

VETERİNER HİSTOLOJİ VE EMBRİYOLOJİSİNDE GÜNCEL KONULAR VE AKADEMİK DEĞERLENDİRMELER

Editör: Dr.Öğr.Üyesi Ayşe AYDOĞAN



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yayınları

**Veteriner Histoloji ve Embriyolojisinde
Güncel Konular ve Akademik Değerlendirmeler**

Editör

Dr.Öğr.Üyesi Ayşe AYDOĞAN

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"Bu kitapta yer alan bölümlerde kullanılan kaynakların, görüşlerin, bulguların, sonuçların, tablo, şekil, resim ve her türlü içeriğin sorumluluğu yazar veya yazarlarına ait olup ulusal ve uluslararası telif haklarına konu olabilecek mali ve hukuki sorumluluk da yazarlara aittir."

RENAL ISCHEMIA–REPERFUSION INJURY: CELLULAR AND MOLECULAR MECHANISMS

Meltem KUMAŞ¹

1. INTRODUCTION

Renal ischemia–reperfusion injury (IRI) is a major cause of acute kidney injury (AKI) and occurs in various clinical settings, including kidney transplantation, partial nephrectomy, sepsis, trauma, and hemorrhagic shock (Bonventre & Yang, 2011; Kalogeris et al., 2012). Renal IRI begins with reduced renal blood flow and disruption of cellular energy metabolism. Although restoration of perfusion is essential for tissue survival, reperfusion may paradoxically exacerbate injury through oxidative stress, endothelial dysfunction, inflammation, and cell death (Kumas et al., 2019).

The kidney is particularly susceptible to ischemic injury because of its high metabolic demand. Proximal tubular epithelial cells and cells of the thick ascending limb are especially vulnerable due to their high ATP requirements (Bonventre & Yang, 2011). Reduced oxygen delivery impairs oxidative phosphorylation, leading to ATP depletion, ionic imbalance, and loss of cellular homeostasis. These early metabolic disturbances initiate a cascade of mitochondrial dysfunction, oxidative stress, microvascular impairment, and inflammatory responses that collectively determine the extent of renal injury (Ferenbach & Bonventre, 2015; Sanz et al., 2023).

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Current understanding of renal IRI has evolved beyond the traditional model of ATP depletion and reactive oxygen species generation. Renal injury is now recognized as a dynamic process involving interconnected metabolic, vascular, inflammatory, and regulated cell death pathways (Galluzzi et al., 2018; Sanz et al., 2023; Chen et al., 2024). Recent single-cell and spatial transcriptomic studies have further revealed heterogeneous responses among tubular epithelial cells, endothelial cells, pericytes, and immune cells following ischemic injury (Kirita et al., 2020). These cellular interactions influence not only the severity of acute injury but also the subsequent balance between successful regeneration and maladaptive repair, thereby contributing to the transition from AKI to chronic kidney disease.

This chapter provides an integrated overview of the major mechanisms underlying renal IRI, with emphasis on metabolic and mitochondrial dysfunction, microvascular alterations, inflammatory responses, regulated cell death, and maladaptive tissue repair. Understanding the interactions among these processes may provide a basis for identifying therapeutic strategies aimed at limiting acute injury and promoting effective renal recovery.

2. ISCHEMIC PHASE

The ischemic phase begins with reduced or interrupted renal blood flow, resulting in inadequate oxygen and nutrient delivery (Kumas et al., 2019; Kulualp et al., 2025). Proximal tubular epithelial cells and the thick ascending limb of the loop of Henle are particularly vulnerable because of their high dependence on oxidative phosphorylation. Reduced oxygen availability rapidly suppresses mitochondrial ATP production, while compensatory anaerobic glycolysis is insufficient to meet

cellular energy demands and contributes to lactate accumulation and intracellular acidosis (Bonventre & Yang, 2011; Kalogeris et al., 2012; Sanz et al., 2023).

ATP depletion impairs energy-dependent ion transport, particularly Na^+/K^+ -ATPase and Ca^{2+} -ATPase activity, resulting in ionic imbalance, cellular swelling, and cytosolic calcium overload. Increased intracellular calcium activates proteases, phospholipases, and other degradative enzymes, further contributing to cellular injury (Kumas et al., 2019). At the same time, disruption of the actin cytoskeleton causes loss of epithelial polarity, redistribution of membrane proteins, and impairment of tight junction integrity. These alterations compromise tubular transport and promote detachment of epithelial cells into the tubular lumen (Molitoris & Sutton, 2004; Ferenbach & Bonventre, 2015).

During early ischemia, adaptive responses such as hypoxia-inducible factor signaling, metabolic reprogramming, autophagy, and mitochondrial quality control attempt to preserve cellular homeostasis. However, when ischemia is prolonged, these protective mechanisms become insufficient, and reversible cellular dysfunction progresses to irreversible tubular injury and cell death (Ferenbach & Bonventre, 2015; Sanz et al., 2023; Chen et al., 2024).

3. THE REPERFUSION PHASE

Reperfusion restores renal blood flow and oxygen delivery after ischemia but may paradoxically exacerbate tissue injury. Mitochondria damaged during ischemia cannot immediately restore normal oxidative phosphorylation, and re-exposure to oxygen promotes excessive production of reactive oxygen species (ROS). When ROS generation exceeds antioxidant capacity, oxidative damage to lipids, proteins, and

nucleic acids further compromises cellular function (Murphy, 2009; Sies & Jones, 2020; Sanz et al., 2023).

Reperfusion also aggravates mitochondrial calcium overload, loss of membrane potential, and impaired ATP production, promoting mitochondrial permeability transition and activation of cell death pathways (Hausenloy et al., 2003; Bernardi & Di Lisa, 2015). At the same time, endothelial dysfunction and impaired microvascular perfusion may persist despite restoration of global renal blood flow, contributing to the no-reflow phenomenon and continued tissue hypoxia. Oxidative and cellular injury also promotes the release of damage-associated molecular patterns (DAMPs), initiating sterile inflammatory responses and leukocyte recruitment that further amplify renal injury (Jang & Rabb, 2015; Sanz et al., 2023; Chen et al., 2024).

Thus, reperfusion represents a critical phase in which oxidative stress, mitochondrial dysfunction, microvascular impairment, and inflammation interact to determine the extent of renal injury. The balance between these injurious mechanisms and endogenous protective and repair responses ultimately influences whether damaged tissue undergoes recovery or progresses toward persistent dysfunction (Ferenbach & Bonventre, 2015; Chen et al., 2024).

4. INFLAMMATORY RESPONSE IN RENAL IRI

Inflammation in renal IRI occurs primarily as a sterile response triggered by endogenous danger signals released from injured cells. Damage-associated molecular patterns (DAMPs), including HMGB1, ATP, mitochondrial DNA, histones, and uric acid, activate pattern recognition receptors such as Toll-like receptors and NOD-like receptors, promoting NF- κ B signaling and the production of pro-inflammatory mediators (Tang et al.,

2012; Takeuchi & Akira, 2010). NLRP3 inflammasome activation further amplifies this response through the maturation of IL-1 β and IL-18 (Broz & Dixit, 2016; Swanson et al., 2019).

Leukocyte recruitment further contributes to renal injury following reperfusion. Neutrophils rapidly infiltrate the kidney and aggravate tissue damage through the release of reactive oxygen species and proteolytic enzymes. Monocyte-derived macrophages subsequently regulate both inflammation and tissue repair, exhibiting heterogeneous functional phenotypes shaped by the local microenvironment (Naved et al., 2022).

Persistent inflammatory signaling may impair tissue recovery and contribute to maladaptive repair and chronic renal damage. Thus, sterile inflammation represents an important link between acute ischemic injury and subsequent renal remodeling (Ferenbach & Bonventre, 2015; Sanz et al., 2023).

5. REGULATED CELL DEATH MECHANISMS

Regulated cell death (RCD) encompasses genetically and molecularly controlled pathways that play important roles in tissue homeostasis and disease (Conrad et al., 2016; Galluzzi et al., 2018). In renal IRI, cell death is no longer viewed solely in terms of apoptosis and necrosis; necroptosis, pyroptosis, and ferroptosis also contribute to tubular injury and inflammation. These pathways are closely interconnected and influenced by common cellular stressors, including mitochondrial dysfunction, oxidative stress, calcium imbalance, and inflammatory signaling. Thus, the extent and pattern of cell death following renal IRI reflect the dynamic interaction of multiple RCD pathways rather than the activation of a single mechanism (Galluzzi et al., 2018; Pandian & Kanneganti, 2022; Sanz et al., 2023).

