



Case Report

The Dynamic Role Of Myofibroblasts In Oral Tissue Homeostasis And Disease

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Abstract

Myofibroblasts are specialized cells that play a crucial role in maintaining the structural integrity and function of oral tissues. These cells exhibit a unique phenotype marked by the expression of alpha-smooth muscle actin (α -SMA), and possess the ability to contract and produce extracellular matrix components. In healthy oral tissues, myofibroblasts contribute to tissue homeostasis by mediating wound healing, tissue remodeling, and matrix turnover. However, the dysregulation of myofibroblast function can lead to pathological conditions such as fibrosis, scarring, and oral cancer. This review aims to explore the dynamic role of myofibroblasts in oral tissue homeostasis and disease. It begins by examining the origin of myofibroblasts in the oral cavity, their phenotypic characteristics, and their interactions with other cell types, including epithelial cells, immune cells, and endothelial cells. The review further highlights the role of myofibroblasts in various oral diseases, such as oral submucous fibrosis, periodontal disease, and oral cancer, and discusses potential therapeutic strategies targeting myofibroblast function. Understanding the dynamic role of myofibroblasts in oral tissue homeostasis and disease is essential for developing innovative therapeutic approaches to modulate myofibroblast function and improve the management of oral diseases.

Keywords: Myofibroblasts, fibrosis, mesenchyme, microenvironment, differentiation

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INTRODUCTION

Myofibroblasts, characterized by alpha-smooth muscle actin (α -SMA) expression, are crucial in oral tissue homeostasis and various oral diseases. They contribute to wound healing, tissue remodeling, and fibrosis¹. These cells are pivotal in tissue repair by producing and organizing extracellular matrix (ECM) into scar tissue, aiding in restoring tissue integrity². In oral squamous cell carcinoma (OSCC), myofibroblasts play a role in the invasive process, with higher expression observed in OSCC cases compared to controls. Additionally, myofibroblasts' involvement in chronic wound healing is highlighted, showing that mesenchymal stem cells can activate myofibroblasts, enhancing the healing efficiency of chronic purulent-necrotic wounds³.

Myofibroblasts play a crucial role in the pathogenesis of various oral diseases, including oral submucous fibrosis, periodontal disease, and oral cancer, by interacting with different cell types in the oral microenvironment⁴. These cells secrete cytokines, growth factors, and extracellular matrix components that influence the behavior of epithelial cells, immune cells, and endothelial cells. In oral submucous fibrosis, increased stiffness of the fibrotic matrix leads to enhanced proliferation and epithelial-mesenchymal transformation of mucosal epithelial cells, mediated by Piezo1-YAP signaling⁵. Furthermore, myofibroblasts have been found to be significantly expressed in oral squamous cell carcinoma, suggesting their potential as stromal markers for tracking disease severity and progression. This intricate interplay underscores the multifaceted role of myofibroblasts in oral health and disease.

Given the critical role of myofibroblasts in oral tissue homeostasis and disease, understanding the mechanisms underlying their function is essential for developing targeted therapeutic strategies. This review aims to provide an overview of the dynamic role of myofibroblasts in oral tissue homeostasis and disease, with a focus on their origin, phenotype, interactions with other cell types, and involvement in oral diseases.

STRUCTURE:

Myofibroblasts are specialized cells with a unique structure that allows them to perform their functions in tissue repair, remodeling, and fibrosis⁶. The structure of myofibroblasts is characterized by several key features:

- a) **Cytoskeleton:** Myofibroblasts are characterized by the presence of a contractile cytoskeleton, which is primarily composed of bundles of actin filaments containing alpha-smooth muscle actin (α -SMA). These actin filaments are organized into stress fibers, which are responsible for the contractile properties of myofibroblasts.
- b) **Cell Shape:** Myofibroblasts typically exhibit a spindle-shaped morphology, with elongated cytoplasmic extensions that allow them to interact with neighboring cells and the extracellular matrix.
- c) **Cellular Organelles:** Like other cells, myofibroblasts contain typical organelles such as the nucleus, mitochondria, endoplasmic reticulum, and Golgi apparatus. These organelles play essential roles in cellular functions such as protein synthesis, energy production, and intracellular signaling.
- d) **Cell-Cell Junctions:** Myofibroblasts can form specialized junctions with other cells, such as adherens junctions and gap junctions, which allow for communication and coordination of activities between neighboring cells.

