

## Bölüm 5

# BÜYÜME FAKTÖRLERİN KEMİK DOKU ÜZERİNE OLAN REJENERATİF ETKİSİ

Ahmad YAHYAZADEH<sup>1</sup>

## GİRİŞ

Kemik gibi vücut dokularının oluşumu ve onarımının önemli olduğu düşünülmektedir ve buna bağlı olarak, araştırmalarda bunları etkileyen önemli faktörler tespit edilerek çok dikkat çekmiştir. Birçok yaşamsal hücre davranışının belirlenmesinde rol oynayan büyümeye faktörleri, hücrenin etrafındaki biyolojik ortamda çözülen, hücrenin çekirdeğine (nükleus) sinyal gönderen ve böylece hücrenin davranışını kontrol eden aktif biyomoleküllerdir. Doku rejenerasyonunda, büyümeye faktörü hakkında bildiklerimiz, hücre simülasyonunda önemeli yeri olduğunu düşündürmektedir. Bu derlemede, büyümeye faktörlerinin kemik defektlerini iyileştirmede rol oynadığını ve aynı zamanda doku rejenerasyonunda ne kadar önem taşıdığını göstermeye çalıştık.

## KEMİK HİSTOLOJİSİ

Kemik, insan vücudunun iskeletini oluşturan canlı ve sert bir maddedir ve birçok yerde hassas dokuların etrafını çevreleyerek onları korur. Kemikler, beyaz ve kırmızı kan hücrelerinin üretildiği yerlerdir ve minerallerin, özellikle kalsiyumun kaynağını oluştururlar. Kemik dokusu, özelleşmiş bir bağ doku olarak hücreler ve hücre dışı mineralize olmuş matriksten oluşur ve ayrıca, kemik iliği, endosteum, periosteum, kan damarı, sinir ve kıkırdak gibi başka dokuları da bulundurmaktadır (Ross & Pawlina, 2003). Kollajen kemik matrisinin yaklaşık %90'ını oluşturan ana yapısal bileşeni tip I kollajen ve daha az ölçüde tip V kollajenden meydana gelmektedir (Ross & Pawlina, 2003). Matriks ayrıca, osteokalsin, osteonektin ve osteopontin gibi küçük glikoproteinler, glikozaminoglikanlardan ve birkaç sialoprotein formunda maddelerde içerir. Kolajen I merkezi bir çekirdek üzerinde mineral maddelerin biriktirilmesi ve kireçlenmesi sonucunda hidroksiapatit kristallerinin oluşumunu gerçekleştirir (Junqueira & Carneiro, 2009). Kemik dokusu hücreleri üç tiptedir: osteoblast, osteoklast ve osteosit. Osteoblast, çok miktarda

<sup>1</sup> Dr. Öğr. Üyesi, Karabük Tıp Fakültesi, yahyazadeh.ahmad@yahoo.com

Sonuç olarak, son birkaç yılda, BMP, PDGF, TGF, VEGF ve FGF gibi büyüme faktörlerinin etkisi üzerindeki araştırmalar büyük dikkat çekmiştir ve bu araştırmalar BMP, PDGF, TGF- $\beta$ , FGF ve VEGF uygulanmasının kemik doku rejenerasyonunu artırabileceğini gösteren kanıtlar sağlamıştır. Büyüme faktörlerinin kemik dokusunun yenilenmesinde rolünü değerlendirmek için daha fazla çalışmaya ihtiyaç vardır. Ayrıca, farklı büyüme faktör tipleri arasındaki ilişki ve diğer taraftan faktörler ve hücre dışı matris arasındaki ilişki hakkında daha fazla çalışma yapılmalıdır.