5.1. Apoptosis

Apoptosis is a form of programmed cell death that preserves plasma membrane integrity and involves caspase activation. In IRI, both the extrinsic death receptor pathway and the intrinsic mitochondrial pathway may be activated. Disruption of the Bax/Bcl-2 balance and release of cytochrome c activate caspase-9 and caspase-3, resulting in the controlled removal of tubular epithelial cells (Gobé et al. 2000; Haylor et al. 2011). Although apoptosis is generally considered a non-inflammatory form of cell death, its biological outcome depends on efficient efferocytosis. Clearance of apoptotic cells by macrophages promotes the resolution of inflammation, whereas defective efferocytosis leads to secondary necrosis, additional DAMP release, and persistent sterile inflammation. Apoptosis should therefore be regarded as an integral component of tissue repair rather than simply a mechanism for eliminating damaged cells (Elmore, 2007; Elliott & Ravichandran, 2016; Galluzzi et al., 2018).

5.2. Necroptosis

Necroptosis is a regulated form of lytic cell death mediated by the receptor-interacting protein kinases RIPK1 and RIPK3 and the executioner protein mixed lineage kinase domain-like pseudokinase (MLKL) (Sun et al. 2012; Chen et al. 2022). Following necroptotic signaling, activated RIPK3 phosphorylates MLKL, triggering its oligomerization and translocation to the plasma membrane, where it compromises membrane integrity and ultimately leads to cell rupture. The subsequent release of damage-associated molecular patterns (DAMPs) can further amplify sterile inflammation, thereby linking necroptotic cell death to the inflammatory response characteristic of IRI. Experimental studies have demonstrated activation of the RIPK1–RIPK3–MLKL pathway in ischemic kidneys and have

shown that genetic or pharmacological interference with necroptotic signaling can attenuate tubular injury and preserve renal function. However, necroptosis does not occur as an isolated process; extensive crosstalk with apoptosis and other regulated cell death pathways may influence both the magnitude and outcome of tissue injury. This mechanistic overlap may partly explain why inhibition of a single cell death pathway often provides incomplete protection against IRI (Linkermann & Green, 2014; Vanden Berghe et al., 2014; Jun et al., 2020; Kolbrink et al., 2023).

5.3. Pyroptosis

Pyroptosis is a pro-inflammatory form of regulated cell death that contributes to the amplification of tissue injury in IRI. Activation of the NLRP3 inflammasome promotes caspase-1-mediated cleavage of Gasdermin D, whose N-terminal fragments form pores in the plasma membrane, leading to loss of membrane integrity and the release of IL-1 β and IL-18 (Ma et al. 2024; Zheng et al., 2022). Mitochondrial dysfunction and excessive ROS production can further promote NLRP3 activation, whereas mitophagy may limit pyroptotic signaling by removing damaged mitochondria. Thus, pyroptosis links cellular injury to inflammatory amplification and may contribute to the progression of renal IRI (Yang et al., 2014; Xin et al., 2025; Ding et al., 2025).

5.4. Ferroptosis

Ferroptosis has become a focal point among regulated cell death pathways implicated in IRI, due to its close association with mitochondrial dysfunction, oxidative stress, and metabolic failure. In contrast to apoptosis or necroptosis, ferroptosis is defined by iron-dependent phospholipid peroxidation, which gradually disrupts membrane integrity and ultimately impairs tubular epithelial cell viability (Dixon et al. 2012; Friedmann et al., 2014; Jiang et al., 2021; Chen et al. 2024; Wen et al. 2025).

The ischemic kidney creates a metabolic environment that strongly promotes ferroptotic cell death. Reperfusion restores oxygen to metabolically compromised tubular cells, initiating a cascade of excessive ROS generation, antioxidant depletion, and iron dysregulation. Together, these metabolic disturbances create a permissive environment for ferroptosis, which is now recognized not simply because of oxidative stress but as a central mechanism amplifying tubular injury during IRI (Wen et al. 2025; Hosohata et al. 2022).

In addition to its direct role in tubular cell death, ferroptosis influences several aspects of IRI pathogenesis. Lipid peroxidation products released from ferroptotic cells can intensify sterile inflammation, promote macrophage activation, and worsen endothelial dysfunction, thereby connecting metabolic injury with immune-mediated tissue damage. This evolving understanding has repositioned ferroptosis as an integral component of the broader pathological network that coordinates oxidative stress, inflammation, and maladaptive tissue repair (Chen et al. 2024).

5.5. Panoptosis

PANoptosis is an emerging concept describing coordinated inflammatory cell death driven by molecular crosstalk among pyroptosis, apoptosis, and necroptosis. Rather than representing an independent cell death pathway, it reflects the integrated activation of these mechanisms through shared regulatory complexes and signaling networks. Growing evidence suggests that PANoptotic signaling may contribute to ischemia–reperfusion injury by linking cell death with inflammatory amplification; however, its specific role in renal IRI remains incompletely defined and requires further investigation (Pandian & Kanneganti, 2022; Yan et al. 2023; Chen et al., 2026).

6. MALADAPTIVE REPAIR AND AKI-TO-CKD TRANSITION

Recovery from IRI does not always result in complete restoration of normal tissue architecture. Following severe or persistent injury, adaptive regeneration may shift toward maladaptive repair, characterized by incomplete tubular recovery, persistent inflammation, microvascular rarefaction, fibroblast activation, and extracellular matrix accumulation. This process provides an important mechanistic link between AKI and subsequent progression to CKD (Ferenbach & Bonventre, 2015; Humphreys, 2018; Kellum et al., 2021).

A subset of injured tubular epithelial cells fails to fully redifferentiate and instead acquires a persistent maladaptive phenotype associated with cell-cycle arrest and sustained production of inflammatory and profibrotic mediators. Through interactions with fibroblasts, endothelial cells, and immune cells, these dysfunctional tubular cells contribute to persistent inflammation, capillary loss, and interstitial fibrosis (Duffield, 2014; Kumas et al., 2019). Recent single-cell RNA sequencing studies have further identified failed-repair proximal tubular cells, a distinct population that persists after severe AKI and exhibits sustained inflammatory, profibrotic, and metabolically altered transcriptional programs (Kirita et al., 2020).

Thus, the transition from AKI to CKD reflects not merely incomplete recovery but a coordinated maladaptive repair response involving persistent tubular dysfunction and pathological epithelial–stromal–immune interactions. Targeting these maladaptive cellular states may therefore provide an important strategy for preventing progressive fibrosis and long-term loss of renal function.

7. CONCLUSION

Renal ischemia–reperfusion injury is increasingly understood as a complex and dynamic process involving mitochondrial dysfunction, oxidative stress, endothelial injury, sterile inflammation, and regulated cell death, all operating through interconnected molecular networks rather than as isolated mechanisms. The progression of IRI is influenced by both the severity of the initial insult and the interplay between adaptive regeneration and maladaptive repair, which together determine the transition from acute kidney injury to chronic kidney disease.

Recent advances in single-cell technologies, spatial transcriptomics, and multi-omics approaches have significantly enhanced understanding of the cellular heterogeneity underlying renal injury and repair, thereby creating new opportunities for biomarker discovery and targeted therapeutic development. Future strategies are anticipated to emphasize modulation of shared regulatory pathways, preservation of mitochondrial and microvascular integrity, and promotion of adaptive tissue repair, rather than focusing on individual pathogenic mechanisms. These integrated approaches are expected to improve long-term renal outcomes following ischemic kidney injury.

