Advances in the Mechanism of Cartilage Formation Mediated by CD90 (THY-1) through Membrane Lipid Raft Homeostasis

Guojiang Li[1#], Lin Chen[1#], Renfa Lai[12] and Zhiqiang Feng[12*]

[1] School of Stomatology, Jinan University, Guangzhou 510632, China
[2] Hospital of stomatology, the First Affiliated Hospital of Jinan University, Guangzhou 510630, China
*Corresponding author. #Equal contribution.

DOI: https://doi.org/10.56293/IJASR.2025.6304

IJASR 2025
VOLUME 8
ISSUE 1 JANUARY - FEBRUARY **ISSN: 2581-7876**

Abstract: Cartilage regeneration is a key research area in tissue engineering and regenerative medicine, and the unique structure of cartilage poses challenges for its repair. Currently, there is a significant lack of understanding regarding the mechanisms of chondrogenic differentiation, necessitating further exploration. Membrane lipid rafts are dynamic microdomains in the cell membrane, enriched with cholesterol and sphingolipids, serving as critical platforms for signal transduction and participating in protein distribution and regulation of cellular functions. CD90 (THY-1) is a glycoprotein anchored to lipid rafts through glycosylphosphatidylinositol (GPI), widely expressed on the surface of cells such as mesenchymal stem cells (MSCs), and regulates cell adhesion, migration, and differentiation. Recent studies have revealed a synergistic role of lipid raft homeostasis and CD90 in the process of cartilage formation, regulating the repair and regeneration of articular cartilage. This review summarizes the mechanisms by which lipid rafts and CD90 contribute to cartilage formation, with a focus on their core roles in signaling pathway regulation and their effects on chondrogenic differentiation. Furthermore, it highlights their potential applications in cartilage tissue engineering.

Keywords: Lipid rafts, CD90 (THY-1), Cartilage formation, Signal transduction, Tissue engineering

1. Introduction

Cartilage regeneration is a critical research area in tissue engineering and regenerative medicine. Articular cartilage is a specialized connective tissue composed of a dense extracellular matrix (ECM), type II collagen, proteoglycans, and chondrocytes with low cellular density. The avascular and aneural nature of articular cartilage, combined with the low density of chondrocytes, severely limits its regenerative capacity. Cartilage damage and degeneration are the hallmark pathological features of degenerative diseases such as osteoarthritis. (1) Currently, mesenchymal stem cells (MSCs) have become the focal point of cartilage regeneration research due to their self-renewal capacity and multipotent differentiation potential. In recent years, tissue engineering has achieved significant advancements in osteogenesis and chondrogenesis. However, there remains a notable gap in understanding the mechanisms of chondrogenic differentiation within tissue engineering. (2) In particular, the roles of lipid rafts and CD90 (THY-1) as key regulatory factors in signal transduction and cellular differentiation have not been systematically elucidated, necessitating further investigation. This research direction has the potential to deepen our understanding of cartilage formation mechanisms and offer novel strategies for treating degenerative joint diseases. Therefore, this review aims to analyze the potential mechanisms of lipid rafts and CD90 in tissue engineering, explore the regulatory effects of lipid raft homeostasis on intracellular and extracellular signal transduction, systematically summarize their critical roles in cellular differentiation, and reveal their impact on chondrogenic differentiation mechanisms and future research trends.

2. Membrane Lipid Raft Homeostasis

Lipids are not uniformly distributed in the membrane but can aggregate to form specific microdomains known as "lipid rafts." Lipid rafts are dynamic microdomains enriched in cholesterol and sphingolipids, whose unique composition confers a special role in membrane structure and function. (3) Cholesterol (and occasionally other lipids, such as carotenoids) binds tightly with sphingolipids and proteins, forming a relatively stable gel-like state (or

liquid-ordered state) that lies between a disordered liquid and liquid crystal state. These regions are densely packed and have low fluidity. (4) Membrane proteins can be classified into three categories: ① proteins localized within lipid rafts, including glycosylphosphatidylinositol (GPI)-anchored proteins, certain transmembrane proteins, Hedgehog