## KAYNAKLAR

- Andrew, J., Hoyland, J., Freemont, A. & Marsh, D. (1995). Platelet-derived growth factor expression in normally healing human fractures. *Bone*, 16 (4), 455-460.
- Arvidson, K., Abdallah, B., Applegate, L., Baldini, N., Cenni, E., Gomez-Barrena, E. & Finne-Wistrand, A. (2011). Bone regeneration and stemcells. *Journal of Cellular and Molecular Medicine*, 15 (4), 718–746. Doi: 10.1111/j.1582-4934.2010.01224.x.
- Blázquez-Medela, A. M., Jumabay, M. & Boström, K. I. (2019). Beyond the bone: Bone morphogenetic protein signaling in adipose tissue. *Obesity reviews*. doi: 10.1111/obr.12822.
- Carpenter, G., & Cohen, S. (1990). Epidermal growth factor. *The Journal of Biological Chemistry*, 265 (14), 7709–7712.
- Carreira, A. C., Alves, G. G., Zambuzzi, W. F., Sogayar, M.C. & Granjeiro, J. M. (2014a). Bone morphogenetic proteins: Structure, biological function and therapeutic applications. *Archives of Biochemistry and Biophysics*, 561, 64-73. Doi: 10.1016/j.abb.2014.07.011.
- Carreira, A. C., Zambuzzi, W. F., Rossi, M. C., Astorino Filho, R., Sogayar, M. C. & Granjeiro, J. M. (2015b). Bone Morphogenetic Proteins: Promising Molecules for Bone Healing, Bioengineering, and Regenerative Medicine. *Vitamins and Hormones*, 99, 293-322. Doi: 10.1016/bs.vh.2015.06.002.
- Cartmell, S. (2009). Controlled release scaffolds for bone tissue engineering. *Journal of Pharmaceutical Sciences*, 98 (2), 430-441. Doi: 10.1002/jps.21431.
- Chen, L., Jiang, W., Huang, J., He, BC., Zuo, G. W., Zhang, W., Luo, Q., Shi, Q., Zhang, B. Q., Wagner, E. R., Luo, J., Tang, M., Wietholt, C., Luo, X., Bi, Y., Su, Y., Liu, B., Kim, S. H., He, C. J., Hu, Y., Shen, J., Rastegar, F., Huang, E., Gao, Y., Gao, J. L., Zhou, J. Z., Reid, R. R., Luu, H. H., Haydon, R. C., He, T. C. & Deng, Z. L. (2010). Insulin-like growth factor 2 (IGF-2) potentiates BMP-9-induced osteogenic differentiation and bone formation. *Journal of Bone and Mineral Research*, 25 (11), 2447-2459. Doi: 10.1002/jbm.r.133.
- Cross, M. J., Dixelius, J., Matsumoto, T. & Claesson-Welsh, L. (2003). VEGF-receptor signal transduction. *Trends in Biochemical Sciences*, 28 (9), 488–494.
- Croteau, S., Rauch, F., Silvestri, A. & Hamdy, R. C. (1999). Bone morphogenetic proteins in orthopedics: from basic science to clinical practice. *Orthopedics*, 22 (7), 686-695.
- Dreyer, C. H., Kjaergaard, K., Ditzel, N., Jørgensen, N. R., Overgaard, S. & Ding, M. (2017). Optimizing combination of vascular endothelial growth factor and mesenchymal stem cells on ectopic bone formation in SCID mice. *Journal of Biomedical Materials Research*, 105 (12), 3326-3332. Doi: 10.1002/jbm.a.36195.