REFERENCES

- Bernardi, P., & Di Lisa, F. (2015). The mitochondrial permeability transition pore: Molecular nature and role as a target in cardioprotection. *Journal of Molecular and Cellular Cardiology*, 78, 100–106. <https://doi.org/10.1016/j.yjmcc.2014.09.023>
- Bonventre, J. V., & Yang, L. (2011). Cellular pathophysiology of ischemic acute kidney injury. *Journal of Clinical Investigation*, 121(11), 4210–4221. <https://doi.org/10.1172/JCI45161>
- Broz, P., & Dixit, V. M. (2016). Inflammasomes: Mechanism of assembly, regulation and signalling. *Nature Reviews Immunology*, 16(7), 407–420. <https://doi.org/10.1038/nri.2016.58>
- Chen, H., Men, J., Gao, T., Ma, F., & Jia, Z. (2026). PANoptosis nexus in ischemia-reperfusion injury: From integrated cell death mechanisms to novel therapeutic opportunities. *Frontiers in Immunology*, 17, 1804503. <https://doi.org/10.3389/fimmu.2026.1804503>
- Chen, T., Liang, L., Wang, Y., Li, X., & Yang, C. (2024). Ferroptosis and cuproptosis in kidney diseases: Dysfunction of cell metabolism. *Apoptosis*, 29(3–4), 289–302. <https://doi.org/10.1007/s10495-023-01915-x>
- Chen, X., Zhu, R., Zhong, J., Ying, Y., Wang, W., Cao, Y., ... Han, J. (2022). Mosaic composition of RIP1–RIP3 signalling hub and its role in regulating cell death. *Nature Cell Biology*, 24(4), 471–482. <https://doi.org/10.1038/s41556-022-00877-3>
- Conrad, M., Angeli, J. P. F., Vandenabeele, P., & Stockwell, B. R. (2016). Regulated necrosis: Disease relevance and therapeutic opportunities. *Nature Reviews Drug*

- Discovery, 15(5), 348–366.
<https://doi.org/10.1038/nrd.2015.6>
- Ding, T., Zhang, P., Wang, K., Du, P., & Duan, B. (2025). FGF4 alleviates renal injury caused by ischemia-reperfusion (I/R) by inhibiting ferroptosis and pyroptosis. *Peptides*, 192, 171438.
<https://doi.org/10.1016/j.peptides.2025.171438>
- Dixon, S. J., Lemberg, M. K., Lamprecht, M. R., Skouta, R., Zaitsev, E. M., Gleason, C. E., ... Stockwell, B. R. (2012). Ferroptosis: An iron-dependent form of nonapoptotic cell death. *Cell*, 149(5), 1060–1072.
<https://doi.org/10.1016/j.cell.2012.03.042>
- Duffield, J. S. (2014). Cellular and molecular mechanisms in kidney fibrosis. *Journal of Clinical Investigation*, 124(6), 2299–2306. <https://doi.org/10.1172/JCI72267>
- Elliott, M. R., & Ravichandran, K. S. (2016). The dynamics of apoptotic cell clearance. *Developmental Cell*, 38(2), 147–160. <https://doi.org/10.1016/j.devcel.2016.06.029>
- Elmore, S. (2007). Apoptosis: A review of programmed cell death. *Toxicologic Pathology*, 35(4), 495–516.
<https://doi.org/10.1080/01926230701320337>
- Ferenbach, D. A., & Bonventre, J. V. (2015). Mechanisms of maladaptive repair after AKI leading to accelerated kidney ageing and CKD. *Nature Reviews Nephrology*, 11(5), 264–276. <https://doi.org/10.1038/nrneph.2015.3>
- Friedmann Angeli, J. P., Schneider, M., Proneth, B., Tyurina, Y. Y., Tyurin, V. A., Hammond, V. J., ... Conrad, M. (2014). Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. *Nature Cell Biology*, 16(12), 1180–1191. <https://doi.org/10.1038/ncb3064>

- Galluzzi, L., Vitale, I., Aaronson, S. A., Abrams, J. M., Adam, D., Agostinis, P., ... Kroemer, G. (2018). Molecular mechanisms of cell death: Recommendations of the Nomenclature Committee on Cell Death 2018. *Cell Death & Differentiation*, 25(3), 486–541. <https://doi.org/10.1038/s41418-017-0012-4>
- Gobé, G., Zhang, X. J., Willgoss, D. A., Schoch, E., Hogg, N. A., & Endre, Z. H. (2000). Relationship between expression of Bcl-2 genes and growth factors in ischemic acute renal failure in the rat. *Journal of the American Society of Nephrology*, 11(4), 454–467. <https://doi.org/10.1681/ASN.V114454>
- Hausenloy, D. D., Duchon, M. R., & Yellon, D. M. (2003). Inhibiting mitochondrial permeability transition pore opening at reperfusion protects against ischaemia-reperfusion injury. *Cardiovascular Research*, 60(3), 617–625. <https://doi.org/10.1016/j.cardiores.2003.09.025>
- Haylor, J. L., Harris, K. P., Nicholson, M. L., Waller, H. L., Huang, Q., & Yang, B. (2011). Atorvastatin improving renal ischemia reperfusion injury via direct inhibition of active caspase-3 in rats. *Experimental Biology and Medicine*, 236(6), 755–763. <https://doi.org/10.1258/ebm.2011.010350>
- Hosohata, K., Harnsirikarn, T., & Chokesuwattanaskul, S. (2022). Ferroptosis: A potential therapeutic target in acute kidney injury. *International Journal of Molecular Sciences*, 23(12), 6583. <https://doi.org/10.3390/ijms23126583>
- Humphreys, B. D. (2018). Mechanisms of renal fibrosis. *Annual Review of Physiology*, 80, 309–326. <https://doi.org/10.1146/annurev-physiol-022516-034227>

- Jang, H. S., & Rabb, H. (2015). Immune cells in experimental acute kidney injury. *Nature Reviews Nephrology*, 11(2), 88–101.
<https://doi.org/10.1038/nrneph.2014.180>
- Jiang, X., Stockwell, B. R., & Conrad, M. (2021). Ferroptosis: Mechanisms, biology and role in disease. *Nature Reviews Molecular Cell Biology*, 22(4), 266–282.
<https://doi.org/10.1038/s41580-020-00324-8>
- Jun, W., Benjanuwattra, J., Chattipakorn, S. C., & Chattipakorn, N. (2020). Necroptosis in renal ischemia/reperfusion injury: A major mode of cell death? *Archives of Biochemistry and Biophysics*, 689, 108433.
<https://doi.org/10.1016/j.abb.2020.108433>
- Kalogeris, T., Baines, C. P., Krenz, M., & Korthuis, R. J. (2012). Cell biology of ischemia/reperfusion injury. *International Review of Cell and Molecular Biology*, 298, 229–317.
<https://doi.org/10.1016/B978-0-12-394309-5.00006-7>
- Kellum, J. A., Romagnani, P., Ashuntantang, G., Ronco, C., Zarbock, A., & Anders, H. J. (2021). Acute kidney injury. *Nature Reviews Disease Primers*, 7(1), 52.
<https://doi.org/10.1038/s41572-021-00284-z>
- Kirita, Y., Wu, H., Uchimura, K., Wilson, P. C., & Humphreys, B. D. (2020). Cell profiling of mouse acute kidney injury reveals conserved cellular responses to injury. *Proceedings of the National Academy of Sciences*, 117(27), 15874–15883.
<https://doi.org/10.1073/pnas.2005477117>
- Kolbrink, B., von Samson-Himmelstjerna, F. A., Murphy, J. M., & Krautwald, S. (2023). Role of necroptosis in kidney health and disease. *Nature Reviews*

Nephrology,19(5),300–314.

<https://doi.org/10.1038/s41581-022-00658-w>

Kulualp, K., Kulualp, M. K., Semen, Z., Bayram, G. G., Çelik, A., Ak, M. Y., & Yilmaz, O. (2025). Exogenous spexin aggravates renal ischemia reperfusion injury and triggers toxicity in healthy kidneys. *Frontiers of Medicine*, 19(5), 842–854. <https://doi.org/10.1007/s11684-025-1159-x>

Kumaş, M., Eşrefoğlu, M., Karataş, E., Duymaç, N., Kanbay, S., Ergün, I. S., ... Koçyiğit, A. (2019). Investigation of dose-dependent effects of berberine against renal ischemia/reperfusion injury in experimental diabetic rats. *Nefrología*, 39(4), 411–423. <https://doi.org/10.1016/j.nefro.2018.10.006>

Linkermann, A., & Green, D. R. (2014). Necroptosis. *New England Journal of Medicine*, 370(5), 455–465. <https://doi.org/10.1056/NEJMr1310050>

Ma, N., Lu, H., Li, N., Ni, W., Zhang, W., Liu, Q., ... Zhang, T. (2024). CHOP-mediated Gasdermin E expression promotes pyroptosis, inflammation, and mitochondrial damage in renal ischemia-reperfusion injury. *Cell Death & Disease*, 15(2), 151. <https://doi.org/10.1038/s41419-024-06525-9>

Meissner, M., Viehmann, S. F., & Kurts, C. (2019). DAMPening sterile inflammation of the kidney. *Kidney International*, 95(3), 489–491. <https://doi.org/10.1016/j.kint.2018.12.007>

