Extracellular Matrix Remodelling of the Periodontium under Orthodontic Force

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As the biological mechanisms of orthodontic tooth movement have been explored further, scholars have gradually focused on the remodelling mechanism of the extracellular matrix (ECM) in the periodontal ligament (PDL). The ECM of the PDL consists of various types of collagens and other glycoproteins. The specific process and mechanism of ECM remodelling during orthodontic tooth movement remains unclear. Collagen I and III, which constitute major components of the PDL, are upregulated under orthodontic force. The changes in the contents of ECM proteins also depend on the expression of ECM-related enzymes, which organise new collagen fibre networks to adapt to changes in tooth position. The matrix metalloproteinase family is the main enzyme that participates in collagen hydrolysis and renewal and changes its expression under orthodontic force. Moreover, ECM adhesion molecules, such as integrins, are also regulated by orthodontic force and participate in the dynamic reaction of cell adhesion and separation with the ECM. This article reviews the changes in ECM components, related enzymes and adhesion molecules in the PDL under orthodontic force to lay the foundation for the exploration of the regulatory mechanism of ECM remodelling during orthodontic tooth movement.

Keywords: *biomechanics, extracellular matrix, orthodontic tooth movement, periodontal ligament, remodelling*

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The biological mechanism of orthodontic treatment involves moving teeth to a new position by way of orthodontic force, accompanied by periodontal tissue remodelling in the process. Periodontal tissue consists of periodontal ligament (PDL), alveolar bone, cementum and gingiva. PDL is a specialised fibrous connective tissue that fixes teeth to alveolar bone through Sharpey fibres. It maintains the structural integrity of periodontal tissue, provides protection and support for the masticatory system and is also the biological basis for orthodontic tooth movement.[1] PDL dysfunction leads to an imbalance in the periodontal microenvironment, causing subsequent root resorption and alveolar bone loss. Previous studies have shown that the removal of PDL results in ankylosis of teeth and restriction of tooth movement.[2] As the main site of mechanical signal transduction and subsequent molecular biological reactions, the PDL is an indispensable part of the mechanism of orthodontic tooth movement.

The extracellular matrix (ECM) is a key component of the noncirculating cell microenvironment. As well as providing structural support, the ECM contributes to maintaining cell viability, regulating intercellular adhesion and transmitting mechanical forces.[3] Studies have found that the ECM derived from PDL cells (PDLCs) promotes cell proliferation and migration and maintains cell stemness.[4,5] Cells respond to mechanical and biochemical signals from the ECM and thereby change their biological behaviours, such as survival, migration and differentiation. Cells also secrete cytokines and growth factors to regulate the ECM environment.[6] The PDL is mainly composed of the ECM and cells within it. The interaction between cells and the ECM constitutes the biological mechanism of orthodontic tooth movement; however, the regulatory mechanism behind the

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ECM changes in the PDL during orthodontic processes remains unclear. This review aims to summarise and review existing studies, explore the change patterns of ECM components and related molecules in the PDL during orthodontic tooth movement, and lay the foundation for exploring the periodontium remodelling mechanism during orthodontic tooth movement.

ECM components of PDL

PDL is mainly composed of cells and ECM. The cell populations comprise fibroblasts, endothelial cells, Malasser epithelial cells, osteoblasts and osteoclasts, cementoblasts, immune cells and cells associated with the sensory system. Among these, fibroblasts, often known as PDLCs, are the main cell type, accounting for approximately 20% to 30% of the PDL volume.[1] PDLCs attach to collagen through focal adhesions and participate in the alignment of collagen fibre nets.

