation underlying DD affects the palmar fascia of the hand and digits. The clinical course can lead to symptomatic contractures, ultimately resulting in functionally limiting declines in range of motion and diminished quality of life.[4] The natural history of DD was initially described, by Luck[5], to occur in three distinct stages. Stage I (proliferative phase) is characterized by increased fibroblast activity and nodule formation within the palmar fascia. The predominant and active cell during this phase is the myofibroblast. Stage II (involutional phase) involves notable nodular thickening and an increase in type III collagen production, which orients along lines of tension within the palm. Joint contracture may begin during this stage. Stage III (residual phase) is

Declaration of interests: No benefits in any form have been received or will be received related directly to this article.

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https://doi.org/10.1016/j.jhsg.2023.06.017

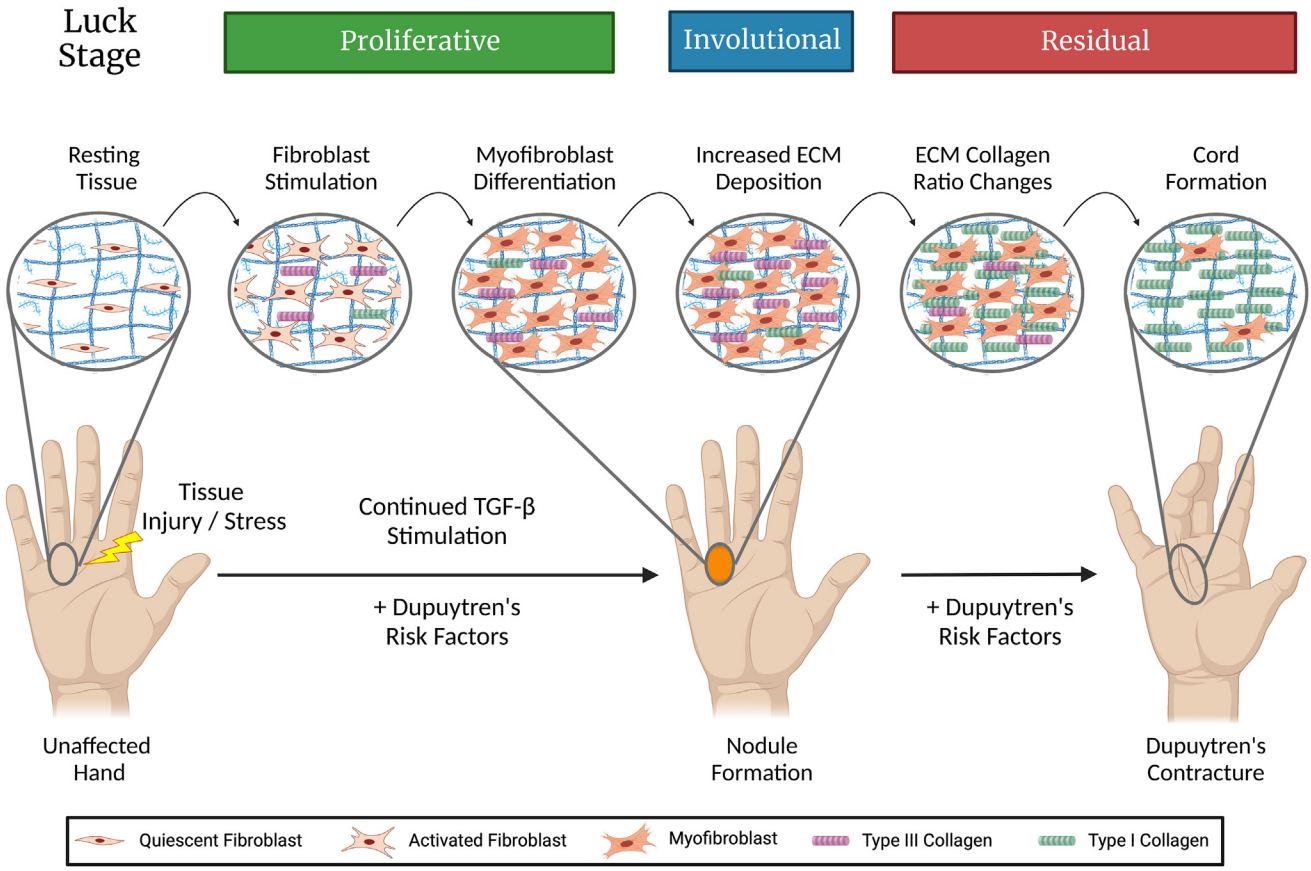

Figure 1. Pathophysiology of Dupuytren contracture. Dupuytren disease progression exists on histological, cellular, and clinical levels. Resting tissue of the unaffected hand contains quiescent fibroblasts. Upon tissue injury or stress, fibroblasts are activated, proliferate, and differentiate into mature myofibroblasts (proliferative stage). With continued transforming growth factor (TGF)-β stimulation and Dupuytren risk factors, disease progresses. Nodule formation occurs as myofibroblasts differentiate and produce extracellular matrix (ECM), with collagen III:I ratio predominating (involutional stage). The ECM collagen ratio changes to I:III, increased collagen crosslinking occurs, and cellularity decreases as cords form and contraction ensues (residual stage) (Reproduced with permission from Lambi et al. Pharmacotherapies in Dupuytren disease: current and novel strategies. *J Hand Surg Am.* 2023[7]).

characterized by a marked disappearance of myofibroblasts and a change in the predominant type of collagen from type III to type I (Fig. 1).[6,7]

The specific mechanisms and triggers that lead to DD development have not yet been fully elucidated. Disease progression varies between individuals and can be influenced by risk factors, such as alcohol intake, smoking, manual labor, metabolic factors (eg, diabetes), anticonvulsant drugs, and genetic predisposition.