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生长因子衍生肽在骨组织工程中的研究进展

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摘　要

通过生物支架递送生长因子是骨组织工程中的常用策略，在过去的几十年里取得了大量令人满意的结果。但生长因子存在的一些缺点诸如稳定性差、分子量大、成本高等阻碍了其广泛使用。近年来，一些具有相似生物活性的生长因子衍生肽由于合成简单、性质稳定等有点受到越来越多关注。本文总结了应用于骨组织工程的生长因子衍生肽。

关键词

骨组织工程，生长因子，衍生多肽，骨再生

Research Progress of Peptides Derived from Growth Factors in Bone Tissue Engineering

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Abstract

The delivery of growth factors through biological scaffolds is a commonly used strategy in bone tissue engineering, which has achieved a large number of satisfactory results in the past few decades. However, some drawbacks of growth factors such as poor stability, high molecular weight and high cost, hinder their widespread use. In recent years, some peptides derived from growth factors with similar biological activities have received increasing attention due to their simple synthesis and stable properties. This article summarizes the application of peptides derived from growth factors in bone tissue engineering.

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Keywords

Bone Tissue Engineering, Growth Factors, Derived Peptide, Bone Regeneration

1. 引言

生长因子在调控骨组织再生方面具有至关重要的功能[1]。通过生物材料支架复合生长因子的策略在骨组织工程中被广泛使用，并且也取得了许多令人满意的结果[2] [3] [4]。然而，生长因子也存在许多局限性，例如价格昂贵、半衰期短、性质不稳定等，限制了其有效的临床转化[5] [6]。近年来，一些生长因子衍生肽被证明具有和生长因子相似的生物活性，由于其合成简单、价格低廉、性质更加稳定等优点受到越来越多关注[7] [8]。

2. 骨组织工程与生长因子

骨再生是一个复杂的过程，受到多种生长因子的调控[9]。生长因子是一类调节细胞功能的蛋白质，包括细胞增殖、迁移和分化等[10]，并且对细胞外基质（ECM）合成有重要意义[11]。过去已经研究了多种与骨再生相关的生长因子，包括骨形态发生蛋白(BMP)、血管内皮生长因子(VEGF)、血小板衍生生长因子(PDGF)、成纤维细胞生长因子(FGF)、骨保护素(OPG)、肿瘤坏死因子 α (TNFα)等[12]。目前，基于生长因子递送的生物材料系统是骨再生研究的最常用策略之一[13]，然而，由于生长因子结构复杂、性质不稳定导致其利用率较低，在体内实现长效缓释也是一个巨大挑战[14]；同时，直接应用生长因子可能会伴随一些严重后果包括异位成骨、炎症反应等[15] [16]，这些局限性阻碍了其在骨组织工程中的进一步应用。因此，寻找理想的生长因子替代品是未来骨组织工程研究面临的巨大挑战之一。

3. 生长因子衍生肽在骨组织工程中的应用

生长因子衍生肽是一类源自生长因子部分氨基酸序列、具有模拟生长因子功能的生物活性多肽[17]。生长因子衍生肽多为单链肽形式，可通过多种修饰方式结合于骨组织工程支架上，以实现缓慢释放及促进骨缺损愈合[18]。在过去的几十年里，已经开发了多种生长因子衍生肽，包括骨形态发生蛋白衍生肽、血管内皮生长因子衍生肽、骨保护素衍生肽等，并且在多种生物材料系统中实现了有效的骨再生。

3.1. 骨形态发生蛋白(BMP)衍生肽

骨形态发生蛋白(BMP)是 TGF-β 超家族的成员，具有调节骨髓间充质干细胞成骨分化的作用，据报道，BMP-2、BMP-4、BMP-6、BMP-7 和 BMP-9 都具有很强的成骨能力[19]；其中 BMP-2 和 BMP-7 已被美国食品药品监督管理局(FDA)批准临床骨再生应用[6]。目前研究了多种 BMP 衍生肽。