- Derynck, R., Zhang, Y. & Feng, X. H. (1998a). Smads: transcriptional activators of TGF-beta responses. *Cell*, 95 (6), 737-740.
- Derynck, R., & Akhurst, R. J. (2007b). Differentiation plasticity regulated by TGF-beta family proteins in development and disease. *Nature cell biology*, 9 (9), 1000–1004.
- Elias, W. Y. (2016). Assessment of the osteogenic potential of morphogenic protein-2 and insulin-like growth factor-I on adipose tissue-derived stem cells. *Journal of Biomedical Sciences*, 5 (1), 1–6. Doi:10.4172/2254-609X.100015.
- Ferrara, N., Gerber, H. P. & LeCouter, J. (2003). The biology of VEGF and its receptors. *Nature Medicine*, 9 (6), 669–676.
- Fredriksson, L., Li, H. & Eriksson, U. (2004). The PDGF family: four gene products form five dimeric isoforms. *Cytokine & Growth Factor Reviews*, 15 (4), 197–204.
- Geiser, A. G., Hummel, C. W., Draper, M. W., Henck, J. W., Cohen, I. R., Rudmann, D. G., Donnelly, K. B., Adrian, M. D., Shepherd, T. A., Wallace, O. B., McCann, D. J., Oldham, S. W., Bryant, H. U., Sato, M. & Dodge, J. A. (2005). A new selective estrogen receptor modulator with potent uterine antagonist activity, agonist activity in bone, and minimal ovarian stimulation. *Endocrinology*, 146 (10), 4524-4535.
- Gemini-Piperni, S., Takamori, E. R., Sartoretto, S. C., Paiva, K. B., Granjeiro, J. M., de Oliveira, R. C. & Zambuzzi, W. F. (2014). Cellular behavior as a dynamic field for exploring bone bioengineering: A closer look at cell-biomaterial interface. *Archives of Biochemistry and Biophysics*, 561, 88-98. Doi: 10.1016/j.abb.2014.06.019.
- Gerber, H. P., Vu, T. H., Ryan, A. M., Kowalski, J., Werb, Z. & Ferrara, N. (1999). VEGF couples hypertrophic cartilage remodeling, ossification and angiogenesis during endochondral bone formation. *Nature Medicine*, 5 (6), 623-628.
- Goetz, R. & Mohammadi, M. (2013). Exploring mechanisms of FGF signalling through the lens of structural biology. *Nature reviews. Molecular cell biology*, 14 (3), 166-180. Doi: 10.1038/nrm3528.
- Granjeiro, J. M., Oliveira, R. C., Bustos-Valenzuela, J. C., Sogayar, M. & Taga, C. R. (2005). Bone morphogenetic proteins: From structure to clinical use. *Brazilian Journal of Medical and Biological Research*, 38 (10), 1463-1473.
- Groeneveld, E. H. & Burger, E. H. (2000). Bone morphogenetic proteins in human bone regeneration. *European Journal of Endocrinology*, 142 (1), 9- 21.
- Guo, Y., Tang, C. Y., Man, X. F., Tang, H. N., Tang, J., Zhou, C. L., Tan, S. W., Wang, M., Feng, Y. Z. & Zhou, H. D. (2017). Insulin-like growth factor-1 promotes osteogenic differentiation and collagen I alpha 2 synthesis via induction of mRNA-binding protein LARP6 expression. *Development, Growth & Differentiation*, 59 (2), 94-103. Doi: 10.1111/dgd.12342.
- Han, B., Perelman, N., Tang, B., Hall, F., Shors, E.C. & Nimni, M. E. (2006). Collagen, targeted BMP3 fusion proteins arrayed on collagen matrices or porous ceramics impregnated with Type I collagen enhance osteogenesis in a rat cranial defect model. *Journal of Dental Research*, 20 (4), 747-757.
- Hoeben, A., Landuyt, B., Highley, M. S., Wildiers, H., Van Oosterom, A. T. & De Bruijn, E. A. (2004). Vascular endothelial growth factor and angiogenesis. *Pharmacological Reviews*, 56 (4), 549–580.
- Howell, T. H., Fiorellini, J. P., Paquette, D. W., Offenbacher, S., Giannobile, W. V. & Lynch, S. E. (1997). A phase I/II clinical trial to evaluate a combination of recombinant human plateletderived growth factor-BB and recombinant human insulin-like growth factor-I in patients with periodontal disease. *Journal of periodontology*, 68 (12), 1186-1193.