[6,8–15] However, it is well-established that the primary cell type responsible for DD progression is the myofibroblast. Derived from fibroblasts, the myofibroblast is characterized by the coexpression of high levels of platelet-derived growth factor and alpha-smooth muscle actin.[16] The contractures seen clinically most likely occur on a cellular level through a contractile apparatus of the myofibroblast that involves bundles of actin microfilaments and contractile proteins (eg, nonmuscle myosin). These interact with extracellular matrix proteins and adjacent myofibroblasts through transmembrane integrin proteins at a cell surface adhesion complex—the fibronexus.[17–21]

Extensive research has been performed to better understand the modulators of fibroblasts and myofibroblasts in DD development. Transforming growth factor-β (TGF-β) signaling has been implicated as critical in DD development.[22] All three mammalian isoforms of TGF-β (TGF-β1, TGF-β2, and TGF-β3) have been identified in DD disease nodules, palmar fascia, and cord tissue.[23,24] Fibroblasts and myofibroblasts in all three histologic stages of DD progression have upregulated TGF-β signaling.[23–26] Exogenous application of TGF-β to either normal or DD fibroblasts leads to increased alpha-smooth muscle actin expression and differentiation of a quiescent fibroblast to a contracting myofibroblast.[6,26–28] In culture, DD fibroblasts are induced to contract with TGF-β treatment.[29] Furthermore, when TGF-β signaling is blocked in DD cells in vitro, decreases in alpha-smooth muscle actin and collagen gene expression are seen.[27] Therefore, the ability to block the profibrotic effects of TGF-β signaling in DD has immense research and clinical potential.

A Novel Target in Dupuytren Disease—The Cell Communication Network Factor 2 Protein

Transforming growth factor-β is a master regulator of tissue growth, from normal healing to abnormal fibrosis. Most TGF-β responses involve stimulation of the cell communication network factor 2 (CCN2), previously known as connective tissue growth factor. CCN2 is the second named member of the CCN protein family.[30] This 38 kDa protein is secreted by a number of cell types, including fibroblasts, and resides in the extracellular matrix, where it confers structural stability and retains biological activity, thus earning the designation as a matricellular protein.[30] Cell communication network factor 2 is known to have a role in embryological development of the skeleton, face, palate, and lungs as well as wound healing, fibrotic disorders, and tumorigenesis.[31–38] Cell