Molitoris, B. A., & Sutton, T. A. (2004). Endothelial injury and dysfunction: Role in the extension phase of acute renal failure. *Kidney International*, 66(2), 496–499. https://doi.org/10.1111/j.1523-1755.2004.761_5.x

- Murphy, M. P. (2009). How mitochondria produce reactive oxygen species. *Biochemical Journal*, 417(1), 1–13. <https://doi.org/10.1042/BJ20081386>
- Naved, B. A., Bonventre, J. V., Hubbell, J. A., Hukriede, N. A., Humphreys, B. D., Kesselman, C., ... Drummond, I. A. (2022). Kidney repair and regeneration: Perspectives of the NIDDK (Re)Building a Kidney consortium. *Kidney International*, 101(5), 845–853. <https://doi.org/10.1016/j.kint.2022.02.023>
- Pandian, N., & Kanneganti, T. D. (2022). PANoptosis: A unique innate immune inflammatory cell death modality. *Journal of Immunology*, 209(9), 1625–1633. <https://doi.org/10.4049/jimmunol.2200508>
- Sanz, A. B., Sanchez-Niño, M. D., Ramos, A. M., & Ortiz, A. (2023). Regulated cell death pathways in kidney disease. *Nature Reviews Nephrology*, 19(5), 281–299. <https://doi.org/10.1038/s41581-023-00694-0>
- Sies, H., & Jones, D. P. (2020). Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. *Nature Reviews Molecular Cell Biology*, 21(7), 363–383. <https://doi.org/10.1038/s41580-020-0230-3>
- Sun, L., Wang, H., Wang, Z., He, S., Chen, S., Liao, D., ... Wang, X. (2012). Mixed lineage kinase domain-like protein mediates necrosis signaling downstream of RIP3 kinase. *Cell*, 148(1–2), 213–227. <https://doi.org/10.1016/j.cell.2011.11.031>
- Swanson, K. V., Deng, M., & Ting, J. P. (2019). The NLRP3 inflammasome: Molecular activation and regulation to therapeutics. *Nature Reviews Immunology*, 19(8), 477–489. <https://doi.org/10.1038/s41577-019-0165-0>

- Takeuchi, O., & Akira, S. (2010). Pattern recognition receptors and inflammation. *Cell*, 140(6), 805–820. <https://doi.org/10.1016/j.cell.2010.01.022>
- Tang, D., Kang, R., Coyne, C. B., Zeh, H. V., & Lotze, M. T. (2012). PAMPs and DAMPs: Signal 0s that spur autophagy and immunity. *Immunological Reviews*, 249(1), 158–175. <https://doi.org/10.1111/j.1600-065X.2012.01146.x>
- Vanden Berghe, T., Linkermann, A., Jouan-Lanhuet, S., Walczak, H., & Vandenabeele, P. (2014). Regulated necrosis: The expanding network of non-apoptotic cell death pathways. *Nature Reviews Molecular Cell Biology*, 15(2), 135–147. <https://doi.org/10.1038/nrm3737>
- Wen, H., Liu, J., Wang, C., Yan, S., Li, Z., Lan, W., ... Ming, S. (2025). Molecular mechanisms of ferroptosis in renal ischemia-reperfusion injury investigated via bioinformatics analysis and animal experiments. *Journal of Investigative Medicine*, 73(1), 134–146. <https://doi.org/10.1177/10815589241288518>
- Xin, L., Kanghao, N., Jiacheng, L., Xiaodong, Y., Juhan, Y., Xinyang, Z., & Xiangdong, L. (2025). Sodium aescinate protects renal ischemia-reperfusion and pyroptosis through AKT/NLRP3 signaling pathway. *Renal Failure*, 47(1), 2488140. <https://doi.org/10.1080/0886022X.2025.2488140>
- Yan, W. T., Zhao, W. J., Hu, X. M., Ban, X. X., Ning, W. Y., Wan, H., ... Zhang, X. (2023). PANoptosis-like cell death in ischemia/reperfusion injury of retinal neurons. *Neural Regeneration Research*, 18(2), 357–363. <https://doi.org/10.4103/1673-5374.346545>

- Yang, J. R., Yao, F. H., Zhang, J. G., Ji, Z. Y., Li, K. L., Zhan, J., ... He, Y. N. (2014). Ischemia-reperfusion induces renal tubule pyroptosis via the CHOP-caspase-11 pathway. *American Journal of Physiology-Renal Physiology*, 306(1), F75–F84.
<https://doi.org/10.1152/ajprenal.00117.2013>
- Zheng, Y., Xu, X., Chi, F., Wang, X., & Wang, Y. (2022). Pyroptosis: A newly discovered therapeutic target for ischemia-reperfusion injury. *Biomolecules*, 12(11), 1625.
<https://doi.org/10.3390/biom12111625>

EMBRYONİK GELİŞİMDE HÜCRE DIŞI MATRİKS VE MEKANOBİYOLOJİ HÜCRESEL FARKLILAŞMADAN ORGANOGENEZE

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1. GİRİŞ

HDM (Hücre Dışı Matris) dokuların hücresel olmayan bileşenidir ve fibriler matris ile bazal membran olmak üzere iki temel histolojik düzende bulunur(Walma & Yamada, 2020). Klasik histoloji HDM'yi morfogenetik hareketleri yalnızca yönlendiren bir yapı olarak tanımlar, güncel bulgular ise embriyonik HDM'nin dinamik olduğunu, morfogenezini yönlendirdiğini ve doku şeklini hücreden bağımsız belirleyebildiğini göstermektedir(Díaz-de-la-Loza & Stramer, 2024). Bu bölüm HDM'nin gelişimdeki yapısal ve mekanik özelliklerini, hücrelerin bunları algılama ve iletilme mekanizmalarını ve bunların farklılaşma ile organogenez üzerindeki etkilerini histoloji ve embriyoloji çerçevesinde ele alan literatüre dayalı bir derlemedir. Kanıt tabanı ağırlıklı olarak fare, civciv, zebra balığı ve *Xenopus* modellerine dayanır, sığır, koyun ve keçi için doğrudan gelişimsel mekanobiyolojik veri tespit edilememiştir.

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2. HDM'NİN YAPISI VE GELİŞİMSEL DEĞİŞİMİ

HDM embriyonik hücreler tarafından en erken evrelerden itibaren sentezlenir ve kollajenler, yapısal glikoproteinler, proteoglikanlar ile elastinler olmak üzere dört sınıfa ayrılır. Farede yürütülen genetik çalışmalar HDM'nin yalnızca yapısal destek sağlamadığını göstermiştir; HDM adezyon, proliferasyon, hücre belirlenmesi, göç, yaşam ve farklılaşmayı düzenler, morfojenlerle etkileşerek göç yolu oluşturur ve morfojen gradyanlarını biçimlendirir. Bazal membran laminin ve tip IV kollajen ağlarından oluşur ve bu ağlar nidogen ile perlekan üzerinden bağlanır(Sekiguchi & Yamada, 2018); kollajen IV kendiliğinden polimerleşir, ancak bu model büyük ölçüde in vitro deneylere dayanır ve sterik engeli hesaba katmaz(Bonche et al., 2022). *Drosophila* yumurta odacıklarında BM sertliğinin esas olarak kollajen IV'e bağlı olduğu gösterilmiştir(Töpfer, Guerra Santillán, Fischer-Friedrich, & Dahmann, 2022). Farede kollajen IV kaybı embriyoların E9.5'e kadar gelişmesine izin verir, letalite E10.5–E11.5 arasında BM'lerdeki yapısal yetersizlikle ortaya çıkar; kollajen IV başlangıç montajı için gerekli değildir, ancak artan mekanik talepler altında BM bütünlüğü için temeldir(Pöschl et al., 2004).

BM'nin kompozisyonu ve mekanik özellikleri gelişim boyunca değişir. Laminin ve tip IV kollajen en kararlı bileşenlerdir ve bildirilen yarı ömürleri yaklaşık 1–10 saat arasındadır, nidogen gibi bazı yapısal proteinler yaklaşık 15–30 dakikalık daha hızlı dönüşüm gösterir(Stramer & Sherwood, 2024). Memelilerde endojen etiketli kollajen IV modelleri hızlı epidermal büyüme dönemlerinde bile BM kollajen IV'ünün son derece kararlı olduğunu göstermiştir(R. A. Jones et al., 2024). BM mekaniği dokuda homojen değildir; *Drosophila* yumurta odacığında BM'de belirgin mekanik anizotropi saptanmış, epitelde saptanmamıştır ve belirleyici olan mutlak sertlik değil

görelî sertliktir(Crest, Diz-Muñoz, Chen, Fletcher, & Bilder, 2017).

