BÖLÜM 13

Kemik Dokusu

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GİRİŞ

Vücutta iskeletin temelini oluşturan kemik, kalsiyum hidroksiapatit kristalleriyle ileri derecede mineralize ekstraselüler matriksi ve kendine özgü hücreleriyle tümüyle yenilenebilen, özelleşmiş bir bağ dokusudur. Kemik dokusu, organizmada mekanik destek, organları koruma, kalsiyum dengesi ve kan yapımına katkı gibi pek çok yaşamsal işlevi yürütür.

Kemik Dokusunun İşlevleri

Kemik dokusu, insan vücuduna biçim kazandıran ve yük taşıyan iskeletin bir parçası olarak dinamik; hücreler ve ekstraselüler matriksten oluşan, organik ve inorganik maddeleri içeren, sürekli yenilenen bir dokudur. Kemik, vücutta diş minesinden sonraki en sert dokudur. Kemiğin;

- Temel olarak; çevre dokular ile beraber (kas, bağ dokusu ve kıkırdak) *destek* görevi bulunmaktadır.
- Kafatası (beyin), vertebralar (omurilik) , sternum ile kostalar (göğüs boşluğu) gibi önemli iç organları çevreleyerek *koruma* görevi bulunmaktadır.
- Kas dokusu ile birlikte vücudun *hareket*ini sağlamaktadır.
- Kırmızı kemik iliğinde bulunan hücreler ile kan yapımı; *hematopoezi* sağlamaktadır.
- Kalsiyum (Ca^{+2}), magnezyum (Mg^{+2}), bikarbonat (HCO_3^-) ve fosfat (PO_4^{-3}) gibi inorganik *mineral depolanmasına* katkıda bulunmaktadır.
- Sarı kemik iliğindeki yağ hücreleri ile *trigliserid depolanması*na katkıda bulunmaktadır.

Kemiğin Anatomik-Makroskopik Türleri

Erişkinde bulunan olgun kemikler şekilleri, farklı yoğunlukları ve yoğunluk bölgelerine göre sınıflandırılabilmektedir. Buna göre iki kemik türü tanımlanır;

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KAYNAKLAR

Alford, A. I., Kozloff, K. M. ve Hankenson, K. D. (2015). "Extracellular matrix networks in bone remodeling." *International Journal of Biochemistry & Cell Biology*, 65, 20-31.

An, Y. ve L Martin, K. (2003). *Handbook of Histology Methods for Bone and Cartilage*.

Aydin, O., Korkusuz, F., Korkusuz, P., Tezcaner, A., Bilgic, E., Yaprakci, V. ve Keskin, D. (2015). "In vitro and in vivo evaluation of doxycycline-chondroitin sulfate/PCLmicrospheres for intraarticular treatment of osteoarthritis." *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, 103(6), 1238-1248.

Bacon, S. ve Crowley, R. (2018). "Developments in rare bone diseases and mineral disorders." *Ther Adv Chronic Dis*, 9(1), 51-60.

Berna, K., Sevil, K., Petek, K., Muharrem, T. ve Feza, K. (2016). "Mesenchymal Stem Cells and Nano-Bioceramics for Bone Regeneration." *Current Stem Cell Research & Therapy*, 11(6), 487-493.

Bianco, P., Riminucci, M., Gronthos, S. ve Robey, P. G. (2001). "Bone marrow stromal stem cells: nature, biology, and potential applications." *Stem Cells*, 19(3), 180-92.

Bolgen, N., Korkusuz, P., Vargel, I., Kilic, E., Guzel, E., Cavusoglu, T., Uckan, D. ve Piskin, E. (2014). "Stem cell suspension injected HEMA-lactate-dextran cryogels for regeneration of critical sized bone defects." *Artif Cells Nanomed Biotechnol*, 42(1), 70-7.

Coutu, D. L., Wu, J. H., Monette, A., Rivard, G. E., Blostein, M. D. ve Galipeau, J. (2008). "Periostin, a member of a novel family of vitamin K-dependent proteins, is expressed by mesenchymal stromal cells." *J Biol Chem*, 283(26), 17991-8001.