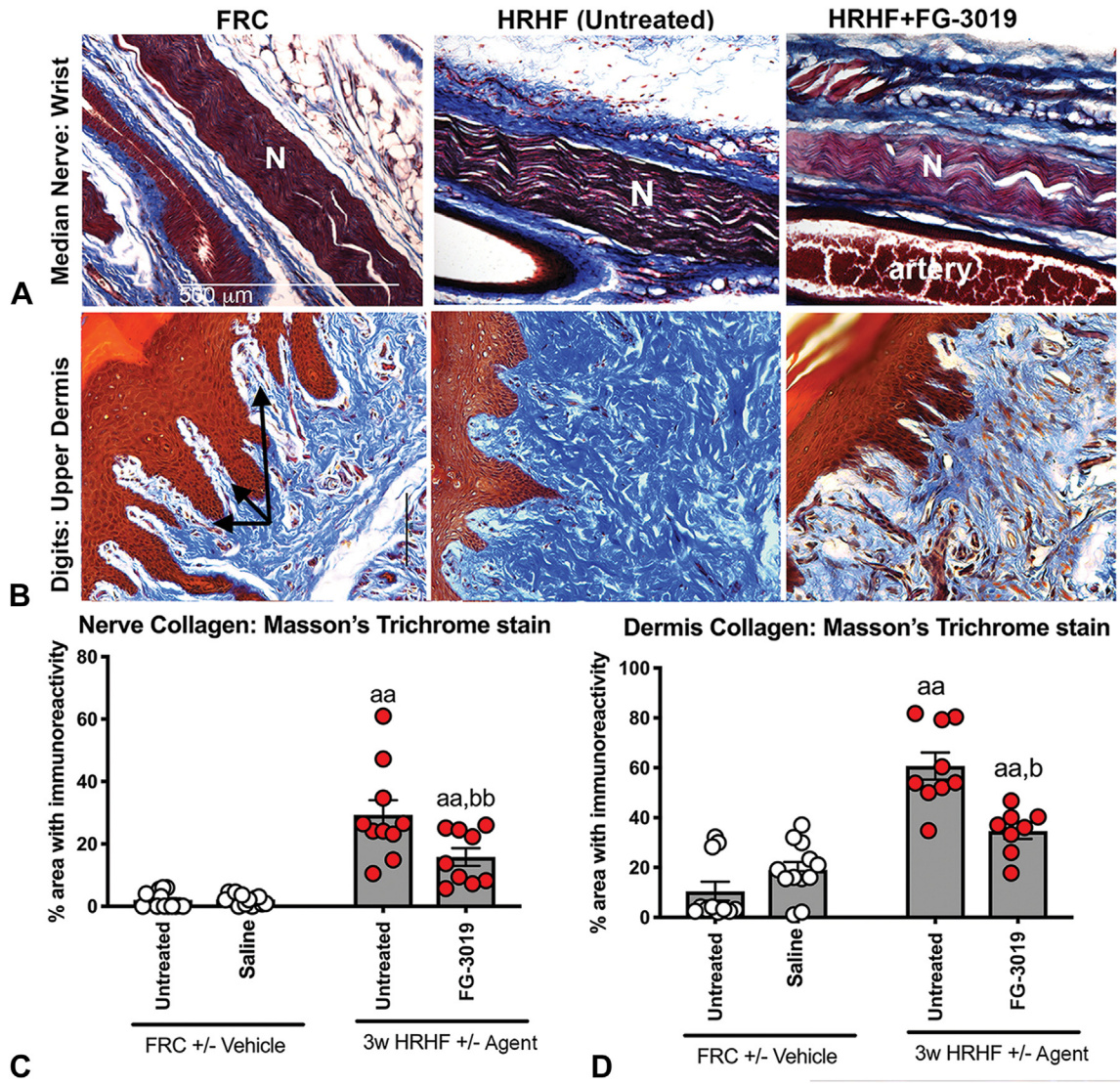

Figure 2. Reduction of nerve and dermal fibrosis after FG-3019 treatment. Masson's trichrome staining around the median nerve branches and in upper dermis of forepaw digits. **A** Masson's trichrome staining, with collagen stained blue around the median nerve (N) at wrist level in longitudinal sections. **B** Masson's trichrome staining in the upper dermis. Arrows indicate regions containing nerves within dermal papillae. **C** Quantification of blue-stained collagen in paraneural regions (ie, areas surrounding nerve) at wrist level. **D** Quantification of blue-stained collagen in the upper dermis. aa: $P < .01$, compared with matched food-restricted control (FRC) group; b: $P < .05$ and bb: $P < .01$, compared with untreated high repetition high force (HRHF) rats (Barbe et al. Blocking CCN2 reduces progression of sensorimotor declines and fibrosis in a rat model of chronic repetitive overuse. *J Orthop Res.* 2019;37:2004[48]).

communication network factor 2 is required for TGF-β–mediated fibrosis.[39] Not only does CCN2 work in concert with TGF-β and other matricellular components to elicit a fibrotic response in tissues but also its production alone can generate fibrosis in models typically resistant to this process.[40] Because of its key downstream role in TGF-β signaling, CCN2 has emerged as a promising target in a host of fibrotic disorders, such as scleroderma and pulmonary, cardiac, hepatic, and renal fibroses.[41]

Targeting Cell Communication Network Factor 2 with Pamrevlumab