Dokuya özgü profiller gelişim boyunca değişir. İnsan derisinde fetal dokunun kollajen tip III/tip I oranı ile glikozaminoglikan düzeyi erişkine göre daha yüksektir ve elastin erişkin dermiste %2–4 oranında bulunur(Coolen, Schouten, Middelkoop, & Ulrich, 2010); insan fetal posterior tibial tendonunda tip III kollajen gelişim boyunca kademeli azalır(Macedo et al., 2022). Akciğerde fertilizasyon sonrası 8–10. haftalar ile 11–14. gestasyonel haftalar arasında dekorin, lumikan ve kollajen tip I, III ve VI bronşiyoler kanalların çevresinde kılıf oluşturur(Godoy-Guzmán, San Martín, & Pereda, 2012) ve kalpte erken evrede hyaluronik asitten zengin kardiyak jel yer alır, farede kalp döngülenmesi E8.5'te gerçekleşir ve trabekül oluşumu E8.0'da başlar(Derrick & Noël, 2021).

3. MEKANOBİYOLOJİNİN TEMEL KAVRAMLARI

Mekanotransdüksiyon hücrelerin HDM'nin elastikiyet, viskozite ve nanotopografi gibi özelliklerini algılayıp biyokimyasal sinyallere dönüştürdüğü süreçtir; embriyonik gelişimde başlıca mekanik uyarılar HDM sertliği, akışkan kayma gerilmesi ve doku gerilmesidir. Doku sertliği organizmada geniş aralıkta değişir; beyin dokusu yaklaşık 0,1–1 kPa ile en yumuşak dokulardandır, çizgili kas yaklaşık 10 kPa, kemik öncüsü osteoid 20–40 kPa düzeyindedir(Zajac & Discher, 2008), doğal dokuların sertliği genel olarak 0,01 kPa ile 100 kPa arasında değişirken kültürde kullanılan plastik yüzeyler gigapaskal düzeyindedir(Kratochvil et al., 2019). Embriyonik dokularda mekanik parametreler tek biçimli değildir; zebra balığı presomitik mezoderminde hücrelerin algıladığı mekanik parametrelerin çoğu farklılaşma sırasında ön-arka eksen boyunca değişir ve bu

gradyanlar morfojenler gibi hücrelere konumsal bilgi sağlayabilir(Mongera et al., 2023).

Hücrelerin sertliği algılamasında adezyon kompleksleri ve aktin-miyozin iskeleti kilit rol oynar; yumuşak substratta aktomiyozin kasılma kuvveti ağırlıklı olarak substratı deforme eder, sert substratta ise adezyon kompleksini deforme ederek proteinlerinde konformasyon değişikliklerine yol açar(Mitrossilis et al., 2009). Substrat sertliği arttıkça (örneğin 3–14 kPa) fare embriyonik fibroblastlarında çeki kuvveti artar ve vinkülinin odak adezyonlardaki lokalizasyonu belirginleşir(Putra, Kilian, & Knothe Tate, 2023). Sertlik hücre kaderinin belirlenmesinde kritik bir etkindir ve insan mezenkimal kök hücreleri yalnızca substrat elastikiyeti değiştirilerek farklı soylara yönlendirilebilir(Muncie & Weaver, 2018). Embriyonik gelişimde mekaniğin rolünün anlaşılmasını, mekanik uyarıların in vivo nicel ölçümünü sağlayan yöntemlerin yokluğu geciktirmiştir(Campàs, 2016).

4. MEKANİK İLETİM YAPILARI

İntegrinler hücre zarını geçen heterodimerik reseptörlerdir ve HDM ligandlarını hücre iskeletine bağlar. Farede $\beta 1$ integrin kuyruğundaki iki sitoplazmik tirozinin (Y783 ve Y795) alanin ile değiştirilmesi $\beta 1$ integrin işlevlerini ortadan kaldırır ve bu mutasyonu taşıyan fareler canlı doğmaz(Chen et al., 2006). İntegrin ile fibronektin etkileşiminin hücre protrüzyonları üzerindeki etkisi *Xenopus* gastrulasyonunda çalışılmıştır; fibronektinin azaltılması konverjan uzamayı ve mediolateral protrüzyon davranışını bloke eder ve integrin $\alpha 5\beta 1$ bağlanması bozulması konverjans hareketlerinin konverjan uzama yerine konverjan kalınlaşma ile sonuçlanmasına yol açar(Davidson, Marsden, Keller, & Desimone, 2006).

Fokal adezyonlar kontraktil aktomiyozin demetlerini plazma zarına bağlar, hücre iskeletinin ürettiği kuvveti HDM'ye iletir ve mikroçevrenin mekanik özelliklerini biyokimyasal sinyallere dönüştürür; olgunlaşmaları miyozin II aracılı iskelet gerilimine bağlıdır ve miyozin II etkinliği FAK/Src aracılı paksillin fosforilasyonunu (Y31 ve Y118) destekler(Pasapera, Schneider, Rericha, Schlaepfer, & Waterman, 2010). Sert substratlarda kültür edilen hücrelerde toplam fokal adezyon sayısı iki kat, 1 μm^2 'den büyük olgun fokal adezyon sayısı dört kat artar(Peng et al., 2019). Durotaksi hücrelerin HDM sertlik gradyanı boyunca yukarı doğru göç etmesidir ve çok hücreli kümeler izole tek hücreler durotaksi göstermese bile durotaksi sergiler(Sunyer et al., 2016). RhoA hücre adezyonu ve iskeletinin kritik düzenleyicisidir, başlıca alt hedefi serin-treonin kinaz ROCK'tur ve ROCK aktomiyozin kontraktil kuvvetini tetikler; meme kanseri hücrelerinde substrat sertliği integrin $\beta 1$ ve FAK'ı doğrudan aktive ederek RhoA/ROCK yolunu tetikler(Jerrell & Parekh, 2016).

YAP ve TAZ Hippo sinyal yolunun temel efektörleridir ve hücrenin fiziksel yapısını, şeklini ve polaritesini algılayan birincil sensörler olarak tanımlanır; etkinlikleri esas olarak hücre içi dağılımları düzeyinde düzenlenir ve nükleusta birikmelerini gerektirir. Epitel hücrelerinde YAP ve TAZ yumuşak HDM üzerinde (tipik olarak 1,5 kPa'nın altında) veya küçük adezyon alanına sahip (300 μm^2) yuvarlak hücrelerde sitoplazmada yerleşir, sert substratlarda (tipik olarak 5 ile 10 kPa üzerinde) veya 3000 μm^2 'yi aşan alana yayılan hücrelerde ise nükleustadır(Totaro, Panciera, & Piccolo, 2018). İki boyutlu kültürde substrat sertliği ile güçlü korelasyon gösteren nükleer lokalizasyon, üç boyutlu ortamlarda sertlik ile artabilir, azalabilir veya değişmeden kalabilir(Scott, Fraley, & Rangamani, 2021). Organ boyutu kontrolünde Hippo kinaz kaskadı YAP/TAZ'ı fosforile ederek inhibe eder ve bu inhibisyon kaynaklanan gen

ifadesi değişiklikleri hücre sayısını, proliferasyonu baskılayarak ve apoptozu teşvik ederek sınırlar(Zhao, Li, Lei, & Guan, 2010). Kuvvetin nükleusa iletilmesi YAP'ın nükleer lokalizasyonu için gereklidir; LINC kompleksi nesprin ile SUN proteinlerinden oluşarak aktin stres liflerini nükleoskelete bağlar(Fischer, Rikeit, Knaus, & Coirault, 2016) ve nesprin baskılanması gerilme sonrası YAP'ın nükleer yeniden yerleşmesini engeller(Kirby & Lammerding, 2018).

PIEZO1 gelişimde en iyi tanımlanmış mekanoduyarlı iyon kanallarındandır; farede gelişen kan damarlarının endotel hücrelerinde ifade edilir ve eksikliği olan embriyolar, kan akışından güçlü biçimde etkilenen damar yeniden şekillenmesindeki kusurlar nedeniyle orta gestasyon döneminde ölür(Ranade et al., 2014). TRPV4 ise iskelet gelişiminde mekanodüzenleyici rol üstlenir; fare embriyo arka bacakları ekz vivo kültürde mekanik olarak uyarıldığında diz kıkırdığı büyümesi ve morfogenezi artar ve yüklenmeye bağlı eklem kıkırdığı gelişimi TRPV4 etkinliğine bağlıdır(N. S. Khatib et al., 2023). Kanaldaki kazanç-işlev mutasyonları iskelet displazilerine yol açar, V620I mutasyonu brakiyolmiye, T89I mutasyonu metatropik displaziye neden olur(Harissa, Kim, Dicks, Steward, & Guilak, 2025).