proteins, and doubly acylated proteins such as non-receptor tyrosine kinase Src, the Gα subunit of G-proteins, and endothelial nitric oxide synthase (NOS); ② proteins present in the disordered liquid phase outside lipid rafts; and (3) intermediate proteins, such as those with low affinity for lipid rafts in the absence of ligands, which migrate to rafts upon ligand binding and oligomerization. Cholesterol in lipid rafts acts like glue, exhibiting high affinity for sphingolipids with saturated fatty acid chains but low affinity for unsaturated fatty acid chains. Removal of cholesterol using methyl-β-cyclodextrin makes detergent-resistant proteins easier to extract. Lipid rafts function as "docking stations" for proteins, providing platforms for protein aggregation, anchoring, and interactions, thereby facilitating signal transmission and information exchange. Among these proteins, one class is anchored to the outer membrane leaflet through a covalent linkage with a specific glycolipid—glycosylphosphatidylinositol (GPI). For example, CD90 is anchored to lipid rafts via GPI. (5, 6) GPI-anchored proteins and other proteins targeted to lipid rafts play crucial roles in signal transduction. Studies have shown that lipid rafts are critical for regulating stem cell self-renewal and pluripotency. Intracellular signaling molecules and extracellular factors (such as bone morphogenetic protein [BMP] and fibroblast growth factor [FGF]) significantly influence the multipotent differentiation potential of cells through interactions with their receptors, processes closely linked to the functions of lipid rafts. (7) Furthermore, sphingolipids in the membrane are primarily localized in the outer leaflet, with most contributing to the formation of lipid rafts. It is estimated that lipid rafts may constitute more than half of the membrane surface area. The size of lipid rafts is adjustable; smaller rafts may play a role in maintaining signal proteins in an inactive state. When required, these small rafts can aggregate to form larger signaling platforms, enabling signal molecules (e.g., receptors) to bind with their partners and initiate signal transduction. For example, allergens can cross-link IgE antibodies and their receptors on the surface of mast cells or basophils in allergic individuals, forming larger lipid rafts. Subsequently, the receptors are phosphorylated by Lyn, a non-receptor tyrosine kinase within the rafts, activating downstream signaling and triggering allergic responses. Research indicates that lipid rafts play a vital role in cellular signal transduction, with their homeostasis maintained by the dynamic balance of membrane cholesterol, sphingolipids, and associated proteins. Disruption of lipid raft homeostasis may significantly impair signal transduction efficiency, thereby interfering with cellular differentiation processes. (8)

The primary functions of membrane lipid rafts include: ① Signal transduction: enhancing signal intensity by promoting receptor clustering and activation. (9) In the Wnt/β-catenin pathway, lipid rafts regulate chondrocyte differentiation and proliferation by enriching related receptors and cofactors. Excessive activation of Wnt signaling may lead to cartilage degeneration. In the TGF-β signaling pathway, the localization of TGF-β receptors within lipid rafts determines signal strength and duration, influencing the synthesis of cartilage matrix components such as type II collagen and chondroitin sulfate. (10) ②Protein sorting: regulating the distribution of transmembrane proteins and GPI-anchored proteins. (11) ③ Cell adhesion and migration: adhesion molecules within lipid rafts facilitate cell and cell-matrix interactions. ④ Extracellular matrix (ECM) regulation: lipid rafts promote interactions between chondrocytes and the ECM through the clustering of integrins and receptor tyrosine kinases, such as FGFR3. Aberrations in lipid rafts may result in the overexpression of matrix-degrading enzymes, such as MMP-13 and ADAMTS-5, accelerating cartilage tissue degradation. ⑤ Antioxidative and anti-inflammatory functions: lipid rafts play a critical role in the signaling of inflammatory factors, such as TNF-α and IL-1β. Disruption of lipid raft homeostasis may exacerbate inflammatory responses, thereby accelerating chondrocyte apoptosis. (12, 13) ⑥ Cartilage aging and degeneration: lipid raft homeostasis plays an important role in the stress responses of chondrocytes, such as mechanical loading. Imbalances in homeostasis may reduce the sensitivity of chondrocytes to mechanical stress, promoting cartilage degeneration. (14) Lipid raft homeostasis influences cartilage formation by regulating critical signaling pathways, such as TGF β/Smad and Wnt/β-catenin, involved in chondrocyte differentiation and joint matrix production. Studies have shown that disrupting the composition of lipid rafts can significantly affect cartilage formation. (15) For example, the recruitment of TGF-β receptors to lipid rafts enhances their interaction with downstream signaling molecules, thereby promoting chondrocyte differentiation. Research has found that lipid raft homeostasis supports the enhancement of cartilage regeneration signals, making it a potential therapeutic target. (16)