BMP-2 蛋白具有两个功能结构域，被称为指关节表位和腕表位，指关节表位被认为和 BMP-2 受体 II 结合[20]，而腕表位则与 BMP-2 受体 I A 结合[21]。Saito 等人开发了一种源自 BMP-2 指关节表位 73-92 位氨基酸残基的衍生肽，氨基酸序列为 KIPKASSVPTELSAISTLYL (简称 KP 肽)，被证明可结合 BMP-2 II 型受体激活 BMP 通路，提高碱性磷酸酶活性和骨钙素基因表达，从而促进成骨分化[22]。这种衍生肽可通过物理或化学结合的形式固定在生物支架上，例如，Park SH 等人通过化学反应将 KP 肽掺入了一种可

注射的点击交联透明质酸水凝胶，在体内观察到了多肽的持续释放，并且在体外促进了人牙髓干细胞成骨分化以及体内骨再生[23]。另外，KP 肽也可通过添加结构域增强与支架的结合，例如，Bain 等人设计了具有七谷氨酸结构域(E7)的 KP 肽，这种源自骨唾液蛋白天然基序结构域显著增强了 KP 肽和无机牛骨的特异性结合，从而提高了骨再生能力[24]。在 Weng 等人的研究中，具有 E7 结构域修饰的 KP 肽也被偶联于一种 3D 杂化的纳米纤维气凝胶，显著增强了大鼠颅骨缺损愈合[25]。KP 肽也可与其他生物活性分子共同递送，在最近的一项研究中，一种骨髓间充质干细胞特异性亲和肽(氨基酸序列 EPLQLKM)和 KP 肽被同步偶联到静电纺丝支架上，可以同时促进骨髓间充质干细胞粘附和成骨分化，实现了协同成骨[26]。除此之外，源自 BMP-2 腕表位的 30~34 位氨基酸残基的 DWIVA 序列也被证明具有成骨潜力[27][28]。Oliver-Cervelló 等人开发了一种含有 DWIVA 基序和整合素结合序列(RGD)的仿生肽，该肽成功模拟了整合素-BMP 信号转导，促进了细胞黏附与成骨分化[29]，并且应用于钛仿生涂层后显著促进了大鼠颅骨再生[30]。在进一步的研究中，这种含有 DWIVA 基序和 RGD 序列的仿生肽被用于一种聚乙二醇(PEG)基水凝胶的功能化，并且联合了基质金属蛋白酶(MMP)可降解序列，显示出理想的可降解性和促成骨分化作用[31]。

BFP-1 是一种源自 BMP-7 未成熟区域的衍生肽，对应于 BMP-7 蛋白序列的第 100~114 位氨基酸残基，序列为 GQGFSYPYKAVFSTQ；体外研究表明，BFP-1 可上调成骨标志的显著表达，并且与 BMP-7 相比，具有更高的成骨分化活性，体内研究也显示了其潜在的成骨活性[32]。因此，BFP-1 可作为生物活性剂用于骨再生研究。例如，Luo 等人将 BFP-1 掺入了多孔海藻酸盐支架，显示出一定的缓释模式和促成骨活性[33]。为了进一步增强 BFP-1 在海藻酸盐支架中的骨再生能力，该研究团队将 BFP-1 联合含有 RGD 序列的粘附肽共同负载于介孔二氧化硅纳米颗粒中，随后掺入海藻酸盐支架中，实现了双功能肽的响应性顺序释放，并且显著改善了药物释放行为，在体内表现出优秀的骨修复效率[34]。另外，也可通过共价结合的方式将 BFP-1 于生物支架结合，在 Jing 等人的研究中，BFP-1 通过交联剂与羧甲基壳聚糖(CMC)共价结合，并最终接枝到脱矿牙本质基质(DDM)表面，结果表明修饰后 DDM 在体外和体内均显示出更好的骨诱导能力[35]。