5. HÜCRESEL DAVRANIŞLAR VE ERKEN GELİŞİM

HDM hücre göçünü hem fiziksel izin vericilik hem sinyal sağlama düzeyinde belirler; yönlü göçte hücreler kemotaksi, haptotaksi ve durotaksi sinyallerini bütünleştirir ve adezyon kinetiği, aktomiyozin kontraktilitesi ile reseptör sinyali arasındaki denge göç hızını ve yönelim kararlılığını belirler(Shellard & Mayor, 2020). HDM'ye bağlı büyüme faktörü gradyanları da rol alır ve *Xenopus* gastrulasyonunda PDGF-A'nın fibronektine

bağlanması yönlü hücre göçü için kritik bulunmuştur(Smith, Mitsi, Nugent, & Symes, 2009). Erken embriyoda mekanik çevre farklılaşmayı yönlendirir ve embriyonik kök hücreler mekanik yüklenme altında pluripotansiyelerini hızla kaybeder(Nelson, 2022). Epitelyal-mezenkimal geçiş gelişimde kardiyak yastıkçık oluşumu, nöral krest göçü ile palatogenez gibi olaylarda görülür ve substrat sertliği ile HDM bileşimi bu süreci tetikleyebilir veya baskılayabilir(Lindsey, Butcher, & Yalcin, 2014); kalpte endokardiyal hücrelerin EMT ile mezenkime dönüşmesi kardiyak jel içindeki hyaluronik asite bağlıdır(Camenisch et al., 2000). Gastrulasyonda fibronektin matrisi sıvı hâldeyken epiboli ve mezoderm göçü gerçekleşebilirken fibriler matris konverjan uzama için gereklidir(Rozario, Dzamba, Weber, Davidson, & DeSimone, 2009) ve Wnt/PCP yolu hücre polaritesini düzenleyerek bu hareketleri etkiler(Roszko, Sawada, & Solnica-Krezel, 2009).

6. ORGANOGENEZDE MEKANOBİYOLOJİ

Kalp gelişiminde matris sertliği belirgin biçimde değişir. Fare kalbinde sertlik 500 Pa'nın altındaki bir mezodermden başlayıp E14'e kadar 10 kPa'ya yükselmekte ve yarılanma süresi yaklaşık 60 saat olarak bildirilmektedir(Young, Kretchmer, Ondeck, Zambon, & Engler, 2014); civciv kalbinde 36. saatten 408. saate kadar yaklaşık 9 kat artış ($0,9 \pm 0,2$ kPa'dan $8,2 \pm 1,3$ kPa'ya) rapor edilmiştir(Young & Engler, 2011). Miyokard sertliği fetal-erişkin geçişte 2–3 kat artış gösterir(Rajendran et al., 2023) ve bu artış kardiyomiyosit olgunlaşmasıyla eş zamanlıdır. 10 kPa sertliğindeki hidrojeller erişkin miyokardı taklit ederek olgun kardiyomiyositlerde ritmik atımı sürdürürken 50 kPa ara sertlik erken mezodermal indükleme aşamasında embriyonik kök hücre farklılaşmasını desteklemektedir(Scuderi & Butcher, 2017). Kardiyak yastıkçık oluşumu endokardiyal hücrelerin EMT

ile mezenkime dönüşmesine dayanır ve hiyaluronan sentaz-2 eksikliği bu süreci bloke eder(Armstrong & Bischoff, 2004).

Akciğer gelişiminde dallanma morfogenezi epitel ile mezenşim arasındaki karşılıklı etkileşime dayanır ve mekanik kuvvetlerin kimyasal sinyalleri geçersiz kılabilirdiği gösterilmiştir(Shao, De Coppi, & Michielin, 2023). Fare akciğerinde düz kas farklılaşmasının manipülasyonu dallanma örüntüsünü değiştirir; düz kasın kaybı ektopik dallanmaya yol açarken düz kasın artışı dallanma başlangıcını ve uzamasını baskılamaktadır(Goodwin et al., 2019). Transmural basınç hava yolu dallanmasını ve gelişimsel olgunlaşma hızını denetler(Nelson et al., 2017) ve Fgf10/Fgfr2b sinyali epitel buruşması ile düz kas farklılaşması gibi fiziksel süreçleri koordine eder(M. R. Jones, Chong, & Bellusi, 2021).

İskelet gelişiminde fetal hareketler iskeleti stres, gerilme ve hidrostatik basınç gibi mekanik biçimlerde etkiler ve yüklenmenin frekansı ile süresi kondral ve kemik gelişimini farklı biçimde etkiler(N. Khatib, Parisi, & Nowlan, 2021). Büyüme plağında uzunlamasına büyüme mekanik yüklenmeye bağlıdır ve proliferatif zondaki kondrosit sayısı ile hipertrofi miktarı mekanik yük ile modüle edilir(Villemure & Stokes, 2009), mekanik yükün kaldırılması kondrosit kolon oluşumunu ve uzuv uzunluğunu etkiler(Serra, 2020). İskelette mekanik sinyalizasyon kemik morfogenetik proteinleri ve hedgehog gibi yollarla kesişir(Ghuloum, Johnson, Riobo-Del Galdo, & Amer, 2022).

7. SENTEZ VE SINIRLILIKLAR

HDM'nin kompozisyonel olgunlaşması ile mekanik olgunlaşması arasında belirgin eşleşme vardır; gelişim ilerledikçe HDM bileşimi kollajen ağırlıklı yapıya kayar, çapraz bağlanma ve mineralizasyon artar ve doku sertliği yükselir. Metodolojik sınırlılıklar bu alanın yorumlanmasında belirleyicidir; in vivo

kuvvet ölçüm yöntemlerinin çoğu yapay sistemler ve kültür hücreleri için geliştirilmiştir ve iki boyutlu kültür bulguları üç boyutlu ortama sınırlı ölçüde genellenebilir. Tür dağılımı belirgin biçimde dengesizdir; organogenez mekanobiyolojisi ağırlıklı olarak fare, civciv, zebra balığı ve *Xenopus* modellerine dayanır, BM mekanik katkı analizleri ise *Drosophila*'da yürütülmüştür. Sığır, koyun ve keçi için gelişimsel mekanobiyolojik kanıt tespit edilememiştir; sığır embriyoları üzerine bulunan mekanik çalışmalar gelişimsel mekanobiyoloji değil yardımcı üreme teknolojileri optimizasyonu kapsamındadır. İn vitro üretimde mekanik mikro-vibrasyon uygulaması (60 dakika aralıklarla 5 saniye, 20, 40 veya 80 Hz) değerlendirilmiş ve 40 Hz grubunda blastosist gelişim oranı kontrol grubuna göre anlamlı biçimde artarken 80 Hz grubunda blastosist hücre sayısı anlamlı olarak azalmıştır(TAKAHASHI et al., 2018). Düşük kaliteli oositlerden elde edilen sığır embriyolarında 15 dakikalık aralıklarla uygulanan vibrasyon(Takehisa, Kondo, Imai, Dochi, & Koyama, 2013), oositlerin 10 dakika santrifüjlenmesinin in vitro gelişim ve kriyotolerans üzerindeki etkisi(Moreski et al., 2025) ile IVF sırasında rocking uygulaması(Serita, Kubota, & Kojima, 2008) da değerlendirilmiştir.