ECM components of PDL include collagens and other noncollagenous glycoproteins. The collagen fibre bundles in the PDL are mainly composed of collagen I and III. Collagen V is embedded in fibre bundles or interstices.[7] Previous studies have shown that collagen I, III and V make up 75%, 20% and 5% of PDL, respectively.[7,8] In recent years, Thant et al[9] performed laser microdissection and lipid chromatography-tandem mass spectrometry to comprehensively analyse the PDL tissue–specific proteome and found that the major collagen types of PDL were type I (86.5%), type III (4.5%), type XII (4.5%) and type V (1.7%) based on the spectral count. The slight difference in the proportion of each major collagen component in various studies is potentially due to factors such as protein extraction and measurement methods and species differences. In addition to the above collagens, there are also small amounts of collagens IV, VI, VIII and XII in the PDL, which jointly participate in the formation of a mature fibre network. Recently, many proteomic studies also found collagen II in rat and mouse PDLCs[10,11], which has been proven to be upregulated under cyclic tension stretch and hypoxic conditions.[12] Collagen II allows the ECM to accommodate more water molecules to dissipate stress[13], but its specific function in the PDL still needs to be further explored.

Changes in ECM components under orthodontic force

The rapid ECM remodelling of the PDL determines its unique adaptability. The coordinated breakdown and synthesis of ECM components take the forms of turnover and remodelling. ECM turnover refers to the dynamic stability of structural organisation, whereas remodelling reflects the adaptive changes in the shape and function of the ECM.[14] The two forms often coexist in the process of orthodontic tooth movement. While maintaining the width and normal function of the PDL, the ECM forms a periodontal microenvironment that is conducive to orthodontic tooth movement by rapid remodelling. The exploration of changes in ECM components in the PDL under different types of forces would facilitate understanding of the process of ECM microenvironment formation.

Collagens

Collagen is the main fibre component of the PDL. Similar to other ECM proteins, collagen is synthesised and modified in the endoplasmic reticulum, transported to the endoplasmic reticulum and the Golgi intermediate compartment in a COPII-dependent manner, and then passes through the cell. Procollagen is secreted into the extracellular space, where it is cleaved and assembled into fibrous structures.[15] At the end of the 20th century, scholars proposed that the PDL remodelling mechanism induced by orthodontic treatment is similar to the wound healing process, accompanied by increased collagen metabolism.[16] Turnover and remodelling of collagens in the PDL under orthodontic force is an important physiological process in orthodontic tooth movement. Changes in the expression levels of collagens in previous studies are summarised in Table 1.

At the macroscopic level, Thant et al[9] used second harmonic generation (SHG) imaging and the CT-FIRE automatic tracking algorithm to detect individual collagen fibres and found that the number, width and length of fibres on the compressed side of the PDL decreased significantly after 14 days of orthodontic force application, whereas no significant change was observed on the tension side. At the microscopic level, the synthesis and degradation of various types of collagens vary with each other under different types of mechanical forces at different times and in different sites in past studies.

Collagen I and III are the main components of the ECM in the PDL. Previous studies have demonstrated that collagen I is mainly responsible for maintaining tissue strength, whereas collagen III contributes to maintaining tissue elasticity and relieving the tension force placed on the PDL during orthodontic tooth movement.[17] Remodelling of the two collagens is dominant in PDL remodelling during orthodontic treatment. Most research has reported that collagen I and III first increase and then decrease in the PDL after orthodon-

tic force application. As early as 1984, Duncan et al[18] verified through animal models that after 3 to 5 days of orthodontic force application, the content of collagen III in the PDL increased significantly. Subsequently, Bumann et al[16], Militi et al[19] and Anastasi et al[20] extracted human premolars after applying orthodontic force and found that collagen I gradually increased on the compression side within 14 to 30 days of force application. Redlich et al[21]and Hacopian et al[22] reported that compression upregulated the expression of collagen I via in vitro experiments as well. Upregulation of collagen III under compression was also reported.[16] Regarding tensional force, Pei et al[2] demonstrated that tension promoted collagen remodelling in the ECM and increased the secretion of collagen I in PDLCs. Howard et al[23] and Kook et al[24] also found that the expression of collagen I and III in PDLCs was upregulated under tension. For in vivo experiments, Militi et al[19] and Anastasi et al[20] observed that collagen I increased on the tension side of extracted human premolars at an early stage, before decreasing gradually. However, unlike most other studies, Wescott et al[25] and Nemoto et al[26] reported downregulation of the short-chain collagen genes *COL3A1* and *COL1A1* in hPDLCs under tension.