pBMP-9 是源自 BMP-9 指关节表位 68~87 位氨基酸残基的衍生肽，序列为 CGGKVGKACCVPTKLSPISVLYK，被证明可通过激活 Smad 通路，从而上调成骨相关基因的表达，增强碱性磷酸酶活性，促进小鼠前成骨细胞 MC3T3-E1 成骨分化，并且不会被 Noggin 抑制，但过高的浓度(400 ng/mL)也会抑制 MC3T3-E1 细胞的增殖[36]。Bergeron 等人开发了一种基于 I 型胶原蛋白凝胶和生物活性玻璃微球的递送系统，掺入了相同浓度的 pBMP-9 和人重组 BMP-2，结果表明掺入 pBMP-9 能观察到更明显的成骨分化[37]；该研究团队随后对递送系统进行了优化，pBMP-9 被负载至一种基于壳聚糖的递送系统，实现了 10 天内的缓慢释放，并且成功诱导了 C57BL/6 小鼠股四头肌中的异位成骨[38]。pBMP-9 联合粘附肽也可进一步增强成骨活性，Beauvais 等人的研究表明，使用源自纤连蛋白粘合肽(pFibro)功能化的聚己内酯(PCL)膜使小鼠 C3H10T1/2 细胞中形成了更多的黏附斑点，并且和 pBMP-9 一起孵育时，观察到更多的 Runx2 表达[39]，表明了基于这两种生物活性肽设计的仿生材料具有良好前景。

3.2. 血管内皮生长因子(VEGF)衍生肽

血管内皮生长因子(VEGF)是具有促血管生成活性的生长因子，对内皮细胞具有促有丝分裂和抗凋亡作用，还可促进细胞迁移，增加血管的通透性等，促进细胞迁移等，因此在调控血管生成方面有重要意义[40]。众所周知，血管生成对于骨组织重建非常关键[9]，实现有效的血管化骨再生是一种理想的策略。

VEGF 衍生肽(QK)是源自 VEGF 与受体结合区域的一段衍生的氨基酸序列，序列为 KLTWQELYQLKYKGI，被证明可通过与 VEGF 受体结合，导致 ERK1/2 激活，促进了内皮细胞增殖和

迁移，在体外诱导血管生成，并且还可增强内皮细胞对 VEGF 的反应[41]。尽管 QK 具有很强的诱导血管生成活性，但单独使用 QK 并不能获得理想的成骨效果，因此 QK 常作为辅助成分与其他成骨活性肽协同促进骨再生，例如，Li 等人将 QK 和成骨肽 KP 一起结合在一种基于甲基丙烯酰化明胶(GelMA)和氧化葡聚糖(ODex)的可注射水凝胶上，在植入体内 4 周后显著促进了大鼠颅骨修复[42]。同样地，QK 和 BMP-7 衍生肽 BFP-1 的组合也加速了牙周骨的再生[43]。QK 也可通过多种方式以增强其成血管活性，如可通过添加七谷氨酸结构域(E7)加强 QK 和磷酸钙基支架之间的亲和力，与未修饰的 QK 相比，E7 修饰的 QK 与磷酸钙基支架的结合增加了 4~6 倍[44]；也可将 QK 与层粘连蛋白衍生肽 AG-73 偶联以增强细胞信号转导，更加有效地促进了人脐静脉内皮细胞(HUVECs)的黏附和增殖[45]。除此之外，QK 在周围神经修复[46]、促进伤口愈合[47]、治疗心肌梗死[48]等方面也具有较强的生物活性。

3.3. 骨保护素(OPG)衍生肽

骨保护素(OPG)是 RANK-RANKL-OPG 系统的重要成员，是调控破骨细胞分化和骨重塑的关键因子[49]。目前已知，核因子 κB 受体活化因子配体(RANKL)与破骨细胞表面的核因子 κB 受体活化因子(RANK)结合可促进破骨细胞分化导致骨吸收，而 OPG 可作为诱导受体与 RANKL 结合抑制 RANK 信号转导，从而抑制破骨细胞形成[50]。

OP3-4 是一种 OPG 的衍生肽，氨基酸序列为 YCEIEFCYLIR，其作用机制是模拟 OPG 与 RANKL 结合，导致 RANK 信号转导减弱，从而抑制破骨细胞形成以减少骨质流失[51]。骨再生过程中成骨与破骨是同时存在的[17]，因此通过减少破骨的方式来增加成骨也是一种合理的策略，例如，Uehara 等人通过将 OP3-4 加入到含有 BMP-2 的可注射明胶水凝胶中，在注射体内 4 周后显著促进了 BMP-2 诱导的上颌骨再生[52]。OP3-4 也可与其他活性分子协同作用，如 OP3-4 联合抗 CXCL9 抗体，同时抑制了破骨细胞分化和促血管生成，从而加速股骨缺损的愈合[53]。由于肽的聚集可能会导致其失去生物活性，因此 Xie 等人将 OP3-4 引入了含胆固醇的支链淀粉(CHP)纳米凝胶支架，改善了 OP3-4 的释放模式，并获得更佳的骨修复效果[54]。