KAYNAKÇA

- Armstrong, E. J., & Bischoff, J. (2004). Heart Valve Development. *Circulation Research*, 95(5), 459–470. <https://doi.org/10.1161/01.res.0000141146.95728.da>
- Bonche, R., Smolen, P., Chessel, A., Boisivon, S., Pisano, S., Voigt, A., ... Pizette, S. (2022). Regulation of the collagen IV network by the basement membrane protein perlecan is crucial for squamous epithelial cell morphogenesis and organ architecture. *Matrix Biology*, 114, 35–66. <https://doi.org/10.1016/j.matbio.2022.10.004>
- Camenisch, T. D., Spicer, A. P., Brehm-Gibson, T., Biesterfeldt, J., Augustine, M. L., Calabro, A., ... McDonald, J. A. (2000). Disruption of hyaluronan synthase-2 abrogates normal cardiac morphogenesis and hyaluronan-mediated transformation of epithelium to mesenchyme. *Journal of Clinical Investigation*, 106(3), 349–360. <https://doi.org/10.1172/jci10272>
- Campàs, O. (2016). A toolbox to explore the mechanics of living embryonic tissues. *Seminars in Cell and Developmental Biology*, 55, 119–130. <https://doi.org/10.1016/j.semcdb.2016.03.011>
- Chen, H., Zou, Z., Sarratt, K. L., Zhou, D., Zhang, M., Sebzda, E., ... Kahn, M. L. (2006). In vivo $\beta 1$ integrin function requires phosphorylation-independent regulation by cytoplasmic tyrosines. *Genes & Development*, 20(8), 927–932. <https://doi.org/10.1101/gad.1408306>
- Coolen, N. A., Schouten, K. C. W. M., Middelkoop, E., & Ulrich, M. M. W. (2009). Comparison between human fetal and adult skin. *Archives of Dermatological Research*, 302(1), 47–55. <https://doi.org/10.1007/s00403-009-0989-8>

- Crest, J., Diz-Muñoz, A., Chen, D.-Y., Fletcher, D. A., & Bilder, D. (2017). Organ sculpting by patterned extracellular matrix stiffness. *eLife*, 6. <https://doi.org/10.7554/elife.24958>
- Davidson, L. A., Marsden, M., Keller, R., & DeSimone, D. W. (2006). *Article Integrin $\alpha 5 \beta 1$ and Fibronectin Regulate Polarized Cell Protrusions Required for Xenopus Convergence and Extension*. Retrieved from [https://www.cell.com/current-biology/pdf/S0960-9822\(06\)01335-2.pdf](https://www.cell.com/current-biology/pdf/S0960-9822(06)01335-2.pdf)
- Derrick, C. J., & Noël, E. S. (2021). The ECM as a driver of heart development and repair. *Development*, 148(5). <https://doi.org/10.1242/dev.191320>
- Díaz-de-la-Loza, M.-C., & Stramer, B. (2023). The extracellular matrix in tissue morphogenesis: No longer a backseat driver. *Cells and Development*, 177, 203883. <https://doi.org/10.1016/j.cdev.2023.203883>
- Fischer, M., Rikeit, P., Knaus, P., & Coirault, C. (2016). YAP-Mediated Mechanotransduction in Skeletal Muscle. *Frontiers in Physiology*, 7, 41. <https://doi.org/10.3389/fphys.2016.00041>
- Ghuloum, F. I., Johnson, C. A., Galdo, N. A. R., & Amer, M. H. (2022). From mesenchymal niches to engineered in vitro model systems: Exploring and exploiting biomechanical regulation of vertebrate hedgehog signalling. *Materials Today Bio*, 17, 100502. <https://doi.org/10.1016/j.mtbio.2022.100502>
- Godoy-Guzmán, C., Martín, S. S., & Pereda, J. (2012). Proteoglycan and collagen expression during human air conducting system development. *European Journal of*

- Histochemistry*, 56(3), 29.
<https://doi.org/10.4081/ejh.2012.e29>
- Goodwin, K., Mao, S., Guyomar, T., Miller, E., Radisky, D. C., Košmrlj, A., & Nelson, C. M. (2019). Smooth muscle differentiation shapes domain branches during mouse lung development. *Development*, 146(22).
<https://doi.org/10.1242/dev.181172>
- Harissa, Z., Kim, Y. S., Dicks, A., Steward, N., & Guilak, F. (2025). Skeletal dysplasia-causing mutations in TRPV4 alter the chondrocyte transcriptomic response to mechanical loading. *American Journal of Physiology-Cell Physiology*, 328(4).
<https://doi.org/10.1152/ajpcell.01066.2024>
- Jerrell, R. J., & Parekh, A. (2016). Matrix rigidity differentially regulates invadopodia activity through ROCK1 and ROCK2. *Biomaterials*, 84, 119–129.
<https://doi.org/10.1016/j.biomaterials.2016.01.028>
- Jones, M. R., Lei, C., & Bellusci, S. (2021). Fgf10/Fgfr2b Signaling Orchestrates the Symphony of Molecular, Cellular, and Physical Processes Required for Harmonious Airway Branching Morphogenesis. *Frontiers in Cell and Developmental Biology*, 8, 620667.
<https://doi.org/10.3389/fcell.2020.620667>
- Jones, R. A., Trejo, B., Sil, P., Little, K. A., Pasolli, H. A., Joyce, B., ... Devenport, D. (2023). An mTurq2-Col4a1 mouse model allows for live visualization of mammalian basement membrane development. *The Journal of Cell Biology*, 223(2). <https://doi.org/10.1083/jcb.202309074>
- Khatib, N., Monsen, J., Ahmed, S., Huang, Y., Hoey, D. A., & Nowlan, N. C. (2023). Mechanoregulatory role of TRPV4

- in prenatal skeletal development. *Science Advances*, 9(4).
<https://doi.org/10.1126/sciadv.ade2155>
- Khatib, N., Parisi, C., & Nowlan, N. C. (2021). Differential effect of frequency and duration of mechanical loading on fetal chick cartilage and bone development. *European Cells and Materials*, 41, 531–545.
<https://doi.org/10.22203/ecm.v041a34>
- Kirby, T. J., & Lammerding, J. (2018). Emerging views of the nucleus as a cellular mechanosensor. *Pure Amsterdam UMC*, 20(4), 373–381. <https://doi.org/10.1038/s41556-018-0038-y>
- Kratochvil, M. J., Seymour, A. J., Li, T. L., Paşca, S. P., Kuo, C. J., & Heilshorn, S. C. (2019). Engineered materials for organoid systems. *Nature Reviews Materials*, 4(9), 606–622. <https://doi.org/10.1038/s41578-019-0129-9>
- Lindsey, S. E. (2014). Mechanical regulation of cardiac development. *Frontiers in Physiology*, 5, 318.
<https://doi.org/10.3389/fphys.2014.00318>
- Macedo, R. S., Teodoro, W. R., Capellozzi, V. L., Rosemberg, D. L., Sposeto, R. B., Netto, C. de C., ... Godoy-Santos, A. L. (2022). Histoarchitecture of the fibrillary matrix of human fetal posterior tibial tendons. *Scientific Reports*, 12(1), 17922. <https://doi.org/10.1038/s41598-022-19695-3>
- Mitrossilis, D., Fouchard, J., Guioy, A., Desprat, N., Rodríguez, N., Fabry, B., & Asnacios, A. (2009). Single-cell response to stiffness exhibits muscle-like behavior. *Proceedings of the National Academy of Sciences*, 106(43), 18243–18248. <https://doi.org/10.1073/pnas.0903994106>
- Mongera, A., Pochitaloff, M., Gustafson, H. J., Stooke-Vaughan, G. A., Rowghanian, P., Kim, S., & Campàs, O. (2022).

- Mechanics of the cellular microenvironment as probed by cells in vivo during zebrafish presomitic mesoderm differentiation. *Nature Materials*, 22(1), 135–143. <https://doi.org/10.1038/s41563-022-01433-9>
- Moreski, D. A. B., Mazucheli, J., Cavalieri, F. L. B., Castilho, A. C. S., Souza, A. K., Costa, C. B., ... Emanuelli, I. P. (2025). Can centrifugation improve cryotolerance of bovine embryos produced in vitro? *Animal Reproduction*, 22(4). <https://doi.org/10.1590/1984-3143-ar2024-0123>
- Muncie, J. M., & Weaver, V. M. (2018). The Physical and Biochemical Properties of the Extracellular Matrix Regulate Cell Fate. *Current Topics in Developmental Biology/Current Topics in Developmental Biology*, 130, 1–37. <https://doi.org/10.1016/bs.ctdb.2018.02.002>
- Nelson, C. M. (2022). Mechanical Control of Cell Differentiation: Insights from the Early Embryo. *Annual Review of Biomedical Engineering*, 24(1), 307–322. <https://doi.org/10.1146/annurev-bioeng-060418-052527>
- Nelson, C. M., Gleghorn, J. P., Pang, M.-F., Jaslove, J. M., Goodwin, K., Varner, V. D., ... Stone, H. A. (2017). Microfluidic chest cavities reveal that transmural pressure controls the rate of lung development. *Development*, 144(23), 4328–4335. <https://doi.org/10.1242/dev.154823>
- Pasapera, A. M., Schneider, I., Rericha, E., Schlaepfer, D. D., & Waterman, C. M. (2010). Myosin II activity regulates vinculin recruitment to focal adhesions through FAK-mediated paxillin phosphorylation. *The Journal of Cell Biology*, 188(6), 877–890. <https://doi.org/10.1083/jcb.200906012>
- Peng, Y., Chen, Z., Chen, Y., Li, S., Jiang, Y., Yang, H., ... Liu, Y. (2019). ROCK isoforms differentially modulate cancer