Crockett, J. C., Rogers, M. J., Coxon, F. P., Hocking, L. J. ve Helfrich, M. H. (2011). "Bone remodelling at a glance." *J Cell Sci*, 124(Pt 7), 991-8.

Cui, D., Cui, D. ve Daley, W. (2011). Atlas of Histology: With Functional and Clinical Correlations: Lippincott Williams & Wilkins.

Dallas, S. L., Prideaux, M. ve Bonewald, L. F. (2013). "The osteocyte: an endocrine cell ... and more." *Endocr Rev*, 34(5), 658-90.

Deckers, M. M., van Bezooijen, R. L., van der Horst, G., Hoogendam, J., van Der Bent, C., Papapoulos, S. E. ve Lowik, C. W. (2002). "Bone morphogenetic proteins stimulate angiogenesis through osteoblast-derived vascular endothelial growth factor A." *Endocrinology*, 143(4), 1545-53.

Dogan, E., Dursun, E., Tosun, E., Bilgic, E., Akman, A. C., Orhan, K., Celik, H. H., Korkusuz, P. ve Caglayan, F. (2017). "Evaluation of hyaluronic matrix efficacy in sinus augmentation: a randomized-controlled histomorphometric and micro–computed tomography analysis." *International Journal of Oral and Maxillofacial Surgery*, 46(7), 931-937.

Eghbali-Fatourechi, G. Z., Lamsam, J., Fraser, D., Nagel, D., Riggs, B. L. ve Khosla, S. (2005). "Circulating osteoblast-lineage cells in humans." *N Engl J Med*, 352(19), 1959-66.

Ekin, O., Calis, M., Aliyev, A., Yar, A. S., Korkusuz, P., Bilgic, E., Aydin, H. M., Celik, H. H., Ozgur, F. ve Vargel, I. (2016). "Poly(L-Lactide)/Poly(epsilon-Caprolactone) and Collagen/beta-Tricalcium Phosphate Scaffolds for the Treatment of Critical-Sized Rat Alveolar Defects: A Microtomographic, Molecular-Biological, and Histological Study." *Cleft Palate Craniofac J*, 53(4), 453-63.

Farr, J. N., Xu, M., Weivoda, M. M., Monroe, D. G., Fraser, D. G., Onken, J. L., Negley, B. A., Sfeir, J. G., Ogrodnik, M. B., Hachfeld, C. M., LeBrasseur, N. K., Drake, M. T., Pignolo, R. J., Pirtskhalava, T., Tchkonia, T., Oursler, M. J., Kirkland, J. L. ve Khosla, S. (2017). "Targeting cellular senescence prevents age-related bone loss in mice." *Nat Med*, 23(9), 1072-1079.

Gartner, L. P. ve Hiatt, J. L. (2014). *Color Atlas and Text of Histology*: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Gordon, J. A. R., Stein, J. L., Westendorf, J. J. ve van Wijnen, A. J. (2015). "Chromatin modifiers and histone modifications in bone formation, regeneration, and therapeutic intervention for bone-related disease." *Bone*, 81, 739-745.

Hock, J. M., Krishnan, V., Onyia, J. E., Bidwell, J. P., Milas, J. ve Stanislaus, D. (2001). "Osteoblast apoptosis and bone turnover." *J Bone Miner Res*, 16(6), 975-84.

Hossler, Fred. Ultrastructure Atlas of Human Tissues. John Wiley & Sons, 2014.

Igwe, J. C., Gao, Q., Kizivat, T., Kao, W. W. ve Kalajzic, I. (2011). "Keratocan is expressed by osteoblasts and can modulate osteogenic differentiation." *Connective tissue research*, 52(5), 401-407.

Ishii, M., Egen, J. G., Klauschen, F., Meier-Schellersheim, M., Saeki, Y., Vacher, J., Proia, R. L. ve Germain, R. N. (2009). "Sphingosine-1-phosphate mobilizes osteoclast precursors and regulates bone homeostasis." *Nature*, 458, 524.