Pamrevlumab, initially described as FG-3019, is a fully humanized monoclonal antibody against CCN2 (FibroGen Inc). Its mechanism specifically involves targeting the von Willebrand factor C domain of the CCN2 protein.[42] This is the domain known to interact with TGF-β.[43] Pamrevlumab has been granted US Food and Drug Administration Fast Track and Orphan Drug Designation for use in pancreatic carcinoma, muscular dystrophy, and idiopathic pulmonary fibrosis and has entered into phase 3 clinical trials.[36] Results of these trials thus far have shown strong potential in decreasing tissue fibrosis, with functional improvements.[44,45] When administered intravenously at a dose of 30 mg/kg every 3 weeks, human safety trials exhibited low rates of adverse events.[36] Thus, these trials support that FG-3019 is safe and well-tolerated in the patient population, although any long-term adverse events will require further monitoring.

Although the primary published results of anti-CCN2 therapy in humans, to date, relate to its utility in treating idiopathic pulmonary fibrosis, it has also been studied in a variety of pathological conditions in rodent models.[41] Outside of solid organ and tumorigenesis models, it has been shown to reduce skin fibrosis and improve muscle function with fibrosis reduction in a model of Duchenne muscular dystrophy.[46,47] Our group developed an operant rat model of overuse injuries, in which noted changes include functionally limiting fibrosis of musculoskeletal tissues.[34,48–55] As