3.4. 肿瘤坏死因子受体(TNFR)衍生肽

TNF-α 是一种细胞因子，可促进多种生物学效应，TNF-α 诱导的破骨细胞募集被认为是与炎症性骨吸收相关疾病(如牙周病)发病机制的核心[8]。WP9QY 肽(简称 W9)是一种肿瘤坏死因子 α (TNF-α)拮抗剂，是一种以 TNF 1 型受体上的 TNF-α 结合位点为模板设计的环肽，序列为 YCWSQYLCY，其作用机制和 OP3-4 相似，主要通过与 RANKL 和 TNF-α 结合来抑制破骨细胞形成，从而减少骨吸收[55]。W9 对炎症也有一定的抑制作用，尽管弱于抗 TNF 抗体，但 W9 对骨破坏的抑制作用与抗 TNF 抗体相似甚至更强[56]。同样地，W9 也被证明可以直接促进骨再生[57]或者增强 BMP-2 诱导的骨形成[58]。利用 W9 的免疫调控作用，也可实现促成骨效果，如 Ma 等人[59]开发的封装有 W9 肽和抗菌肽 LL37 的猪小肠黏膜下层(SIS)水凝胶，不仅表现出良好的抗菌能力，还通过 W9 调控巨噬细胞向 M2 型极化，促进骨髓间充质干细胞成骨分化，表明了其在免疫调控和骨再生方面的优势。

3.5. 成纤维细胞生长因子(FGF)衍生肽

成纤维细胞生长因子(FGF)是骨骼发育的重要调节因子，其中 FGF-2 是软骨内骨形成和骨膜内成骨的关键调节剂[60]。据报道，FGD-2 和肝素/硫酸乙酰肝素蛋白聚糖(HSPG)的相互作用可调控细胞生长和迁移[61]，因此，FGF-2 中的肝素结合位点在调节其生物活性方面起着重要作用。F105 和 F119 是源自 FGF-2 肝素结合位点的两段衍生肽，分别对应于第 105-111 (F105, YKRSRYT)和 119-135 (F119,

KRTGQYKLGSKTGPGQK)位氨基酸残基，体外结果表明 F105 和 F119 与肝素有很高的结合亲和力，并且促进了骨髓间充质干细胞黏附和铺展；进一步研究表明，F105 和 F119 通过提高细胞外调节蛋白激酶(ERK)的磷酸化水平，最终导致了骨髓间充质干细胞碱性磷酸酶过表达和钙沉积的增加[62]。目前尚无体内研究证据表明这两种肝素结合肽具有成骨活性，未来有望用于生物支架材料的功能化，以增强骨再生。

4. 总结

对生长因子的研究推动了骨组织工程技术的应用和进一步拓展，但生长因子潜在的免疫原性、大分子量、复杂的递送模式以及体内的不稳定性等缺点阻碍了它们的广泛使用。大量的研究表明，生长因子衍生肽同样具有较强的生物活性。肽作为小分子药物，合成简单，克服了成本问题，多样化的修饰及释放模式也是其优势之一。未来值得探索更多具有成骨活性的多肽序列；多种肽组合以实现不同药物调控的复杂再生过程也值得进一步探索。总而言之，生长因子衍生肽有望作为理想的生长因子替代品，在骨组织工程领域具有良好的应用前景。

参考文献

[1] Siddiqui, J.A. and Partridge, N.C. (2016) Physiological Bone Remodeling: Systemic Regulation and Growth Factor Involvement. *Physiology* (*Bethesda*), **31**, 233-245. https://doi.org/10.1152/physiol.00061.2014