- Ito, Y. (2008). Covalently immobilized biosignal molecule materials for tis-sue engineering. *Soft Matter*, 4 (1), 46–56. DOI: 10.1039/b708359a.
- Itoh, N. & Ornitz, D. M. (2008). Functional evolutionary history of the mouse Fgf gene family. *Developmental Dynamics*, 237 (1), 18–27. DOI: 10.1002/dvdy.21388.
- Jehle, P. M., Schulten, K., Schulz, W., Jehle, D. R., Stracke, S., Manfras, B., Boehm, B. O., Baylink, D. J. & Mohan, S. (2003). Serum levels of insulin-like growth factor (IGF)-I and IGF binding protein (IGFBP)-1 to-6 and their relationship to bone metabolism in osteoporosis patients. *European Journal of Internal Medicine*, 14 (1), 32-38.
- Thaller, S. R., Dart, A. & Tesluk, H. (1993). The effects of insulin-like growth factor-1 on critical-size calvarial defects in SpragueDawley rats. *Annals of Plastic Surgery*, 31 (5), 429-433.
- Junqueira L. C. & Carneiro, J. (2009). Temel histoloji. (Seyhun Solakoqlu, S., & Aytekin, YÇev, Ed.). İstanbul: Nobel Tip Kitabevleri.
- Kaigler, D., Wang, Z., Horger, K., Mooney, D. J. & Krebsbach, PH. (2006). VEGF scaffolds enhance angiogenesis and bone regeneration in irradiated osseous defects. *Journal of Bone and Mineral Research*, 21 (5), 735-744.
- Kalinichenko, S. G., Matveeva, N. Y., Kostiv, R. E. & Puz', A. V. (2017). Role of Vascular Endothelial Growth Factor and Transforming Growth Factor- $\beta$ 2 in Rat Bone Tissue after Bone Fracture and Placement of Titanium Implants with Bioactive Bioreversible Coatings. *Bulletin of Experimental Biology and Medicine*, 162 (5), 671-675. DOI: 10.1007/s10517-017-3684-3.
- Kawai, M. & Rosen, C. J. (2012). The insulin-like growth factor system in bone: basic and clinical implications. *Endocrinology and Metabolism Clinics of North America*, 41 (2), 323-33. DOI: 10.1016/j.ecl.2012.04.013.
- Kempen, D. H., Lu, L., Heijink, A., Hefferan, T. E., Creemers, L. B., Maran, A., Yaszemski, M. J. & Dhert, W. J. (2009). Effect of local sequential VEGF and BMP-2 delivery on ectopic and orthotopic bone regeneration. *Biomaterials*, 30 (14), 2816-2825. DOI: 10.1016/j.biomaterials.2009.01.031.
- Khan, S. N., Bostrom, M., Lane & J. M. (2000). Bone growth factors. *The Orthopedic clinics of North America*, 31 (3):375-388.
- Kim, K., Lee, C. H., Kim, B. K. & Mao, J. J. (2010). Anatomically shaped tooth and periodontal regeneration by cell homing. *Journal of Dental Research*, 89 (8), 842-847. DOI: 10.1177/0022034510370803.
- Kimura, T., Kuwata, T., Ashimine, S., Yamazaki, M., Yamauchi, C., Nagai, K. & Occhiali, A. (2010). Targeting of bone-derived insulin-like growthfactor-II by a human neutralizing antibody suppresses the growth of prostate cancer cells in a human bone environment. *Clinical Cancer Research*, 16 (1), 121–129. DOI: 10.1158/1078-0432.CCR-09-0982.
- Kronenberg, H. M. (2003). Developmental regulation of the growth plate. *Nature*, 423 (6937), 332-336.
- Lind, M., Schumacker, B., Søballe, K., Keller, J., Melsen, F. & Bünger, C. (1993). Transforming growth factor- $\beta$  enhances fracture healing in rabbit tibiae. *Acta Orthopaedica Scandinavica*, 64 (5), 553-556.
- Lisignoli, G., Fini, M., Giavaresi, G., Nicoli Aldini, N., Toneguzzi, S. & Facchini, A. (2002). Osteogenesis of large segmental radius defects enhanced by basic fibroblast growth factor activated bone marrow stromal cells grown on non-woven hyaluronic acid-based polymer scaffold. *Biomaterials*, 23 (4), 1043-1051.
- Liu, H., Su, H., Wang, X. & Hao, W. (2018). MiR-148a regulates bone marrow mesen-