In the early stage of collagen remodelling, although the synthesis of collagen I and III generally show an upward trend, studies also found that the rate of increase of the two is not consistent. The deposition of collagen III is more significant than that of collagen I, which leads to an increase in the ratio of collagen III to I. Over time, the content of collagen I gradually increases to maintain a balanced ratio of the two.[17] Li et al[27] compared orthodontic tooth movement between diabetic rats and normal rats. They found that in normal rats, the ratio of collagen III to I gradually increased in the early stage, then decreased, and gradually returned to the baseline level on the 14th day. In the diabetes group, the ratio of the two continued to increase and did not show a downward trend, suggesting that diabetes causes abnormal collagen remodelling during orthodontic tooth movement.[27] In another study, Li et al[28] used Sirius red staining and immunohistochemistry to examine the regional distribution of collagen III and I in PDL after applying orthodontic force and found that the ratio of collagen III to I increased, especially in the apical region, which corresponds to the stress concentration area. The above studies suggest that in the early phase of orthodontics, the elasticity of the PDL increases to adapt to tooth movement, especially in the compression area. Then, as the ratio of collagen III to I increases to normal levels, the hardness and toughness of the PDL gradually recover.

The hydrolysate of collagen IV can promote angiogenesis, thereby improving the proliferation, stemness and osteogenic differentiation of PDL stem cells.[29] In aged oral fibroblasts, the expression of collagen IV decreased, and the arrangement of ECM collagen changed from network to line, suggesting the role of collagen IV in the arrangement of the collagen fibre network.[30] In previous studies, the expression of IV collagen in the PDL mainly showed a downward trend under mechanical force. Anastasi et al[20] reported that the synthesis of collagen IV was significantly decreased on both the compression side and the tension side of human teeth after orthodontic treatment. Militi et al[19] found that the expression of collagen IV first decreased and then rose slightly on the tension side within 30 days of force application, and on the compression side, collagen IV decreased and then returned to the baseline level. The downregulation of collagen IV partly explains the disordered arrangement of collagen fibres under orthodontic force.

Collagen VI is closely related to the posttranslational modification of collagen fibres, participates in collagen fibre assembly and 3D structural organisation, and increases the stiffness of collagen I fibres.[31] It was reported that the PDL in the cervical area was harder and more viscoelastic than that in other areas, the abundance of collagen VI was higher in the cervical area, and the collagen fibre network was denser.[10] Saminathan et al[32] found a significant downregulation of the expression of the short-chain collagen gene *COL6A1* after applying cyclic tension. Thant et al[9] demonstrated that the proportion of collagen VI in the PDL decreased on the compression side in orthodontically treated mice. Bumann et al[16] reported an increase in collagen VI on the compression side as well, and the changes were not significant on the tension side in this study. The changes in the expression of collagen VI under orthodontic forces remain to be clarified.

At present, there are few studies related to other types of collagens. Bumann et al[16] found that the secretion of collagen V increased under compression. Ma et al[33] also reported that stretching force upregulated the expression of *COL5A1* in PDLCs. In the study conducted by Saminathan et al[32], the expression of *COL8A1* was downregulated in PDLCs under tension. Regarding collagen XI, studies demonstrated consistent results that stretching force downregulates *COL11A1* in PDLCs.[25,32,33] Thant et al[9] found that collagen XII increased on the tension side of the PDL in mice. Further research is needed on the changes and roles of collagen in ECM remodelling.

Table 1 Collagens outcome from all included studies.