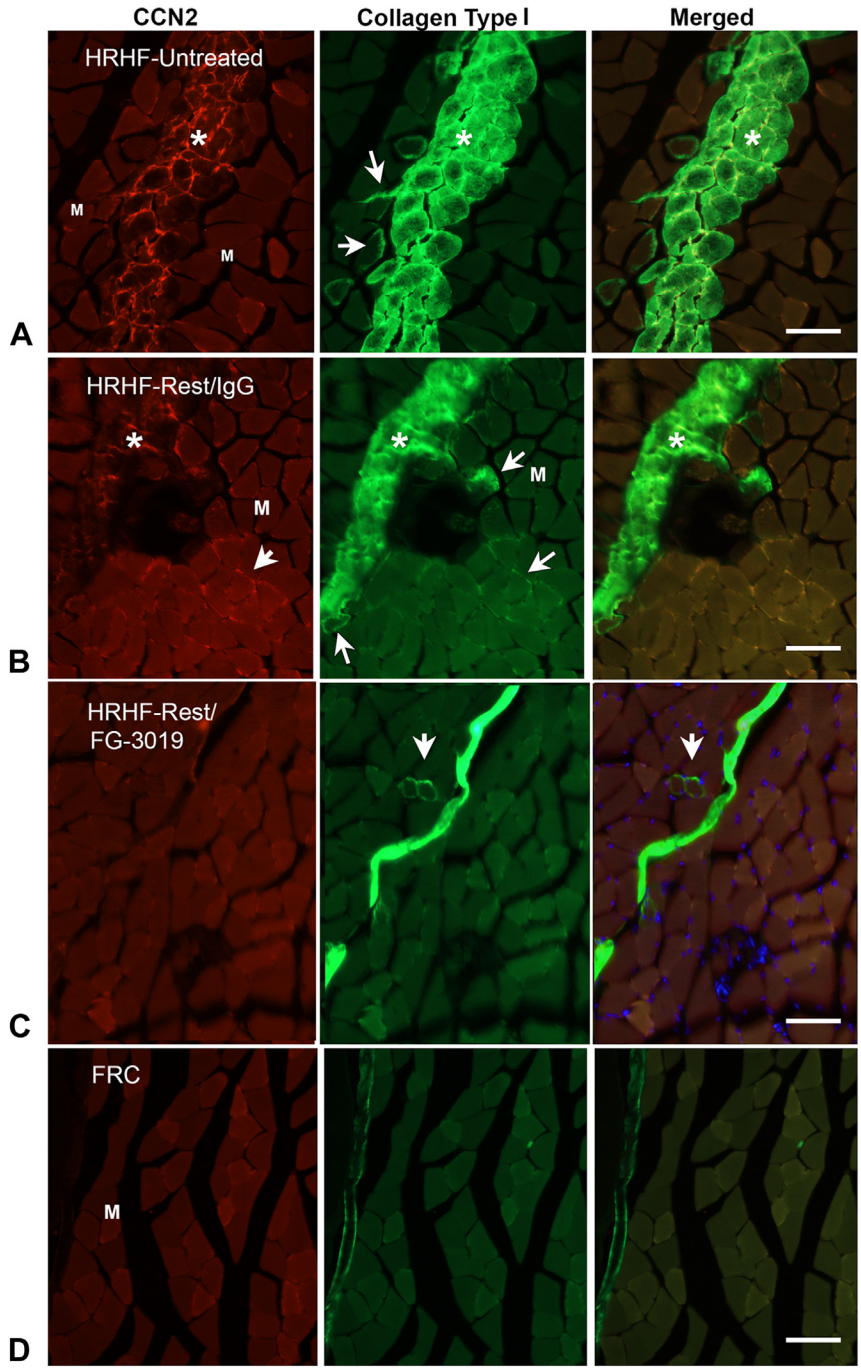

Figure 3. Reduction of type I collagen in skeletal muscle after FG-3019 treatment. Representative cell communication network factor 2 (CCN2; red) and collagen type I (green) immunoexpression in the flexor digitorum muscles of each group. Representative images of mid-forearm cross-sections are shown. **A** and **B** High repetition high force (HRHF)–untreated and HRHF-rest/immunoglobulin (Ig) G muscles showing areas with dense endomyseal deposition of CCN2 and collagen type I around individual myofibers and in band-like formations. Asterisks indicate the band-like formations. Arrows indicate examples of myofibers surrounded by endomyseal CCN2 or collagen type I. **C** The HRHF-rest/FG-3019 muscles in the same flexor muscle region showed clear reductions in CCN2 and collagen type I deposition. **D** Food-restricted control (FRC) rat muscles in the same flexor muscle region showed little to no endomyseal CCN2 or collagen type I deposition. M, muscle. Scale bar = 50 microns (Reproduced with permission from Barbe et al. Blocking CTGF/CCN2 reduces established skeletal muscle fibrosis in a rat model of overuse injury. *FASEB J.* 2020;34:6560[57]).

fibroproliferation occurs with deposition of extracellular matrix proteins, such as type I collagen, we have shown that CCN2 production concomitantly increases.[48,56,57] We have administered treatment with Pamrevlumab in this model with remarkable success. In our model, CCN2 blockade is not only able to prevent the development of fibrosis but also reverse it once established (Figs. 2 and 3). These reductions in dermal, muscle, and neural collagen deposition and fibrosis lead to improvements in functional declines, including increased grip strength and median nerve conduction velocity and reduced cold temperature sensitivity.[34,48,56,57]

A Role for Pamrevlumab in Dupuytren Disease?