- chymal stem cells-mediated fracture healing by targeting insulin-like growth factor 1. *Journal of Cellular Biochemistry*. Doi: 10.1002/jcb.27121.
- Maes, C., Kobayashi, T., Selig, M. K., Torrekens, S., Roth, S. I., Mackem, S., Carmeliet, G. & Kronenberg, H. M. (2010). Osteoblast Precursors, but Not Mature Osteoblasts, Move into Developing and Fractured Bones along with Invading Blood Vessels. *Developmental Cell*, 19 (2), 329–344. Doi: 10.1016/j.devcel.2010.07.010.
- Manzat Saplakan, R. M., Balacescu, L., Gherman, C., Chira, R. I., Craiu, A., Mircea, P.A., Lisencu, C. & Balacescu, O. (2017). The role of PDGFs and PDGFRs in colorectal cancer. *Mediators of Inflammation*, 2017, 4708076. Doi: 10.1155/2017/4708076.
- Mason, J. C., Lidington, E. A., Ahmad, S. R. & Haskard, D. O. (2002). bFGF and VEGF synergistically enhance endothelial cytoprotection via decay-accelerating factor induction. *American Journal of Physiology*, 282 (3), dC578-587.
- Moerth, C., Schneider, M. R., Renner-Mueller, I., Blutke, A., Elmlinger, M. W., Erben, R. G., Camacho-Hübler, C., Hoeflich, A. & Wolf, E. (2007). Postnatally elevated levels of insulin-like growth factor (IGF)-II fail to rescue the dwarfism of IGF-I-deficient mice except kidney weight. *Endocrinology*, 148 (1), 441-51.
- Nakamura, T., Hara, Y., Tagawa, M., Tamura, M., Yuge, T., Fukuda, H. & Nigi, H. (1998). Recombinant human basic fibroblast growth factor accelerates fracture healing by enhancing callus remodeling in experimental dog tibial fracture. *Journal of Bone and Mineral Research*, 13, 942-949.
- Nash, T., Howlett, C., Martin, C., Steele, J., Johnson, K. & Hicklin, D. (1994). Effect of platelet-derived growth factor on tibial osteotomies in rabbits. *Bone*, 15 (2), 203-208.
- Neufeld, G., Cohen, T., Gengrinovitch, S. & Poltorak, Z. (1999). Vascular endothelial growth factor (VEGF) and its receptors. *FASEB Journal*, 13 (1), 9-22.
- Ornitz, D. M., Xu, J., Colvin, J. S., McEwen, D. G., MacArthur, C. A., Coulier, F., Gao, G. & Goldfarb, M. (1996). Receptor specificity of the fibroblast growth factor family. *The Journal of Biological Chemistry*, 271 (25), 15292–15297.
- Papanas, D. & Maltezos, E. (2010). Benefit-risk assessment of becaplermin in the treatment of diabetic foot ulcers. *Drug Safety*, 33 (6), 455–461. Doi: 10.2165/11534570-000000000-00000.
- Peng, H., Wright, V., Usas, A., Gearhart, B., Shen, H. C., Cummins, J. & Huard, J. (2002a). Synergistic enhancement of bone formation and healing by stem cell-expressed VEGF and bone morphogenetic protein-4. *The Journal of Clinical Investigation*, 110 (6):751-759.
- Peng, H., Usas, A., Olshanski, A., Ho, A. M., Gearhart, B., Cooper, G. M. & Huard, J. (2005b). VEGF improves, whereas sFlt1 inhibits, BMP2-induced bone formation and bone healing through modulation of angiogenesis. *Journal of Bone and Mineral Research*, 20 (11), 2017-2027.
- Power, R., Iwaniec, U. & Wronski, T. (2002). Changes in gene expression associated with the bone anabolic effects of basic fibroblast growth factor in aged ovariectomized rats. *Bone*, 31 (1), 143-148.
- Ingber, D. E. & Folkman, J. (1989). Mechanochemical switching between growth and differentiation during fibroblast growth factor-stimulated angiogenesis in vitro: role of extracellular matrix. *The Journal of Cell Biology*, 109 (1), 317-330.
- Ramoshebi, L. N., Matsaba, T. N., Teare, J., Renton, L., Patton, J. & Ripamonti, U. (2002). Tissue engineering: TGF-beta superfamily members and delivery systems in bone regeneration. *Expert Reviews in Molecular Medicine*, 4 (20), 1-11.
- Ripamonti, U. & Duneas, N. (1998). Tissue morphogenesis and regeneration by bone