Study	Force type	Methods	Object	Outcome	
				COL-I	
Howard et al[23]	Tension	ELISA	hPDLCs	Upregulated significantly (5%, 24 h), non-significant (10%, 24 h)	
Redlich et al[21]	Compression	RT-PCR	hPDLCs	Upregulated significantly (within 60 min), non-significant (90 min)	
Wescott et al[25]	Tension	RT-PCR	hPDLCs	NR	
Nemoto et al[26]	Tension	RT-PCR	hPDLCs	Downregulated significantly (within 7 d)	
Kook et al[24]	Tension	RT-PCR	hPDLCs	Upregulated significantly (within 12 h)	
Hacopian et al[22]	Compression	RT-PCR	hPDLCs	Upregulated significantly (30 min)	
Saminathan et al[32]	Tension	RT-PCR	hPDLCs	NR	
Ma et al[33]	Tension	RT-PCR	hPDLCs	NR	
Pei et al[2]	Magnetic stretch	IHC	hPDLCs	Upregulated significantly (within 15 d)	
Duncan et al[18]	NR	Radiolabelling	Mice	NR	
Li et al[27]	Compression and tension	IHC	Sprague-Dawley rats	Upregulated significantly (7 d), non-significant (14 d), non-significant (within 14 d)	
Li et al[28]	Compression tension	Picrosirius red staining, IHC	Sprague-Dawley rats	Downregulated significantly (7 d), downregulated significantly (7 d)	
Thant et al[9]	Compression tension	Picrosirius red staining, IHC	C57BL/6J mice	Downregulated significantly (14 d), non-significant (14 d)	
Bumann et al[16]	Compression tension	ELISA	Extracted human premolars	Upregulated significantly (14 d), non-significant (14 d)	
Anastasi et al[20]	Compression tension	IHC	Extracted human premolars	Upregulated significantly (within 14 d), upregulated significantly (3, 72 h), downregulated significantly (7, 14 d)	
Militi et al[19]	Compression tension	IHC	Extracted human premolars	Upregulated significantly (within 30 d), upregulated significantly (1 d), downregulated significantly (7, 14 d), non-significant (30 d)	

Significance compared to unstimulated control.

ELISA, enzyme-linked immunosorbent assay; IHC, immunohistochemistry; NR, not reported.

	COL-III	COL-IV	COL-VI	Other collagens
	Upregulated significantly (5%, 24 h)	NR	NR	NR
	NR	NR	NR	NR
	Downregulated significantly (12 h)	NR	NR	*COL2A1* upregulated significantly (12 h)
	NR	Upregulated significantly (within 7 d)	NR	NR
	NR	NR	NR	NR
	NR	NR	NR	NR
	NR	NR	NR	*COL6A1* downregulated significantly (12 h), *COL8A1* downregulated significantly (12 h), *COL11A1* downregulated significantly (24 h)
	NR	NR	NR	*COL5A1* upregulated significantly (24 h), *COL11A1* downregulated significantly (6 h)
	NR	NR	NR	NR
	Upregulated significantly (3 d)	NR	NR	NR
	NR Upregulated significantly (3, 7 d), non-significant (14 d)	NR	NR	NR
	Upregulated significantly (7 d), upregulated significantly (7 d)	NR	NR	NR
	Non-significant (14 d), non-significant (14 d)	NR	Upregulated significantly (14 d), non-significant (14 d)	COL-II non-significant (14 d), COL-XII upregulated (14 d), COL-II non-significant (14 d), COL-XII non-significant (14 d)
	Upregulated significantly (14 d), non-significant (14 d)	NR	Upregulated significantly (14 d), non-significant (14 d)	COL-V upregulated significantly (14 d), non-significant (14 d)
	NR	Downregulated significantly (3, 72 h), upregulated significantly (7, 14 d), downregulated significantly (3, 72 h), upregulated significantly (7, 14 d)	NR	NR
	NR	Downregulated significantly (1, 7, 14 d), upregulated significantly (21, 30 d), downregulated significantly (within 30 d)	NR	NR

Noncollagenous glycoproteins

In addition to collagens, there are other glycoproteins in the ECM. Most of them are multifunctional macromolecules that combine with cells and other ECM components to affect biological behaviours such as cell survival, proliferation and migration; however, the remodelling pattern of these noncollagenous glycoproteins under orthodontic force remains unclear.