Ishii, M., Kikuta, J., Shimazu, Y., Meier-Schellersheim, M. ve Germain, R. N. (2010). "Chemorepulsion by blood S1P regulates osteoclast precursor mobilization and bone remodeling in vivo." *The Journal of Experimental Medicine*, 207(13), 2793-2798.

Kalamajski, S., Aspberg, A., Lindblom, K., Heinegård, D. ve Oldberg, Å. (2009). "Asporin competes with decorin for collagen binding, binds calcium and promotes osteoblast collagen mineralization." *Biochemical Journal*, 423(1), 53-59.

Kankilic, B., Bilgic, E., Korkusuz, P. ve Korkusuz, F. (2014). "Vancomycin containing PLLA/β-TCP controls experimental osteomyelitis in vivo." *Journal of Orthopaedic Surgery and Research*, 9(1), 114.

Karsdal, M. A., Larsen, L., Engsig, M. T., Lou, H., Ferreras, M., Lochter, A., Delaisse, J. M. ve Foged, N. T. (2002). "Matrix metalloproteinase-dependent activation of latent transforming growth factor-beta controls the conversion of osteoblasts into osteocytes by blocking osteoblast apoptosis." *J Biol Chem*, 277(46), 44061-7.

Karsenty, G. (2008). "Transcriptional control of skeletogenesis." *Annu Rev Genomics Hum Genet*, 9, 183-96.

Kierszenbaum A, Tres L. Histology and cell biology. 3rd ed. Philadelphia, PA: Elsevier Saunders; 2012.

Kii, I., Nishiyama, T., Li, M., Matsumoto, K., Saito, M., Amizuka, N. ve Kudo, A. (2010). "Incorporation of tenascin-C into the extracellular matrix by periostin underlies an extracellular meshwork architecture." *J Biol Chem*, 285(3), 2028-39.

Koga, T., Matsui, Y., Asagiri, M., Kodama, T., de Crombrugghe, B., Nakashima, K. ve Takayanagi, H. (2005). "NFAT and Osterix cooperatively regulate bone formation." *Nat Med*, 11(8), 880-5.

Komori, T. (2008). "Regulation of bone development and maintenance by Runx2." *Front Biosci*, 13, 898-903.

Lian, J. B., Stein, G. S., van Wijnen, A. J., Stein, J. L., Hassan, M. Q., Gaur, T. ve Zhang, Y. (2012). "MicroRNA control of bone formation and homeostasis." *Nat Rev Endocrinol*, 8(4), 212-27.

Manduca, P., Castagnino, A., Lombardini, D., Marchisio, S., Soldano, S., Ulivi, V., Zanotti, S., Garbi, C., Ferrari, N. ve Palmieri, D. (2009). "Role of MT1-MMP in the osteogenic differentiation." *Bone*, 44(2), 251-265.

Mansour, A., Mezour, M. A., Badran, Z. ve Tamimi, F. (2017). "Extracellular Matrices for Bone Regeneration: A Literature Review." *Tissue Engineering Part A*, 23(23-24), 1436-1451.

Marie, P. J. ve Cohen-Solal, M. (2018). "The Expanding Life and Functions of Osteogenic Cells: From Simple Bone-Making Cells to Multifunctional Cells and Beyond." *Journal of Bone and Mineral Research*, 33(2), 199-210.

Marsell, R. ve Einhorn, T. A. (2011). "The biology of fracture healing." *Injury*, 42(6), 551-5.

Martino, M. M., Briquez, P. S., Maruyama, K. ve Hubbell, J. A. (2015). "Extracellular matrix-inspired growth factor delivery systems for bone regeneration." *Advanced Drug Delivery Reviews*, 94, 41-52.

Mehmet, Y., Başbuğ, A., Ellibeş Kaya, A., Çağlar, M., Özkara, A., Sungur, M. A. ve Ataoğlu, S. (2017). "Osteoporoz Sıklığı ve Tarama Programı Başlangıç Yaşının Belirlenmesi: Düzce Üniversitesi Araştırma ve Uygulama Hastanesi Örneklemi." *Konuralp Tıp Dergisi*.