- morphogenetic proteins. *Plastic and Reconstructive Surgery*, 101 (1), 227-239.
- Ripamonti, U., Duneas, N., Van Den Heever, B., Bosch, C. & Crooks, J. (1997a). Recombinant Transforming Growth Factor, $\beta$ 1 Induces Endochondral Bone in the Baboon and Synergizes with Recombinant Osteogenic Protein,1 (Bone Morphogenetic Protein,7) to Initiate Rapid Bone Formation. *Journal of Bone and Mineral Research*, 12 (10), 1584-1595.
- Ripamonti, U., Ferretti, C., Teare, J. & Blann, L. (2009b). Transforming growth factor-beta isoforms and the induction of bone formation: implications for reconstructive craniofacial surgery. *The Journal of Craniofacial Surgery*, 20 (5), 1544-1555. Doi: 10.1097/SCS.0b013e3181b09ca6.
- Ross M. H. & Pawlina W. (2003). Bone. Wolters Kluwer (Fourth edit), Histology: A Text and Atlas, with Correlated Cell and Molecular Biology (180-201). Philadelphia: Lippincott Williams & Wilkins Health.
- Schmid, G. J., Kobayashi, C., Sandell, L. J. & Ornitz, D. M. (2009). Fibroblast growth factor expression during skeletal fracture healing in mice. *Developmental Dynamics*, 238 (3), 766-774. Doi: 10.1002/dvdy.21882.
- Sheng, M. H., Lau, K. H. & Baylink, D. J. (2014). Role of Osteocyte-derived Insulin-Like Growth Factor I in Developmental Growth, Modeling, Remodeling, and Regeneration of the Bone. *Journal of Bone Metabolism*, 21 (1), 41-54. Doi: 10.11005/jbm.2014.21.1.41.
- Simpson, A. H., Mills, L. & Noble, B. (2006). The role of growth factors and related agents in accelerating fracture healing. *The Journal of Bone and Joint Surgery*, 88 (6), 701-705.
- Sinclair, K. L., Mafi, P., Mafi, R. & Khan, W. S. (2017). The Use of Growth Factors and Mesenchymal Stem Cells in Orthopaedics: In particular, their use in Fractures and Non-Unions: A Systematic Review. *Current Stem Cell Research and Therapy*, 12 (4), 312-325. Doi: 10.2174/1574888X11666160614104500.
- Srouji, S., Rachmiel, A., Blumenfeld, I. & Livne, E. (2005). Mandibular defect repair by TGF-beta and IGF-1 released from a biodegradable osteoconductive hydrogel. *Journal of Cranio-Maxillo-facial Surgery*, 33 (2):79-84.
- Steinbrech, D. S., Mehrara, B. J., Rowe, N. M., Dudziak, M. E., Saadeh, P. B., Gittes, G. K. & Longaker, M. T. (1999). Gene expression of insulin-like growth factors I and II in rat membranous osteotomy healing. *Annals of plastic surgery*, 42 (5), 481-487.
- Tada, S., Kitajima, T. & Ito, Y. (2012). Design and synthesis of binding growthfactors. *International Journal of Molecular Sciences*, 13 (5), 6053–6072. doi: 10.3390/ijms13056053.
- Tallquist, M. & Kazlauskas, A. (2004). PDGF signaling in cells and mice. *Cytokine & Growth Factor Reviews*, 15 (4), 205–213.
- Mulloy, B. & Rider C. C. (2015). The Bone Morphogenetic Proteins and Their Antagonists. *Vitamins and Hormones*, 99, 63-90. Doi: 10.1016/bs.vh.2015.06.004.
- Vögelin, E., Jones, N. F., Huang, J. I., Brekke, J. H. & Toth, J. M. Practical illustrations in tissue engineering: Surgical considerations relevant to the implantation of osteoinductive devices. *Tissue Engineering*, 2004, 6 (4), 449-460. Doi: org/10.1089/107632700418155
- Yakar, S., Werner, H. & Rosen, C. J. (2018). Insulin-like growth factors: actions on the skeleton. *Journal of Molecular Endocrinology*, 61 (1), T115-T137. Doi: 10.1530/JME-17-0298.
- Yang, Y. Q., Tan, Y. Y., Wong, R., Wenden, A., Zhang, L. K. & Rabie, A. B. (2012). The