[2] Oliveira, É.R., Nie, L., Podstawczyk, D., Allahbakhsh, A., Ratnayake, J., Brasil, D.L. and Shavandi, A. (2021) Advances in Growth Factor Delivery for Bone Tissue Engineering. *International Journal of Molecular Sciences*, **22**, Article No. 903. https://doi.org/10.3390/ijms22020903

[3] Cicciù, M. (2020) Growth Factor Applied to Oral and Regenerative Surgery. *International Journal of Molecular Sciences*, **21**, Article No. 7752. https://doi.org/10.3390/ijms21207752

[4] Seims, K.B., Hunt, N.K. and Chow, L.W. (2021) Strategies to Control or Mimic Growth Factor Activity for Bone, Cartilage, and Osteochondral Tissue Engineering. *Bioconjugate Chemistry*, **32**, 861-878. https://doi.org/10.1021/acs.bioconjchem.1c00090

[5] James, A.W., LaChaud, G., Shen, J., Asatrian, G., Nguyen, V., Zhang, X., Ting, K. and Soo, C. (2016) A Review of the Clinical Side Effects of Bone Morphogenetic Protein-2. *Tissue Engineering Part B*: *Reviews*, **22**, 284-297. https://doi.org/10.1089/ten.teb.2015.0357

[6] Schmidt-Bleek, K., Willie, B.M., Schwabe, P., Seemann, P. and Duda, G.N. (2016) BMPs in Bone Regeneration: Less Is More Effective, a Paradigm-Shift. *Cytokine & Growth Factor Reviews*, **27**, 141-148. https://doi.org/10.1016/j.cytogfr.2015.11.006

[7] Senta, H., Park, H., Bergeron, E., Drevelle, O., Fong, D., Leblanc, E., Cabana, F., Roux, S., Grenier, G. and Faucheux, N. (2009) Cell Responses to Bone Morphogenetic Proteins and Peptides Derived from Them: Biomedical Applications and Limitations. *Cytokine & Growth Factor Reviews*, **20**, 213-222. https://doi.org/10.1016/j.cytogfr.2009.05.006

[8] Aoki, K., Alles, N., Soysa, N. and Ohya, K. (2012) Peptide-Based Delivery to Bone. *Advanced Drug Delivery Reviews*, **64**, 1220-1238. https://doi.org/10.1016/j.addr.2012.05.017

[9] Einhorn, T.A. and Gerstenfeld, L.C. (2015) Fracture Healing: Mechanisms and Interventions. *Nature Reviews Rheumatology*, **11**, 45-54. https://doi.org/10.1038/nrrheum.2014.164

[10] Timin, A.S., Muslimov, A.R., Zyuzin, M.V., Peltek, O.O., Karpov, T.E., Sergeev, I.S., Dotsenko, A.I., Goncharenko, A.A., Yolshin, N.D., Sinelnik, A., *et al*. (2018) Multifunctional Scaffolds with Improved Antimicrobial Properties and Osteogenicity Based on Piezoelectric Electrospun Fibers Decorated with Bioactive Composite Microcapsules. *ACS Applied Materials & Interfaces*, **10**, 34849-34868. https://doi.org/10.1021/acsami.8b09810

[11] Briquez, P.S., Hubbell, J.A. and Martino, M.M. (2015) Extracellular Matrix-Inspired Growth Factor Delivery Systems for Skin Wound Healing. *Advances in Wound Care*, **4**, 479-489. https://doi.org/10.1089/wound.2014.0603

[12] Ai-Aql, Z.S., Alagl, A.S., Graves, D.T., Gerstenfeld, L.C. and Einhorn, T.A. (2008) Molecular Mechanisms Controlling Bone Formation during Fracture Healing and Distraction Osteogenesis. *Journal of Dental Research*, **87**, 107-118. https://doi.org/10.1177/154405910808700215

[13] Ho-Shui-Ling, A., Bolander, J., Rustom, L.E., Johnson, A.W., Luyten, F.P. and Picart, C. (2018) Bone Regeneration Strategies: Engineered Scaffolds, Bioactive Molecules and Stem Cells Current Stage and Future Perspectives. *Biomaterials*, **180**, 143-162. https://doi.org/10.1016/j.biomaterials.2018.07.017