Fibronectin is a common ECM glycoprotein. It coats type I and type III collagen fibres in the PDL, covers the gap between adjacent collagen fibrils and cell membranes, and facilitates cell migration and osteogenic differentiation.[34] The regulation of fibronectin reflects the process of damage and remodelling of the periodontal fibre network. The changes in fibronectin content also adapt to the process of orthodontic tooth movement by regulating cell migration and osteogenic activity. Howard et al[23] first reported the upregulation of fibronectin in PDLCs under stretching force. Subsequently, Militi et al[19] found that after applying orthodontic force to human teeth, the expression of fibronectin decreased at first and then increased to the baseline level on the tension side, whereas its expression on the pressure side increased constantly within 30 days after the force was applied. Similarly, Anastasi et al[20] also found that fibronectin increased on the compression side and decreased on the tension side of the moved teeth; however, He et al[35] reported that compression caused a downregulation of fibronectin expression. After applying centrifugal force to PDLCs, Theilig et al[36] also observed a decrease in fibronectin expression accompanied by a decrease in tenascin and laminin. It is known that tenascin can inhibit cell adhesion to the ECM by binding fibronectin.[37] Elastin is a component of the elastic fibre networks in the ECM, which is conducive to the rapid recovery of the original shape after external force pulling. Currently, only one study mentions that its monomeric form, tropoelastin, was downregulated under tension force.[23] The pattern of changes in other glycoproteins under orthodontic force remains to be defined.

Changes in ECM-related enzymes under orthodontic force

The degradation of ECM collagen fibre bundles and other protein components occurs mainly through intracellular phagocytosis and extracellular enzymatic degradation. Previous studies have shown that PDL fibroblasts can phagocytose collagen. There are cysteine proteases in their lysosomes, which participate in the degradation of phagocytosed collagen.[1] Svoboda et al[38] demonstrated that the turnover rate of collagen in periodontal tissue was related to the amount of collagen ingested by fibroblasts. Nakamura et al[39] showed that inhibition of autophagy induced collagen accumulation in the cytoplasm and led to a decrease in collagen production by PDLCs. Under healthy and stable PDL conditions, the aforementioned intracellular phagocytosis is conducive to more precise and selective degradation of collagen; however, under force application and inflammation conditions, this pathway appears cumbersome and delayed and is easily influenced by cell states. The release of extracellular collagenolytic enzymes is beneficial for rapid and extensive regulation.[40] Matrix metalloproteinases (MMPs) and their inhibitors, tissue inhibitors of matrix metalloproteinases (TIMPs) and ADAM metallopeptidase with thrombospondin (ADAMTS) are common ECM-related enzymes that all participate in periodontal tissue remodelling processes.

MMPs and TIMPs

MMPs are a family of calcium- and zinc-dependent endopeptidases known to contain 23 types in the human genome. According to the arrangement of their structural domains and substrate preferences, they are divided into six categories: collagenase (MMP-1, 8, 13 and 18), gelatinase (MMP-2 and 9), stromelysins (MMP-3 and 10), matrilysins (MMP-7 and 26), membrane-type MMP (MMP-14, 15, 16, 17, 24 and 25), and other types (MMP-12, 19, 20, 22 and 27).[41] To sustain homeostatic ECM conditions, MMPs are mainly regulated through their expression, zymogen processing activation and the endogenous inhibitor TIMPs. Most studies have focused on the expression changes of MMPs and TIMPs under orthodontic force. Changes in the expression levels of MMPs in previous studies are summarised in Table 2.