- e) **Extracellular Matrix (ECM) Interactions:** Myofibroblasts interact closely with the ECM, producing and remodeling ECM components such as collagen, fibronectin, and proteoglycans. These interactions are essential for maintaining tissue structure and function.
- f) **Markers:** Myofibroblasts are characterized by the expression of specific markers, including α -SMA, vimentin, and fibroblast-specific protein 1 (FSP-1). These markers help identify and distinguish myofibroblasts from other cell types in tissues⁷.

ORIGIN OF MYOFIBROBLAST:

Myofibroblasts can arise from various precursor cells, and their origin can vary depending on the tissue and context⁸. The three main sources of myofibroblasts are:

- a) **Fibroblasts:** In many tissues, including the oral cavity, myofibroblasts are thought to originate from resident fibroblasts. Upon stimulation by factors such as transforming growth factor-beta (TGF- β) released during tissue injury or inflammation, fibroblasts can differentiate into myofibroblasts.
- b) **Pericytes:** Pericytes are perivascular cells that surround the endothelial cells of capillaries and venules. Under certain conditions, pericytes can differentiate into myofibroblasts and contribute to tissue repair and fibrosis, particularly in the context of vascular remodeling.
- c) **Epithelial and endothelial cells:** In some situations, epithelial cells or endothelial cells can undergo a process called epithelial-to-mesenchymal transition (EMT) or endothelial-to-mesenchymal transition (EndMT), respectively. During these transitions, these cells acquire a mesenchymal phenotype and can differentiate into myofibroblasts (**Figure 1**).

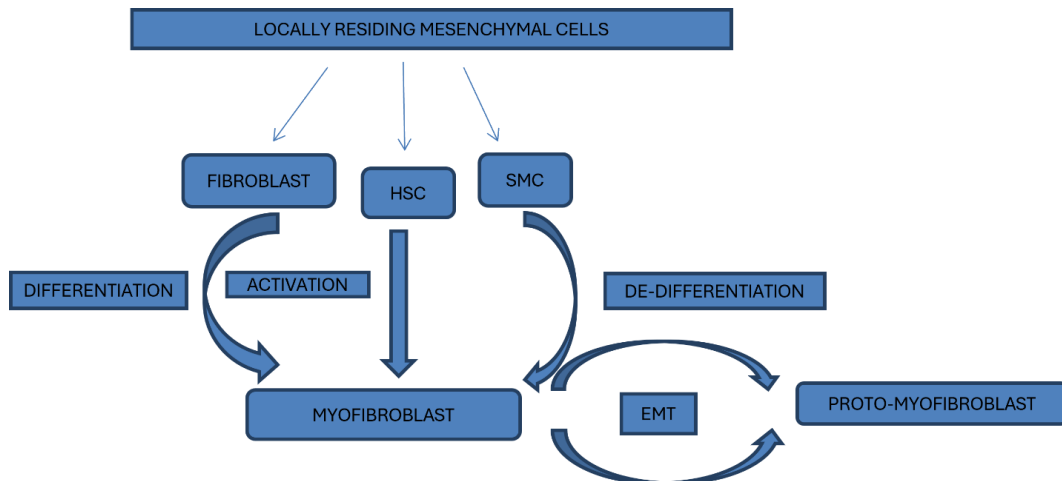


Figure 1 depicting the possible origin of Myofibroblasts & role of EMT during the formation

DIFFERENTIATION OF MYOFIBROBLAST:

The differentiation of myofibroblasts is a complex process that involves changes in gene expression, cell morphology, and function. The differentiation of myofibroblasts can be triggered by various stimuli, including growth factors, cytokines, mechanical stress, and interactions with the extracellular matrix. The differentiation process typically involves several key steps: Stimulation, Activation of signalling pathways, Expression of Smooth Muscle Actin (α -SMA), Maintenance of differentiation. The differentiation of myofibroblasts is often initiated by the release of pro-fibrotic factors, such as transforming growth factor-beta (TGF- β), platelet-derived growth factor (PDGF), and connective tissue growth factor (CTGF), in response to tissue injury or inflammation⁹. These pro-fibrotic factors activate signaling pathways within fibroblasts and other precursor cells, leading to changes in gene expression. The canonical TGF- β signaling pathway, for example, involves the activation of Smad proteins, which regulate the expression of genes involved in myofibroblast differentiation. One of the hallmarks of myofibroblast differentiation is the expression of alpha-smooth muscle actin (α -SMA). α -SMA is a cytoskeletal protein that is essential for the contractile function of myofibroblasts and is regulated by TGF- β and other signaling pathways. Once differentiated, myofibroblasts can maintain their phenotype through autocrine and paracrine signaling loops involving factors such as TGF- β and PDGF¹⁰. These signaling pathways help sustain the activation of myofibroblasts and promote their continued function in tissue repair and remodeling.