[14] King, W.J. and Krebsbach, P.H. (2012) Growth Factor Delivery: How Surface Interactions Modulate Release *in Vitro* and *in Vivo*. *Advanced Drug Delivery Reviews*, **64**, 1239-1256. https://doi.org/10.1016/j.addr.2012.03.004

[15] Martin, V. and Bettencourt, A. (2018) Bone Regeneration: Biomaterials as Local Delivery Systems with Improved Osteoinductive Properties. *Materials Science & Engineering C-Materials for Biological Applications*, **82**, 363-371. https://doi.org/10.1016/j.msec.2017.04.038

[16] Van Griensven, M. (2015) Preclinical Testing of Drug Delivery Systems to Bone. *Advanced Drug Delivery Reviews*, **94**, 151-164. https://doi.org/10.1016/j.addr.2015.07.006

[17] Safari, B., Davaran, S. and Aghanejad, A. (2021) Osteogenic Potential of the Growth Factors and Bioactive Molecules in Bone Regeneration. *International Journal of Biological Macromolecules*, **175**, 544-557. https://doi.org/10.1016/j.ijbiomac.2021.02.052

[18] Pountos, I., Panteli, M., Lampropoulos, A., Jones, E., Calori, G.M. and Giannoudis, P.V. (2016) The Role of Peptides in Bone Healing and Regeneration: A Systematic Review. *BMC Medicine*, **14**, Article No. 103. https://doi.org/10.1186/s12916-016-0646-y

[19] Katagiri, T. and Watabe, T. (2016) Bone Morphogenetic Proteins. *Cold Spring Harbor Perspectives in Biology*, **8**, A021899. https://doi.org/10.1101/cshperspect.a021899

[20] Kirsch, T., Nickel, J. and Sebald, W. (2000) BMP-2 Antagonists Emerge from Alterations in the Low-Affinity Binding Epitope for Receptor BMPR-II. *EMBO Journal*, **19**, 3314-3324. https://doi.org/10.1093/emboj/19.13.3314

[21] Kirsch, T., Sebald, W. and Dreyer, M.K. (2000) Crystal Structure of the BMP-2-BRIA Ectodomain Complex. *Nature Structural & Molecular Biology*, **7**, 492-496. https://doi.org/10.1038/75903

[22] Saito, A., Suzuki, Y., Ogata, S.I., Ohtsuki, C. and Tanihara, M. (2003) Activation of Osteo-Progenitor Cells by a Novel Synthetic Peptide Derived from the Bone Morphogenetic Protein-2 Knuckle Epitope. *Biochimica et Biophysica Acta*, **1651**, 60-67. https://doi.org/10.1016/S1570-9639(03)00235-8

[23] Park, S.H., Park, J.Y., Ji, Y.B., Ju, H.J., Min, B.H. and Kim, M.S. (2020) An Injectable Click-Crosslinked Hyaluronic Acid Hydrogel Modified with a BMP-2 Mimetic Peptide as a Bone Tissue Engineering Scaffold. *Acta Biomaterialia*, **117**, 108-120. https://doi.org/10.1016/j.actbio.2020.09.013

[24] Bain, J.L., Bonvallet, P.P., Abou-Arraj, R.V., Schupbach, P., Reddy, M.S. and Bellis, S.L. (2015) Enhancement of the Regenerative Potential of Anorganic Bovine Bone Graft Utilizing a Polyglutamate-Modified BMP2 Peptide with Improved Binding to Calcium-Containing Materials. *Tissue Engineering Part A*, **21**, 2426-2436. https://doi.org/10.1089/ten.tea.2015.0160

[25] Weng, L., Boda, S.K., Wang, H., Teusink, M.J., Shuler, F.D. and Xie, J. (2018) Novel 3D Hybrid Nanofiber Aerogels Coupled with BMP-2 Peptides for Cranial Bone Regeneration. *Advanced Healthcare Materials*, **7**, E1701415. https://doi.org/10.1002/adhm.201701415

[26] Li, W., Xu, H., Han, X., Sun, S., Chai, Q., Xu, X. and Man, Z. (2020) Simultaneously Promoting Adhesion and Osteogenic Differentiation of Bone Marrow-Derived Mesenchymal Cells by a Functional Electrospun Scaffold. *Colloids and Surfaces B*: *Biointerfaces*, **192**, Article ID: 111040. https://doi.org/10.1016/j.colsurfb.2020.111040