3. CD90

CD90, also known as THY-1, is a glycosylated cell membrane protein with a molecular weight of 25-37 kDa, anchored to the outer leaflet of the cell membrane via a glycosylphosphatidylinositol (GPI) moiety at its C-terminus. (17, 18) CD90 was initially identified as a surface antigen on thymocytes, hence the name THY-1. The human CD90 gene, located on chromosome 11, consists of four exons and three introns. Although three transcript variants exist, they all encode the same protein. Studies have shown that CD90 is widely expressed on the surface of various cell types, including periodontal ligament mesenchymal stem cells, hematopoietic stem cells, natural killer cells, neurons, endothelial cells, follicular dendritic cells, fibroblasts, and myofibroblasts. (19, 20) CD90 also plays an important role in differentiation processes, though the mechanisms remain unclear. (21) CD90 is crucial in regulating cell adhesion, migration, and differentiation. CD90 is localized within lipid rafts, where it cooperates with specific receptors, such as TGF-β receptors, to regulate the activity of downstream signaling molecules, such as Fyn and Src kinases. This regulation affects the generation of the extracellular matrix (ECM) and stem cell differentiation. Additionally, CD90 regulates fibroblast apoptosis through Fas-, Bcl-, and caspase-dependent pathways, highlighting its extensive involvement in various cellular behaviors. Under pathological conditions, the loss of CD90 leads to the persistence of pulmonary fibrosis, associated with collagen accumulation and impaired fibrosis resolution. In tumors, high CD90 expression is closely associated with stromal cell-mediated protection of tumor cells from apoptosis and enhanced CXCR4 expression. Its role in regulating the expression of inflammatory factors (e.g., TNF-α and IL-1) and tumor migration makes it an important biomarker and therapeutic target. (22-24) Lipid rafts, as dynamic microdomains, provide an efficient platform for cellular signal transduction. Lipid raft homeostasis has a critical impact on stem cell differentiation and ECM production. Based on this, this article further explores the synergistic roles of lipid rafts and CD90 in cartilage formation and their mechanisms in regulating signal transduction.

4. The Role of Lipid Rafts and Thy-1 in Cartilage Formation

Lipid rafts serve as platforms for CD90 aggregation, facilitating its interaction with other signaling molecules. This spatial organization is critical for regulating signaling pathways involved in stem cell differentiation and extracellular matrix (ECM) remodeling. During cartilage formation, lipid rafts enhance signal specificity and intensity by enriching signaling molecules such as growth factor receptors and integrins, thereby influencing the chondrogenic differentiation efficiency of MSCs. CD90, a glycoprotein anchored to lipid rafts via GPI, provides an efficient platform for signal transduction. CD90 can recruit TGF-β receptors and integrin β1, enhancing the activity of downstream signaling molecules, thereby promoting chondrogenic differentiation of MSCs and ECM production (e.g., collagen and glycosaminoglycans). Additionally, its functions include regulating signal transduction, cell adhesion, and mechanotransduction, all of which depend on the integrity of lipid rafts. (25) CD90 expression plays a critical role in the differentiation of MSCs, with high expression associated with the undifferentiated state of MSCs, while its downregulation promotes chondrogenic differentiation. CD90's interaction with the ECM regulates signaling pathways such as TGF-β and Wnt/β-catenin, driving cartilage formation. (26, 27) TGF-β/BMP pathway: Lipid rafts enhance signaling efficiency by enriching TGF-β receptors and downstream SMAD proteins, promoting chondrocyte differentiation and ECM production (e.g., type II collagen and chondroitin sulfate). CD90 further enhances the chondrogenic potential of MSCs by increasing Smad2/3 activity. (28, 29) Wnt/β-catenin pathway: Lipid rafts regulate Wnt signaling activity, facilitating the chondrogenic differentiation of MSCs. CD90 recruits Wnt receptors via lipid rafts and inhibits excessive β-catenin activation, maintaining signal balance and promoting cartilage formation. (30, 31)