Méndez-Ferrer, S., Michurina, T. V., Ferraro, F., Mazloom, A. R., Macarthur, B. D., Lira, S. A., Scadden, D. T., Ma'ayan, A., Enikolopov, G. N. ve Frenette, P. S. (2010). "Mesenchymal and haematopoietic stem cells form a unique bone marrow niche." *Nature*, 466(7308), 829-834.

Mescher, A. (2013). *Junqueira's Basic Histology: Text and Atlas, Thirteenth Edition*: McGraw-Hill Education.

Mizuno, H., Kikuta, J. ve Ishii, M. (2018). "In vivo live imaging of bone cells." *Histochemistry and Cell Biology*, 149(4), 417-422.

Nakashima, T., Hayashi, M., Fukunaga, T., Kurata, K., Oh-Hora, M., Feng, J. Q., Bonewald, L. F., Kodama, T., Wutz, A., Wagner, E. F., Penninger, J. M. ve Takayanagi, H. (2011). "Evidence for osteocyte regulation of bone homeostasis through RANKL expression." *Nat Med*, 17(10), 1231-4.

Ortega, N., Behonick, D. J. ve Werb, Z. (2004). "Matrix remodeling during endochondral ossification." *Trends in Cell Biology*, 14(2), 86-93.

Oryan, A., Monazzah, S. ve Bigham-Sadegh, A. (2015). "Bone injury and fracture healing biology." *Biomed Environ Sci*, 28(1), 57-71.

Ovalle, W. K. ve Nahirney, P. C. (2013). *Netter's Essential Histology E-Book*: Elsevier Health Sciences.

Öztuna, V. (2005). «Osteomiyelit Patofizyolojisi ve Tedavi Prensipleri.» *TOTBID (Türk Ortopedi ve Travmatoloji Birliği Derneği) Dergisi*, 4(1-2), 63-71.

Paic, F., Igwe, J. C., Nori, R., Kronenberg, M. S., Franceschetti, T., Harrington, P., Kuo, L., Shin, D. G., Rowe, D. W., Harris, S. E. ve Kalajzic, I. (2009). "Identification of differentially expressed genes between osteoblasts and osteocytes." *Bone*, 45(4), 682-92.

Paiva, K. B. S. ve Granjeiro, J. M. (2017). "Matrix Metalloproteinases in Bone Resorption, Remodeling, and Repair", in R. A. Khalil, (ed.), *Matrix Metalloproteinases and Tissue Remodeling in Health and Disease: Target Tissues and Therapy*. pp. 203-303.

Rangaswami, H., Bulbule, A. ve Kundu, G. C. (2006). "Osteopontin: role in cell signaling and cancer progression." *Trends in Cell Biology*, 16(2), 79-87.

Ravindran, S. ve George, A. (2014). "Multifunctional ECM proteins in bone and teeth." *Experimental Cell Research*, 325(2), 148-154.

Ross, M. H. (2011). *Histology : a text and atlas with correlated cell and molecular biology*, Philadelphia: Lippincott Williams & Wil.

Runyan, C. M. ve Gabrick, K. S. (2017). "Biology of Bone Formation, Fracture Healing, and Distraction Osteogenesis." *J Craniofac Surg*, 28(5), 1380-1389.

Sacchetti, B., Funari, A., Michienzi, S., Di Cesare, S., Piersanti, S., Saggio, I., Tagliafico, E., Ferrari, S., Robey, P. G., Riminucci, M. ve Bianco, P. (2007). "Self-renewing osteoprogenitors in bone marrow sinusoids can organize a hematopoietic microenvironment." *Cell*, 131(2), 324-36.

Shaker, J. L., Albert, C., Fritz, J. ve Harris, G. (2015). "Recent developments in osteogenesis imperfecta." *F1000Res*, 4(F1000 Faculty Rev), 681.

Sirin, H. T., Vargel, I., Kutsal, T., Korkusuz, P. ve Piskin, E. (2016). "Ti implants with nanostructured and HA-coated surfaces for improved osseointegration." *Artif Cells Nanomed Biotechnol*, 44(3), 1023-30.