ROLE OF MYOFIBROBLAST IN WOUND HEALING:

Myofibroblasts play a crucial role in wound healing, particularly in the later stages of the process known as the remodeling phase. Their functions are essential for wound closure, tissue repair, and restoration of tissue function. The key roles of myofibroblasts in wound healing include contraction of the wound, which helps to reduce the size of the wound and bring the edges closer together, facilitating closure. Myofibroblasts also synthesize and deposit extracellular matrix (ECM) components such as collagen, fibronectin, and proteoglycans, providing structural support to the newly formed tissue. They remodel the ECM by secreting enzymes such as matrix metalloproteinases (MMPs) that degrade the old ECM and facilitate the deposition of new ECM, leading to tissue restructuring. Additionally, myofibroblasts promote angiogenesis by secreting angiogenic factors like vascular endothelial growth factor (VEGF), which is essential for supplying oxygen and nutrients to the healing tissue¹¹. They also modulate inflammation by secreting cytokines and chemokines that regulate the activity of immune cells, helping to resolve inflammation and promote the transition to the later stages of wound healing. However, excessive or prolonged activation of myofibroblasts can lead to the formation of excessive scar tissue (fibrosis), impairing tissue function and leading to cosmetic disfigurement¹². Understanding the role of myofibroblasts in wound healing is crucial for developing therapies to promote healing and prevent excessive scarring.

ROLE OF MYOFIBROBLAST IN FIBROSIS:

Myofibroblasts play a central role in the pathogenesis of fibrosis, a condition characterized by excessive deposition of extracellular matrix (ECM) components, leading to tissue scarring and dysfunction. In fibrosis, myofibroblasts are persistently activated and contribute to the excessive production and remodeling of ECM, disrupting the normal tissue architecture. Several key mechanisms underlie the role of myofibroblasts in fibrosis, including their production of ECM components such as collagen and fibronectin, their contractility leading to tissue stiffness, their ability to migrate to sites of

injury in response to chemotactic signals, their dysregulated transforming growth factor-beta (TGF- β) signaling, their interactions with other cell types in the fibrotic microenvironment, and their contribution to chronic inflammation¹³. Targeting the activation, recruitment, and function of myofibroblasts may offer new strategies for the treatment of fibrosis and the prevention of tissue scarring and dysfunction.

ROLE OF MYOFIBROBLAST IN ORAL CANCER:

Myofibroblasts play a crucial role in oral squamous cell carcinoma (OSCC) by contributing to its invasive process and pathogenesis. Studies have shown that myofibroblasts are significantly expressed in OSCC tissues compared to normal controls, indicating their involvement in creating a permissive environment for cancer invasion¹⁴. Additionally, the presence of myofibroblasts has been linked to the progression and metastasis of OSCC, making them a potential marker for monitoring the disease's severity and development¹⁵. These activated myofibroblasts within the tumor microenvironment promote growth, invasion, and resistance to various therapies, ultimately impacting the prognosis of OSCC patients¹⁶. Therefore, targeting myofibroblasts therapeutically could be a promising approach in managing OSCC and improving treatment outcomes.

CONCLUSION

In conclusion, myofibroblasts play critical and multifaceted roles in both physiological and pathological processes, including wound healing and fibrosis. In wound healing, myofibroblasts contribute to tissue repair by facilitating wound contraction, ECM production, and tissue remodeling. However, in fibrosis, dysregulated myofibroblast activation leads to excessive ECM deposition, tissue scarring, and organ dysfunction. Understanding the complex mechanisms underlying myofibroblast function in these processes is essential for developing targeted therapies to promote wound healing and prevent or treat fibrotic diseases. Future research should focus on elucidating the signaling pathways and interactions that regulate myofibroblast behavior, with the ultimate goal of improving clinical outcomes for patients with wound healing disorders and fibrotic conditions.