The synergistic interaction between lipid rafts and CD90 significantly enhances the chondrogenic differentiation efficiency of MSCs by regulating key signaling pathways, offering new therapeutic targets for cartilage regeneration.

5. Conclusion

This review focuses on the complex relationship between lipid rafts, cartilage formation, and CD90 (Thy-1), particularly their central roles in signal transduction and cellular differentiation. Lipid rafts provide a signaling platform for CD90, whose interaction with signaling molecules regulates extracellular matrix remodeling and the efficiency of chondrogenic differentiation. Disruption of lipid raft homeostasis weakens CD90-mediated signal transduction, highlighting the functional interdependence between the two. Future research should focus on elucidating the precise mechanisms by which lipid rafts, cholesterol, and signaling molecules regulate the process of

cartilage formation. CD90 is a potential therapeutic target. Optimizing its interaction with lipid rafts or developing targeted drugs and functionalized materials could effectively enhance cartilage tissue regeneration and intervene in the progression of osteoarthritis and related diseases.

6. Clinical Applications and Future Perspectives

The synergistic interaction between lipid rafts and CD90 offers new insights into cartilage regeneration. Lipid rafts play a crucial role in maintaining cartilage function and treating degenerative diseases by regulating signal transduction, matrix metabolism, and inflammatory responses. Drug interventions targeting lipid raft homeostasis may represent a novel strategy for treating osteoarthritis in the future. Developing functionalized biomaterials based on the interaction between CD90 and lipid rafts holds promise for advancing cartilage tissue engineering and clinical translation. Although existing studies have laid the foundation, further exploration is needed to elucidate the specific mechanisms and clinical relevance of lipid rafts and CD90 in regulating cartilage formation and regeneration.

Acknowledgement

Not applicable.

Funding

This study was supported by Science and Technology Projects in Guangzhou (No. 202201020072).

Corresponding authors

Correspondence to Zhiqiang Feng.