It has been shown that CCN2 expression is increased in DD fibroblasts.[28] Cell communication network factor 2 functions as a key

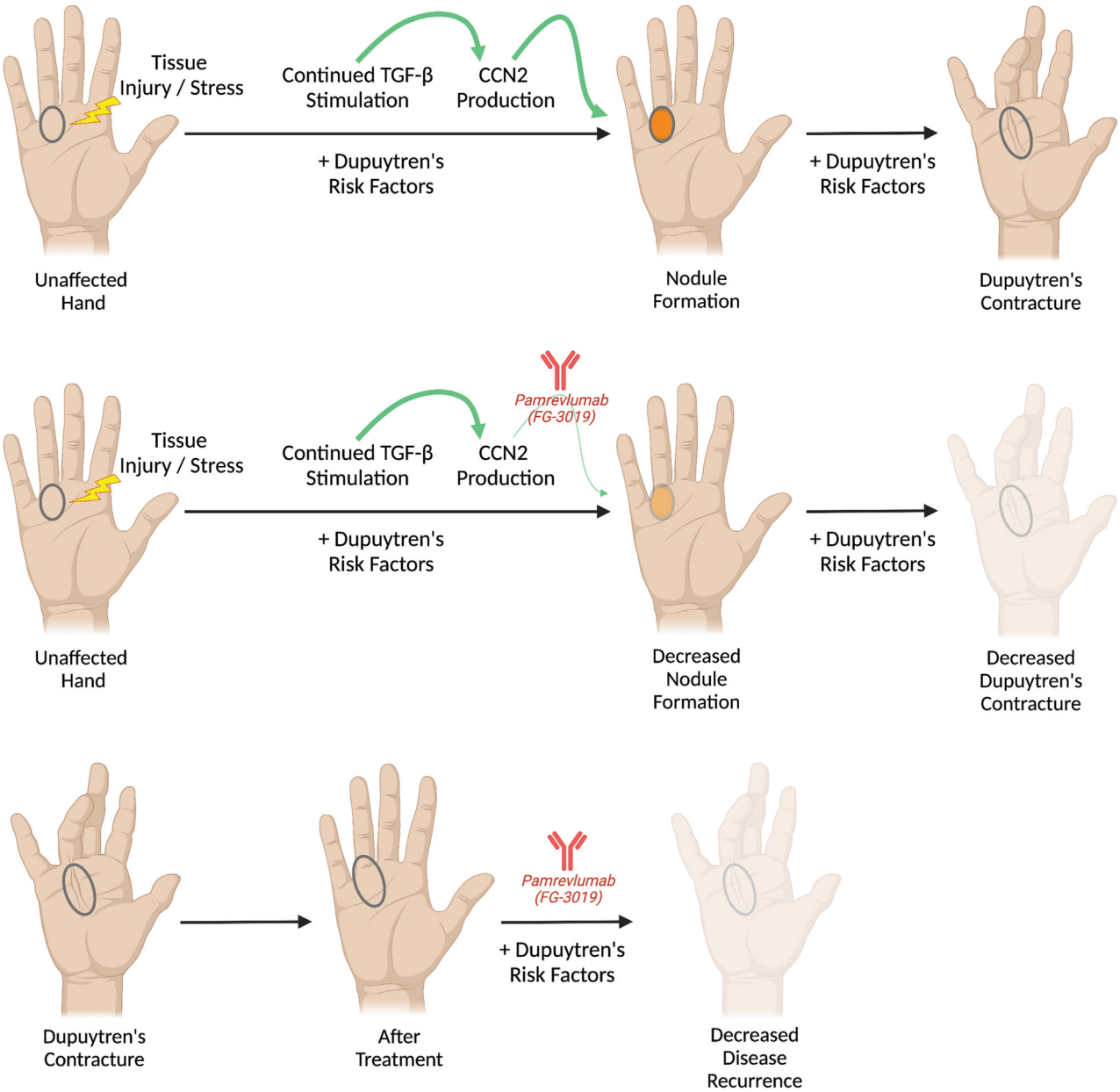

Figure 4. A role for Pamrevlumab in Dupuytren disease treatment. Following tissue injury or stress, nodule formation can occur in the presence of Dupuytren risk factors and continued transforming growth factor (TGF)-β stimulation and cell communication network factor 2 (CCN2) production. This can progress to contracture (top row). Treatment with Pamrevlumab (FG-3019) prevents the profibrotic role of TGF-β through inhibition of its downstream mediator, CCN2. This could lead to decreased nodule formation and less contracture development (middle row). After treatment with established modalities, adjunct therapy with Pamrevlumab could prevent disease recurrence in susceptible individuals (bottom row).