MMP-8 is the most abundantly expressed in periodontal tissue and is also one of the main collagenases responsible for collagen I and III degradation. Grimm et al[42] and Nettelhoff et al[43] found that MMP-8 was upregulated in PDLCs under compressive force; however, the results are diverse under tensional force. Ma et al[33] and Saminathan et al[32] found that the expression of the MMP-8 gene was significantly downregulated under tension, whereas Jacobs et al[44] reported the opposite upward trend.

MMP-1 and MMP-2 are common collagenases in periodontal tissue as well. Researchers applied tension to PDLCs for periods ranging from 1 hour to 7 days and found that the expression of MMP-1 was upregulated.[24,26,45,46] Under compression, others found simi-

lar results that the expression of MMP-1 increases in PDLCs.[21,22,47,48] In addition to traditional compression and tension, Zheng et al[49] found that the expression of MMP-1 was significantly upregulated in PDLCs under shear force. Regarding experiments in vivo, Zhang et al[50] and Bildt et al[51] observed that the content of MMP-1 in the gingival crevicular fluid from the compression side and the tension side were both upregulated after orthodontic treatment.

Concerning MMP-2, Bolcato-Bellemin et al[45], Tantilertanant et al[46] and Chen et al[52] found that the expression of MMP-2 in PDLCs was increased under tension, and the results recorded by Lisboa et al[53] showed a downregulation of MMP-2 expression under compression. Zheng et al[49] demonstrated that shear force downregulated MMP-2 in PDLCs in a short period of time and then upregulated MMP-2 after 8 hours. Studies collected gingival crevicular fluid from patients undergoing orthodontic treatment, and the experimental results showed an increase in MMP-2 content, which was consistent with the tension and compression sides.[50,51,54] These studies suggest that under compression, MMP-1 and MMP-8 show an upregulation trend, while MMP-1 and MMP-2 are upregulated under tension. These MMPs increase and jointly participate in the hydrolysis and remodelling of collagen fibres in the PDL.

MMP-9 mainly degrades collagen IV, V, XI and other glycoproteins. Most studies have reported the upregulation of MMP-9 content in gingival crevicular fluid during orthodontic treatment.[50,51,55-57] MMP-3 mainly degrades noncollagenous glycoproteins. Only three studies have reported the relationship between MMP-3 and orthodontic force. Nemoto et al[26] found that MMP-3 expression is downregulated in PDLCs under tension, whereas Tantilertanant et al[46] reported the opposite trend. Under compression, Lisboa et al[48] found that MMP-3 was downregulated. Apart from the mentioned MMPs, a study reported the responses of MMP-10, MMP-11, MMP-14, etc.[41]; however, there are limited data and significant differences.

TIMPs are matrix metalloproteinase inhibitors that can nonspecifically bind to MMPs to inhibit their activity. There are four types of TIMPs (TIMP-1, 2, 3 and 4). Under compression, Redlich et al[21] found that TIMP-1 and TIMP-2 were upregulated; however, Grimm et al[42] and Nettelhoff et al[43] observed that the expression of TIMP-1 decreased instead. Regarding tensional force, most studies have shown that TIMP-1 and TIMP-2 are significantly upregulated at both the mRNA and protein levels in PDLCs.[33,44,45] Bildt et al[51] and Grant et al[55] found that the expression of TIMP-1 and TIMP-2 was significantly upregulated in gingival crevicular fluid regardless of the tension side or the compression side. Jacobs et al[58] also noted a decrease in the expression of TIMP-2 under shear force.

Although there is heterogeneity in the above studies, it is obvious that most types of MMPs and TIMPs showed upregulation trends under orthodontic force and participated in the ECM remodelling of PDL. The process has spatiotemporal differences and is influenced by mechanical force types, involving various collagen and glycoproteins, forming a complex regulatory network. The specific mechanisms still require more detailed and comprehensive experiments and exploration.