- cell motility by mechanosensing the substrate stiffness. *Acta Biomaterialia*, 88, 86–101. <https://doi.org/10.1016/j.actbio.2019.02.015>
- Pozzi, A., Yurchenco, P. D., & Iozzo, R. V. (2016). The nature and biology of basement membranes. *Matrix Biology*, 1–11. <https://doi.org/10.1016/j.matbio.2016.12.009>
- Pöschl, E., Schlötzer-Schrehardt, U., Brachvogel, B., Saito, K., Ninomiya, Y., & Mayer, U. (2004). Collagen IV is essential for basement membrane stability but dispensable for initiation of its assembly during early development. *Development*, 131(7), 1619–1628. <https://doi.org/10.1242/dev.01037>
- Putra, V. D. L., Kilian, K., & Tate, M. L. K. (2023). Biomechanical, biophysical and biochemical modulators of cytoskeletal remodelling and emergent stem cell lineage commitment. *Communications Biology*, 6(1), 75. <https://doi.org/10.1038/s42003-022-04320-w>
- Rajendran, A. K., Sankar, D., Amirthalingam, S., Kim, H., Jayakumar, R., & Hwang, N. S. (2023). Trends in mechanobiology guided tissue engineering and tools to study cell-substrate interactions: a brief review. *Biomaterials Research*, 27(1), 55. <https://doi.org/10.1186/s40824-023-00393-8>
- Ranade, S. S., Qiu, Z., Woo, S.-H., Hur, S. S., Murthy, S. E., Cahalan, S. M., ... Patapoutian, A. (2014). Piezo1, a mechanically activated ion channel, is required for vascular development in mice. *Proceedings of the National Academy of Sciences*, 111(28), 10347–10352. <https://doi.org/10.1073/pnas.1409233111>
- Roszko, I., Sawada, A., & Solnica-Krezel, L. (2009). Regulation of convergence and extension movements during

- vertebrate gastrulation by the Wnt/PCP pathway. *Seminars in Cell and Developmental Biology*, 20(8), 986–997. <https://doi.org/10.1016/j.semcdb.2009.09.004>
- Rozario, T., Dzamba, B. J., Weber, G. F., Davidson, L. A., & DeSimone, D. W. (2008). The physical state of fibronectin matrix differentially regulates morphogenetic movements in vivo. *Developmental Biology*, 327(2), 386–398. <https://doi.org/10.1016/j.ydbio.2008.12.025>
- Scott, K. E., Fraley, S. I., & Rangamani, P. (2021). A spatial model of YAP/TAZ signaling reveals how stiffness, dimensionality, and shape contribute to emergent outcomes. *Proceedings of the National Academy of Sciences*, 118(20). <https://doi.org/10.1073/pnas.2021571118>
- Scuderi, G. J., & Butcher, J. T. (2017). Naturally Engineered Maturation of Cardiomyocytes. *Frontiers in Cell and Developmental Biology*, 5, 50. <https://doi.org/10.3389/fcell.2017.00050>
- Sekiguchi, R., & Yamada, K. M. (2018). Basement Membranes in Development and Disease. *Current Topics in Developmental Biology/Current Topics in Developmental Biology*, 130, 143–191. <https://doi.org/10.1016/bs.ctdb.2018.02.005>
- Serita, Y., Kubota, C., & Kojima, T. (2008). 221 EFFECT OF ROCKING ON IN VITRO PRODUCTION OF BOVINE EMBRYOS. *Reproduction Fertility and Development*, 21(1), 209. <https://doi.org/10.1071/rdv21n1ab221>
- Serra, R. (2020). Role of Mechanical Force on the Growth Plate. *The FASEB Journal*, 34, 1. <https://doi.org/10.1096/fasebj.2020.34.s1.02252>

- Shao, Z., Coppi, P. D., & Michielin, F. (2023). Leveraging mechanobiology and biophysical cues in lung organoids for studying lung development and disease. *Frontiers in Chemical Engineering*, 5. <https://doi.org/10.3389/fceng.2023.1255783>
- Shellard, A., & Mayor, R. (2020). All Roads Lead to Directional Cell Migration. *Trends in Cell Biology*, 30(11), 852–868. <https://doi.org/10.1016/j.tcb.2020.08.002>
- Smith, E., Mitsi, M., Nugent, M. A., & Symes, K. (2009). PDGF-A interactions with fibronectin reveal a critical role for heparan sulfate in directed cell migration during *Xenopus* gastrulation. *Proceedings of the National Academy of Sciences*, 106(51), 21683–21688. <https://doi.org/10.1073/pnas.0902510106>
- Stramer, B., & Sherwood, D. R. (2024). Basement membrane dynamics in living animals: Insights and pitfalls. *PubMed*, 223(7). <https://doi.org/10.1083/jcb.202402113>
- Sunyer, R., Conte, V., Escribano, J., Elósegui-Artola, A., Labernadie, A., Valon, L., ... Trepas, X. (2016). Collective cell durotaxis emerges from long-range intercellular force transmission. *Science*, 353(6304), 1157–1161. <https://doi.org/10.1126/science.aaf7119>
- Takahashi, M., HONDA, T., Hatoya, S., Inaba, T., Kawate, N., & Tamada, H. (2018). Efficacy of mechanical micro-vibration in the development of bovine embryos during *in vitro* maturation and culture. *Journal of Veterinary Medical Science*, 80(3), 532–535. <https://doi.org/10.1292/jvms.17-0607>
- Takehisa, M., Kondo, S., Imai, K., Dochi, O., & Koyama, H. (2013). 140 THE EFFECTS OF INTERVALS OF MECHANICAL VIBRATION DURING IN VITRO

CULTURE ON THE DEVELOPMENT OF BOVINE EMBRYO DERIVED FROM LOW-QUALITY OOCYTES. *Reproduction Fertility and Development*, 26(1), 183. <https://doi.org/10.1071/rdv26n1ab140>

Totaro, A., Panciera, T., & Piccolo, S. (2018). YAP/TAZ upstream signals and downstream responses. *Padua Research Archive (University of Padova)*, 20(8), 888–899. <https://doi.org/10.1038/s41556-018-0142-z>

Töpfer, U., Santillán, K. Y. G., Fischer-Friedrich, E., & Dahmann, C. (2022). Distinct contributions of ECM proteins to basement membrane mechanical properties in *Drosophila*. *Development*, 149(10). <https://doi.org/10.1242/dev.200456>

Villemure, I., & Stokes, I. A. F. (2009). Growth plate mechanics and mechanobiology. A survey of present understanding. *Journal of Biomechanics*, 42(12), 1793–1803. <https://doi.org/10.1016/j.jbiomech.2009.05.021>

Walma, D. A. C., & Yamada, K. M. (2020). The extracellular matrix in development. *Development*, 147(10). <https://doi.org/10.1242/dev.175596>

Young, J. L., & Engler, A. J. (2010). Hydrogels with time-dependent material properties enhance cardiomyocyte differentiation in vitro. *Biomaterials*, 32(4), 1002–1009. <https://doi.org/10.1016/j.biomaterials.2010.10.020>

Young, J. L., Kretschmer, K., Ondeck, M. G., Zambon, A. C., & Engler, A. J. (2014). Mechanosensitive Kinases Regulate Stiffness-Induced Cardiomyocyte Maturation. *Scientific Reports*, 4(1), 6425. <https://doi.org/10.1038/srep06425>

Zajac, A. L., & Discher, D. E. (2008). Cell differentiation through tissue elasticity-coupled, myosin-driven remodeling.

Current Opinion in Cell Biology, 20(6), 609–615.
<https://doi.org/10.1016/j.ceb.2008.09.006>

Zhao, B., Li, L., Lei, Q., & Guan, K. (2010). The Hippo–YAP pathway in organ size control and tumorigenesis: an updated version. *Genes & Development*, 24(9), 862–874.
<https://doi.org/10.1101/gad.1909210>

VETERİNER HİSTOLOJİ VE EMBRİYOLOJİSİNDE
GÜNCEL KONULAR VE
AKADEMİK DEĞERLENDİRMELER

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