[27] Lee, J.Y., Choo, J.E., Choi, Y.S., Suh, J.S., Lee, S.J., Chung, C.P. and Park, Y.J. (2009) Osteoblastic Differentiation of Human Bone Marrow Stromal Cells in Self-Assembled BMP-2 Receptor-Binding Peptide-Amphiphiles. *Biomaterials*, **30**, 3532-3541. https://doi.org/10.1016/j.biomaterials.2009.03.018

[28] Minguela, J., Müller, D.W., Mücklich, F., Llanes, L., Ginebra, M.P., Roa, J.J. and Mas-Moruno, C. (2021) Peptidic Biofunctionalization of Laser Patterned Dental Zirconia: A Biochemical-Topographical Approach. *Materials Science & Engineering C-Materials for Biological Applications*, **125**, Article ID: 112096. https://doi.org/10.1016/j.msec.2021.112096

[29] Oliver-Cervelló, L., Martin-Gómez, H., Reyes, L., Noureddine, F., Ada Cavalcanti-Adam, E., Ginebra, M.P. and Mas-Moruno, C. (2021) An Engineered Biomimetic Peptide Regulates Cell Behavior by Synergistic Integrin and Growth Factor Signaling. *Advanced Healthcare Materials*, **10**, E2001757. https://doi.org/10.1002/adhm.202001757

[30] Oliver-Cervelló, L., Martin-Gómez, H., Mandakhbayar, N., Jo, Y.W., Cavalcanti-Adam, E.A., Kim, H.W., Ginebra, M.P., Lee, J.H. and Mas-Moruno, C. (2022) Mimicking Bone Extracellular Matrix: From BMP-2-Derived Sequences to Osteogenic-Multifunctional Coatings. *Advanced Healthcare Materials*, **11**, E2201339. https://doi.org/10.1002/adhm.202201339

[31] Oliver-Cervelló, L., Martin-Gómez, H., Gonzalez-Garcia, C., Salmeron-Sanchez, M., Ginebra, M.P. and Mas-Moruno, C. (2023) Protease-Degradable Hydrogels with Multifunctional Biomimetic Peptides for Bone Tissue Engineering. *Frontiers in Bioengineering and Biotechnology*, **11**, Article ID: 1192436. https://doi.org/10.3389/fbioe.2023.1192436

[32] Kim, H.K., Kim, J.H., Park, D.S., Park, K.S., Kang, S.S., Lee, J.S., Jeong, M.H. and Yoon, T.R. (2012) Osteogenesis Induced by a Bone Forming Peptide from the Prodomain Region of BMP-7. *Biomaterials*, **33**, 7057-7063. https://doi.org/10.1016/j.biomaterials.2012.06.036

[33] Luo, Z., Yang, Y., Deng, Y., Sun, Y., Yang, H. and Wei, S. (2016) Peptide-Incorporated 3D Porous Alginate Scaffolds with Enhanced Osteogenesis for Bone Tissue Engineering. *Colloids and Surfaces B*: *Biointerfaces*, **143**, 243-251. https://doi.org/10.1016/j.colsurfb.2016.03.047

[34] Luo, Z., Zhang, S., Pan, J., Shi, R., Liu, H., Lyu, Y., Han, X., Li, Y., Yang, Y., Xu, Z., Sui, Y., Luo, E., Zhang, Y. and Wei, S. (2018) Time-Responsive Osteogenic Niche of Stem Cells: A Sequentially Triggered, Dual-Peptide Loaded, Alginate Hybrid System for Promoting Cell Activity and Osteo-Differentiation. *Biomaterials*, **163**, 25-42. https://doi.org/10.1016/j.biomaterials.2018.02.025

[35] Jing, X., Xie, B., Li, X., Dai, Y., Nie, L. and Li, C. (2021) Peptide Decorated Demineralized Dentin Matrix with Enhanced Bioactivity, Osteogenic Differentiation via Carboxymethyl Chitosan. *Dental Materials*, **37**, 19-29. https://doi.org/10.1016/j.dental.2020.09.019