Other enzymes

The ADAMTS family is involved in the maturation of collagens and the hydrolysis of ECM. Saminathan et al[32] and Ma et al[33] found that *ADAMTS1* and *ADAMTS8* in PDLCs were upregulated under tension; however, due to the relatively low expression abundance of the ADAMTS family in periodontal tissue, studies in this field are relatively lacking at present. Thant et al[9] observed that mechanical force leads to an increase in the production of other collagen modifying enzymes, such as proline hydroxylase, lysine hydroxylase and transglutaminase, which collectively affect the formation of intermolecular crosslinking and alter tissue structure and mechanical properties.

Changes in ECM adhesion molecules under orthodontic force

The expression changes of ECM-related adhesion molecules can reflect the separation and reattachment that occur during cell rearrangement under mechanical forces. The two processes were kept in a dynamic balanced condition. Integrins are the main adhesion molecules in the PDL and can also serve as mechanical signal receptors, play a mechanical transduction role, mediate various biochemical reactions within cells and promote adaptive changes in cells. Other adhesion molecules include intercellular cell adhesion molecule-1 (ICAM1), osteonectin and tenascin C. There is relatively little research on the changes and functions of various adhesive molecules in the PDL under mechanical force.

Integrins

Integrin is a transmembrane mechanoreceptor that connects ECM components and the intracellular skeleton

Table 2 MMP outcomes from all included studies.

Study	Force type	Methods	Object	Outcome	
				MMP-1	
Bolcato-Bellemin et al[45]	Tension	RT-PCR	hPDLCs	Upregulated significantly (12 h)	
Redlich et al [21]	Compression	RT-PCR	hPDLCs	Upregulated significantly (within 60 min), non-significant (90 min)	
Huang et al[47]	Compression	RT-PCR, ELISA	hPDLCs	Upregulated significantly (30, 60, 90 min)	
Nemoto et al[26]	Tension	RT-PCR, WB	hPDLCs	Upregulated significantly (2–7 d)	
Kook et al[24]	Tension	RT-PCR	hPDLCs	Upregulated significantly (within 12 h)	
Hacopian et al[22]	Compression	RT-PCR	hPDLCs	Upregulated significantly (60 min)	
Saminathan et al[32]	Tension	RT-PCR	hPDLCs	NR	
Zheng et al[49]	Fluid shear stress	RT-PCR, ELISA	hPDLCs	Upregulated significantly (within 12 h)	
Lisboa et al[48]	Compression	ELISA, WB	hPDLCs	Upregulated significantly (30 min)	
Lisboa et al[53]	Compression	Zimography	hPDLCs	NR	
Ma et al[33]	Tension	RT-PCR	hPDLCs	NR	
Nettelhoff et al[43]	Compression	RT-PCR, ELISA	hPDLCs	NR	
Jacobs et al[44]	Tension	RT-PCR, ELISA	hPDLCs	NR	
Tantilertanant et al46	Tension	RT-PCR, ELISA	hPDLCs	Upregulated significantly (6, 24 h)	
Bildt et al51	Compression tension	Zimography, WB	Human GCF	Upregulated significantly (4 wk), upregulated significantly (4 wk)	
Zhang et al50	Compression tension	RT-PCR	Human GCF	Non-significant (within 12 wk), non-significant (within 12 wk)	

Significance compared to unstimulated control.

ELISA, enzyme-linked immunosorbent assay,; GCF, gingival crevicular fluid; NR, not reported; RT-PCR, reverse transcription-polymerase chain reaction; WB, Western blot.

and plays an important role in mechanotransduction and cell migration.[59] Integrin receptors are composed of 18 α subunits and 8 β subunits, forming a total of 24 kinds of αβ heterodimers. According to the types of ECM ligands they bind, integrins can be divided into different subfamilies. The integrins expressed by PDLCs mainly include α1β1, α2β1, α3β1, α4β1, α5β1, α11β1, αvβ3 and αvβ5. Previous studies have explored the changes in the expression patterns of different integrin subunits in periodontitis. It has been demonstrated that changes in cell adhesion and migration mediated by integrins play a crucial role in the formation of the periodontal microenvironment; however, the impact of mechanical force on integrins is still unclear.