Stapleton, M., Sawamoto, K., Almeciga-Diaz, C. J., Mackenzie, W. G., Mason, R. W., Orii, T. ve Tomatsu, S. (2017). "Development of Bone Targeting Drugs." *Int J Mol Sci*, 18(7).

Takahashi, T., Yokogawa, K., Sakura, N., Nomura, M., Kobayashi, S. ve Miyamoto, K. (2008). "Bone-targeting of quinolones conjugated with an acidic oligopeptide." *Pharm Res*, 25(12), 2881-8.

Tekin, U., Ozgul, O., Tüz, H., Korkusuz, P., Kocyigit, I. D., At, l, F., Bilgiç, E. ve Önder, M. E. (2017). "Effect of Locally Administered Alendronate on Onlay Grafts." *Journal of Biomaterials and Tissue Engineering*, 7(8), 650-654.

Vural, A. C., Odabas, S., Korkusuz, P., Yar Saglam, A. S., Bilgic, E., Cavusoglu, T., Piskin, E. ve Vargel, I. (2017). "Cranial bone regeneration via BMP-2 encoding mesenchymal stem cells." *Artif Cells Nanomed Biotechnol*, 45(3), 544-550.

Wagner, E. F. (2002). "Functions of AP1 (Fos/Jun) in bone development." *Ann Rheum Dis*, 61 Suppl 2, ii40-2.

Wang, M., Yang, N. ve Wang, X. (2017). "A review of computational models of bone fracture healing." *Med Biol Eng Comput*, 55(11), 1895-1914.

Worthley, D. L., Churchill, M., Compton, J. T., Tailor, Y., Rao, M., Si, Y., Levin, D., Schwartz, M. G., Uygur, A., Hayakawa, Y., Gross, S., Renz, B. W., Setlik, W., Martinez, A. N., Chen, X., Nizami, S., Lee, H. G., Kang, H. P., Caldwell, J. M., Asfaha, S., Westphalen, C. B., Graham, T., Jin, G., Nagar, K., Wang, H., Kheirbek, M. A., Kolhe, A., Carpenter, J., Glaire, M., Nair, A., Renders, S., Manieri, N., Muthupalani, S., Fox, J. G., Reichert, M., Giraud, A. S., Schwabe, R. F., Pradere, J. P., Walton, K., Prakash, A., Gumucio, D., Rustgi, A. K., Stappenbeck, T. S., Friedman, R. A., Gershon, M. D., Sims, P., Grikscheit, T., Lee, F. Y., Karsenty, G., Mukherjee, S. ve Wang, T. C. (2015). "Gremlin 1 identifies a skeletal stem cell with bone, cartilage, and reticular stromal potential." *Cell*, 160(1-2), 269-84.

Xie, H., Cui, Z., Wang, L., Xia, Z., Hu, Y., Xian, L., Li, C., Xie, L., Crane, J., Wan, M., Zhen, G., Bian, Q., Yu, B., Chang, W., Qiu, T., Pickarski, M., Duong, L. T., Windle, J. J., Luo, X., Liao, E. ve Cao, X. (2014). "PDGF-BB secreted by preosteoclasts induces angiogenesis during coupling with osteogenesis." *Nat Med*, 20(11), 1270-8.

Yue, R., Zhou, B. O., Shimada, I. S., Zhao, Z. ve Morrison, S. J. (2016). "Leptin Receptor Promotes Adipogenesis and Reduces Osteogenesis by Regulating Mesenchymal Stromal Cells in Adult Bone Marrow." *Cell Stem Cell*, 18(6), 782-96.

Zhang, X., Li, Y., Chen, Y. E., Chen, J. ve Ma, P. X. (2016). "Cell-free 3D scaffold with two-stage delivery of miRNA-26a to regenerate critical-sized bone defects." *Nat Commun*, 7, 10376.

Zhou, X., von der Mark, K., Henry, S., Norton, W., Adams, H. ve de Crombrugghe, B. (2014). "Chondrocytes Transdifferentiate into Osteoblasts in Endochondral Bone during Development, Postnatal Growth and Fracture Healing in Mice." *PLOS Genetics*, 10(12), e1004820.