player in TGF-β–mediated fibrosis. Cell communication network factor 2 also functions downstream of other factors, including tumor necrosis factor.[41] Taking into account that both the inhibition of TGF-β signaling as well as tumor necrosis factor signaling result in a decreased DD development in vitro, one could envision that blockade of CCN2 downstream of both pathways in this disease would have a similar or greater effect. Therefore, we propose that anti-CCN2 therapy with Pamrevlumab constitutes a potential target in the treatment of DD (Fig. 4). To date, no studies have looked at the potential of blocking CCN2 for DD treatment and prevention of recurrence and no studies have evaluated the effect of Pamrevlumab administered as a local injection in any fibrotic tissue model (eg, DD nodules).

Several steps must be taken to determine the efficacy of Pamrevlumab as a potential antifibrotic agent for DD. First, a local injectable formulation of Pamrevlumab must be developed. This would allow focused administration at the site of disease while minimizing any potential systemic side effects. The drug is currently only developed for intravenous administration. However, there is interest in developing a formulation for local administration (personal communication with FibroGen Inc research team), and precedence already exists for this strategy with other systemically administered antifibrotic pharmacotherapies, such as pirfenidone.[58] We anticipate the dosing would be significantly lower than what is being used for current systemic therapy in clinical applications. Second, the timing of Pamrevlumab treatment

would need to be determined. It may be that utility exists for injection at both early disease occurrence (eg, nodule development), to prevent progression, as well as following treatment, to prevent recurrence. For a targeted, streamlined approach, one could first choose those who have undergone treatment for symptomatic contracture. Local injection would occur at the time of definitive treatment (eg, fasciectomy, needle aponeurotomy, and manipulation), which is similar to other proposed adjuvants, such as fat grafting,[59] as well as at distinct time points after treatment to prevent recurrence, such as at 6 weeks and 3 months, which is consistent with published data on corticosteroid injection.[60] Third, we anticipate that the potential side effect profile would be acceptable. Clinical trials thus far have shown that systemic administration of Pamrevlumab is well-tolerated.[44] We surmise that since local injection dosing would be lower than systemic dosing and that only a fraction of this is likely to be systemically absorbed, local application is unlikely to have an undesirable risk profile.

Conclusion

Despite our notable advances in understanding the mechanisms underlying fibrosis, DD remains a challenging clinical entity to treat. Invasive procedures have historically been the mainstay of treatment. More recently, enzymatic digestion with collagenase has become a staple for over a decade. However, there is still a large void in the hand surgeon's armamentarium for an adjunct therapy that can either stop disease progression in 30% to 50% of patients in early stages, at risk, or prevent disease recurrence following treatment with the current approaches. We have previously underscored the need to take an antifibrogenic approach in finding pharmacotherapies for Dupuytren treatment.[7] In this article, we highlighted the role of TGF-β signaling in DD and owing to its critical role in TGF-β–induced fibrosis, proposed CCN2 as a new potential high-yield target. The monoclonal antibody Pamrevlumab has already shown strong efficacy as systemic therapy in the treatment of fibrotic disorders. Our group has demonstrated a clear antifibrotic role in blocking CCN2 in an in vivo model of musculoskeletal and dermal tissue fibrosis. These results provide a strong rationale for future feasibility studies and subsequent clinical trials using Pamrevlumab in patients with DD.

Acknowledgments

All authors contributed to the preparation of the manuscript, including design and figure preparation. Figures 1 and 4 were created with BioRender.com. This work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Grant 5R01AR056019-13 to senior author (M.F.B.).

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