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Conflicts of interest

There are no conflicts of interest

REFERENCES

1. S., abdel, ghani., Shaimaa, M., Masloub., A., Ahmed., Inas, Helwa. Potential role of myofibroblasts in behavior of oral ossifying fibroma. Egyptian dental journal, (2023). doi: 10.21608/edj.2023.199706.2487
2. S., V., Slobodanyk., Sergiy, Vernygorodskiy., S., D., Khimich., V., S., Shkolnikov. The role of myofibroblasts in the healing of chronic wounds. Reports of Morphology, (2022). doi: 10.31393/morphology-journal-2022-28(2)-07
3. Ronen, Schuster., Fereshteh, Younesi., Maya, Ezzo., Boris, Hinz. The Role of Myofibroblasts in Physiological and Pathological Tissue Repair. Cold Spring Harbor Perspectives in Biology, (2022). doi: 10.1101/cshperspect.a041231

4. Vaishali, Gandhi., Anupama, Mahajan., Yash, Kansal. An Immunohistochemical Analysis for Evaluating the Diagnostic Role of Myofibroblasts in Oral Squamous Cell Carcinoma using α -Smooth Muscle Actin Antibody. *Advanced Biomedical Research*, (2023). doi: 10.4103/abr.abr_160_21
5. Koji, Naruishi. Biological Roles of Fibroblasts in Periodontal Diseases. *Cells*, (2022). doi: 10.3390/cells11213345
6. Yifan, Tai., Emma, L., Woods., Jordanna, Dally., Deling, Kong., Robert, Steadman., Ryan, Moseley., Adam, C., Midgley. Myofibroblasts: Function, Formation, and Scope of Molecular Therapies for Skin Fibrosis. (2021). doi: 10.3390/BIOM11081095
7. Astrid, Hirschmann., Eva, Camarillo, Retamosa., Caroline, Ospelt., Alexander, Vogetseder. Protein atlas of fibroblast specific protein 1 (FSP1)/S100A4.. *Histology and Histopathology*, (2023). doi: 10.14670/HH-18-621
8. Giulio, Gabbiani. 50 Years of Myofibroblasts: How the Myofibroblast Concept Evolved.. *Methods of Molecular Biology*, (2021). doi: 10.1007/978-1-0716-1382-5_1
9. Wensheng, Chen., Darrell, Pilling., Richard, H., Gomer. Inhibiting a mRNA motif binding protein that mediates TGF- β 1 upregulation of translation attenuates pulmonary fibrosis in mice. *bioRxiv*, (2022). doi: 10.1101/2022.10.23.513405
10. Katarina, Zmajkovicova., Yasmina, Bauer., Katalin, Menyhart., Marie, Schnoebelen., Diego, Freti., Maxime, Boucher., Bérengère, Renault., Rolf, Studer., Magdalena, Birker-Robaczewska., Axel, Klenk., Oliver, Nayler., John, Gatfield. GPCR-induced YAP activation sensitizes fibroblasts to profibrotic activity of TGF β 1.. *PLOS ONE*, (2020). doi: 10.1371/JOURNAL.PONE.0228195
11. Ying-Ying, Teng., Ming-Li, Zou., Xiao-Jin, Zhou., Jun-jie, Wu., Si-Yu, Liu., Zheng-Dong, Yuan., Yuan, Jia., Kai-Wen, Zhang., Xia, Li., Jun-Xing, Ye., Feng-Lai, Yuan. Novel prospects for scarless wound healing: The roles of myofibroblasts and adipocytes. *Journal of Cellular and Molecular Medicine*, (2022). doi: 10.1111/jcmm.17535
12. Prakash, Monika., Prabhakar, Veena, Waiker., Mathikere, Naganna, Chandraprabha., Annapoorni, Rangarajan., Kotamballi, N., Chidambara, Murthy. Myofibroblast progeny in wound biology and wound healing studies. *Wound Repair and Regeneration*, (2021). doi: 10.1111/WRR.12937
13. The myofibroblast: Role in fibrosis development. (2022). doi: 10.1016/b978-0-323-90546-6.00010-1
14. Vaishali, Gandhi., Anupama, Mahajan., Yash, Kansal. Establishment of the role of myofibroblasts in invasive process of oral squamous cell carcinoma: A pilot study. *Journal of family medicine and primary care*, (2022). doi: 10.4103/jfmpe.jfmpe_1123_21
15. Hagar, Alaudien, El-naggar., Manal, I., El, Nouaem., Zeinab, E., Darwish., Gamal, A., Swaify., Marwa, M., Essawy. Role of myofibroblasts in the primary lesions and lymph node metastasis of oral squamous cell carcinoma. (2021). doi: 10.21608/ADJALEXU.2021.165446
16. Piyush, Gandhi., Manmeet, Kaur., Ramandeep, S, Punia., Thippeswamy, Shamenahalli, Halappa., Harkanwal, Preet, Singh. Myofibroblasts as important diagnostic and prognostic indicators of oral squamous cell carcinoma: An immunohistochemical study using alpha-smooth muscle actin antibody. *Journal of Oral and Maxillofacial Pathology*, (2022). doi: 10.4103/jomfp.jomfp_389_20



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