Ma et al[33] found that *ITGA5* and *ITGAL* were significantly upregulated in PDLCs after applying tension. Kawamura et al[59] revealed that the expression of ITGA3 and ITGA5 was upregulated in migrated PDLCs and demonstrated the important role of ITGA5 in the migration behaviour of PDLCs. Thus, the upregulation of integrins under mechanical force may indicate an enhanced migration ability of PDLCs. Saminathan et al[32] and Ma et al[33] reported an increase in the expression of ITGA6, ITGB1 and ITGB2 after applying tension. Integrin α6β1 binds to laminin, the downregulation of which may be related to the separation of PDLCs and ECM under mechanical force.

Other adhesion molecules

Osteonectin is a type of calcium binding matrix cell glycoprotein that has anti-adhesion properties and can disrupt cell matrix interactions. Ma et al[33] and Liu et al[60] observed that osteonectin was upregulated in PDLCs after applying cyclic stretch. Ma et al[33] found that tenascin C, which can weaken cell adhesion and upregulate MMP expression and activation, was upregulated in PDLCs under tension. TNC encodes tenascin C, which

	MMP-2	MMP-8	MMP-9	Other MMPs
	Upregulated significantly (12 h)	NR	NR	NR
	NR	NR	NR	NR
	NR	NR	NR	NR
	NR	NR	NR	MMP-3 downregulated significantly (1–7 d)
	NR	NR	NR	NR
	NR	NR	NR	NR
	NR	Downregulated significantly (24 h)	NR	MMP11 downregulated significantly (12 h)
	Upregulated significantly (within 12 h)	NR	NR	NR
	NR	NR	NR	MMP-3 downregulated significantly (30 min), MMP-10 upregulated significantly (30 min)
	Downregulated significantly (30 min)	NR	NR	NR
	NR	Downregulated significantly (6 h)	NR	NR
	NR	Upregulated significantly (12 h)	NR	NR
	NR	Upregulated significantly (12 h)	NR	NR
	Upregulated significantly (6 h)	Non-significant (6, 24 h)	NR	MMP-14 upregulated significantly (6 h)
	Upregulated significantly (4 wk), upregulated significantly (4 wk)	NR	Upregulated significantly (4 wk), non-significant (4 wk)	NR
	Upregulated significantly (12 h–4 k), upregulated significantly (12 h–4 wk)	Non-significant (within 12 wk), non-significant (within 12 wk)	Upregulated significantly (12 h–4 wk), upregulated significantly (12 h–4 wk)	MMP-14 Upregulated significantly (12 h–4 wk), upregulated significantly (12 h–4 wk)

can weaken cell adhesion and upregulate MMP expression and activation. ICAM1 is an intercellular adhesion molecule. Some studies reported that *ICAM1* was upregulated in PDLCs after stretching.[25,32,33] This may be related to the enhanced adhesion between PDLCs under mechanical force. In addition, studies have found changes in the expression of other adhesion-related molecular genes, such as *CTGF*, *CTNND2*, *TGFBI* and *CLEC3B* in PDLCs under mechanical force, but their specific functions and mechanisms still need to be explored.

Conclusion

This article reviewed the effects of mechanical forces on ECM remodelling in the PDL. Exploring the process of PDL remodelling under mechanical force can facilitate understanding of the mechanism of orthodontic tooth movement. By regulating some of these targets, it is able to accelerate tooth movement and avoid periodontal damage caused by excessive inflammatory reactions during orthodontic tooth movement.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

Dr Qian Yao YU contributed to the literatures collection and manuscript draft; Dr Yi Ping HUANG contributed to manuscript revision; Dr Wei Ran LI contributed to the study design. All the authors approved the final manuscript.

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