- role of vascular endothelial growth factor in ossification. *International Journal of Oral Science*, 4 (2), 64–68. Doi: 10.1038/ijos.2012.33.
- Zelzer, E., McLean, W., Ng, Y. S., Fulkai, N., Reginato, A. M., Lovejoy, S., D'Amore, P. A. & Olsen, B. R. (2002). Skeletal defects in VEGF(120/120) mice reveal multiple roles for VEGF in skeletogenesis. *Development*, 129 (8), 1893–1904.
- Zhang, X., Ibrahimi, O. A., Olsen, S. K., Umemori, H., Mohammadi, M. & Ornitz, D. M. (2006). Receptor specificity of the fibroblast growth factor family. The complete mammalian FGF family. *The Journal of Biological Chemistry*, 281 (23), 15694–15700. Doi: 10.1074/jbc.M601252200.
- Zhang, M., Yu, W., Niibe, K., Zhang, W., Egusa, H., Tang, T. & Jiang, X. (2018). The Effects of Platelet-Derived Growth Factor-BB on Bone Marrow Stromal Cell-Mediated Vascularized Bone Regeneration. *Stem cells international*, 2018, 3272098. Doi: 10.1155/2018/3272098. eCollection 2018.
- Zhang, W., Wang, X., Wang, S., Zhao, J., Xu, L., Zhu, C., Zeng, D., Chen, J., Zhang, Z., Kaplan, D.L. & Jiang, X. (2011). The use of injectable sonication-induced silk hydrogel for VEGF(165) and BMP-2 delivery for elevation of the maxillary sinus floor. *Biomaterials*, 32 (35), 9415-9424. Doi: 10.1016/j.biomaterials.2011.08.047.
- Zhao, J., Shen, G., Liu, C., Wang, S., Zhang, W., Zhang, X., Zhang X, Ye D, Wei J, Zhang Z. & Jiang X. (2012). Enhanced healing of rat calvarial defects with sulfated chitosancoated calcium-deficient hydroxyapatite/bone morphogenetic protein 2 scaffolds. *Tissue engineering part A*, 18 (1-2), 185-197. Doi: 10.1089/ten.TEA.2011.0297.
- Zisch, A. H., Lutolf, M. P. & Hubbell, J. A. (2003). Biopolymeric delivery matrices for angiogenic growth factors. *Cardiovascular pathology*, 12 (6), 295-310.
- Zhou, W. L., Li, L. L., Qiu, X. R., An, Q. & Li, M. H. (2017). Effects of Combining Insulin-like Growth Factor 1 and Platelet-derived Growth Factor on Osteogenesis around [SEP]Dental Implants. *The Chinese Journal of Dental Research*, 20 (2), 105-109. Doi: 10.3290/j.cjdr.a38275.
- Zou, D., Zhang, Z., He, J., Zhang, K., Ye, D., Han, W., Zhou, J., Wang, Y., Li, Q., Liu, X., Zhang, X., Wang, S., Hu, J., Zhu, C., Zhang, W., zhou, Y., Fu, H., Huang, Y. & Jiang, X. (2012). Blood vessel formation in the tissue-engineered bone with the constitutively active form of HIF-1 $\alpha$  mediated BMSCs. *Biomaterials*, 33 (7), 2097–2108. Doi: 10.1016/j.biomaterials.2011.11.053.