References

1. Becerra J, Andrades JA, Guerado E, Zamora-Navas P, López-Puertas JM, Reddi AH. Articular cartilage: structure and regeneration. Tissue Eng Part B Rev. 2010;16(6):617-27.
2. Gugjoo MB, Sharma GT, Aithal HP, Kinjavdekar P. Cartilage tissue engineering: Role of mesenchymal stem cells along with growth factors & scaffolds. Indian J Med Res. 2016;144(3):339-47. 3. Shaw AS. Lipid rafts: now you see them, now you don't. Nature immunology. 2006;7(11):1139-42. 4. Mlinac-Jerkovic K, Ilic K, Zjalić M, others. Who's in, who's out? Re-evaluation of lipid raft residents. Journal of Neurochemistry. 2021.
3. Hu P, Barker TH. Thy-1 in integrin mediated mechanotransduction. Frontiers in cell and developmental biology. 2019; 7:22.
4. Dietrich C, Volovyk ZN, Levi M, others. Partitioning of Thy-1, GM1, and cross-linked phospholipid analogs into lipid rafts reconstituted in supported model membrane monolayers. Proceedings of the National Academy of Sciences. 2001;98(19):10642-7.
5. Dawson G. Isolation of Lipid Rafts (Detergent-Resistant Microdomains) and Comparison to Extracellular Vesicles (Exosomes). Lipid Rafts: Humana, New York, NY; 2021. p. 99-112. 8. Yang J, Zhan XZ, Malola J, others. The multiple roles of Thy-1 in cell differentiation and regeneration. Differentiation. 2020; 113:38-48.
6. Simons K, Ikonen E. Functional rafts in cell membranes. Nature. 1997;387(6633):569-72. 10. Goto H, others. Role of lipid rafts in the regulation of chondrocyte signaling and extracellular matrix production. Matrix Biology. 2020.
7. Brown DA, London E. Structure and function of sphingolipid- and cholesterol-rich membrane rafts. The Journal of Biological Chemistry. 2000;275(23):17221-4.
8. Loeser RF, others. Cholesterol and lipid raft regulation of signaling in osteoarthritis. Arthritis Research & Therapy. 2016.
9. Firth AL, et al. The interplay between lipid rafts, oxidative stress, and chondrocyte apoptosis. Free Radical Biology & Medicine. 2017.
10. Martin JA, Buckwalter JA. Lipid rafts and their role in chondrocyte mechanotransduction and cartilage degeneration. Osteoarthritis and Cartilage. 2019.

11. Cushman DM, others. Lipid rafts orchestrate TGF-β signaling in cartilage regeneration. Biochemical Journal. 2014;461(1):19-28.
12. Zhang L, et al. Lipid rafts modulate growth factor signaling in chondrocyte regeneration. Stem Cell Research & Therapy. 2021.
13. Reif AE, Allen JMV. The AKR thymic antigen and its distribution in leukemias and nervous tissues. Journal of Experimental Medicine. 1964;120(3):413-33.
14. Kumar A, others. Multiple roles of CD90 in cancer. Tumor Biology. 2016;37(9):11611-22. 19. Lin C-S, others. Commonly used mesenchymal stem cell markers and tracking labels: Limitations and challenges. Histology and histopathology. 2013;28(9):1109.
15. Rege TA, Hagood JS. Thy-1 as a regulator of cell-cell and cell-matrix interactions in axon regeneration, apoptosis, adhesion, migration, cancer, and fibrosis. The FASEB journal. 2006;20(8):1045-54. 21. Lu H, others. A breast cancer stem cell niche supported by juxtacrine signalling from monocytes and macrophages. Nature cell biology. 2014;16(11):1105.
16. Lobba ARM, others. Differential expression of CD90 and CD14 stem cell markers in malignant breast cancer cell lines. Cytometry Part A. 2012;81(12):1084-91.
17. Saalbach A, others. Interaction of human Thy-1 (CD 90) with the integrin αvβ3 (CD51/CD61): an important mechanism mediating melanoma cell adhesion to activated endothelium. Oncogene. 2005;24(29):4710.
18. Shi J, others. CD90 highly expressed population harbors a stemness signature and creates an immunosuppressive niche in pancreatic cancer. Cancer letters. 2019; 453:158-69. 25. Stipp CS, others. Thy-1-CAPRI signaling regulates cellular adhesion. The Journal of Cell Biology. 2003;162(3):479-90.
19. Lingwood D, Simons K. Lipid rafts as a membrane-organizing principle. Science. 2010. 27. Simons K, Ikonen E. How cells handle cholesterol. Science. 2000.
20. Zhu H, others. Thy-1 regulates cartilage differentiation through Wnt/β-catenin signaling. Molecular Medicine Reports. 2020;22(5):4002-10.
21. Chen X, others. Thy-1 promotes TGF-β signaling to induce cartilage formation. Stem Cell Research & Therapy. 2017;8(1):243.
22. Chatterjee N, others. Thy-1 promotes ECM synthesis and chondrogenesis in MSCs. Journal of Cell Science. 2010.
23. Barker TH, others. Thy-1 interactions with integrins: Implications for fibrosis and chondrogenesis. Biochemical Society Transactions. 2004.