[36] Bergeron, E., Senta, H., Mailloux, A., Park, H., Lord, E. and Faucheux, N. (2009) Murine Preosteoblast Differentiation Induced by a Peptide Derived from Bone Morphogenetic Proteins-9. *Tissue Engineering Part A*, **15**, 3341-3349. https://doi.org/10.1089/ten.tea.2009.0189

[37] Bergeron, E., Marquis, M.E., Chrétien, I. and Faucheux, N. (2007) Differentiation of Preosteoblasts Using a Delivery System with BMPs and Bioactive Glass Microspheres. *Journal of Materials Science*: *Materials in Medicine*, **18**, 255-263. https://doi.org/10.1007/s10856-006-0687-4

[38] Bergeron, E., Leblanc, E., Drevelle, O., Giguère, R. and Faucheux, N. (2011) The Evaluation of Ectopic Bone Formation Induced by Delivery Systems for BMP-9 or Its Derived Peptide. *Tissue Engineering Part A*, **18**, 342-352. https://doi.org/10.1089/ten.tea.2011.0008

[39] Beauvais, S., Drevelle, O., Lauzon, M.A., Daviau, A. and Faucheux, N. (2016) Modulation of MAPK Signalling by Immobilized Adhesive Peptides: Effect on Stem Cell Response to BMP-9-Derived Peptides. *Acta Biomaterialia*, **31**, 241-251. https://doi.org/10.1016/j.actbio.2015.12.005

[40] Melincovici, C.S., Boşca, A.B., Şuşman, S., Mărginean, M., Mihu, C., Istrate, M., Moldovan, I.M., Roman, A.L. and Mihu, C.M. (2018) Vascular Endothelial Growth Factor (VEGF)—Key Factor in Normal and Pathological Angiogenesis. *Romanian Journal of Morphology and Embryology*, **59**, 455-467.

[41] D'Andrea, L.D., Iaccarino, G., Fattorusso, R., Sorriento, D., Carannante, C., Capasso, D., Trimarco, B. and Pedone, C. (2005) Targeting Angiogenesis: Structural Characterization and Biological Properties of a De Novo Engineered VEGF Mimicking Peptide. *Proceedings of the National Academy of Sciences of the United States of America*, **102**, 14215-14220. https://doi.org/10.1073/pnas.0505047102

[42] Li, R., Zhou, C., Chen, J., Luo, H., Li, R., Chen, D., Zou, X. and Wang, W. (2022) Synergistic Osteogenic and Angiogenic Effects of KP and QK Peptides Incorporated with an Injectable and Self-Healing Hydrogel for Efficient Bone Regeneration. *Bioactive Materials*, **18**, 267-283. https://doi.org/10.1016/j.bioactmat.2022.02.011

[43] Xiang, M., Zhu, M., Yang, Z., He, P., Wei, J., Gao, X. and Song, J. (2020) Dual-Functionalized Apatite Nanocomposites with Enhanced Cytocompatibility and Osteogenesis for Periodontal Bone Regeneration. *ACS Biomaterials Science & Engineering*, **6**, 1704-1714. https://doi.org/10.1021/acsbiomaterials.9b01893

[44] Pensa, N.W., Curry, A.S., Reddy, M.S. and Bellis, S.L. (2019) The Addition of a Polyglutamate Domain to the Angiogenic QK Peptide Improves Peptide Coupling to Bone Graft Materials Leading to Enhanced Endothelial Cell Activation. *PLOS ONE*, **14**, E0213592. https://doi.org/10.1371/journal.pone.0213592

[45] Bai, S., Zhang, J., Gao, Y., Chen, X., Wang, K. and Yuan, X. (2023) Surface Functionalization of Electrospun Scaffolds by QK-AG73 Peptide for Enhanced Interaction with Vascular Endothelial Cells. *Langmuir*, **39**, 14162-14172. https://doi.org/10.1021/acs.langmuir.3c02174

[46] Xu, W., Wu, Y., Lu, H., Zhang, X., Zhu, Y., Liu, S., Zhang, Z., Ye, J. and Yang, W. (2023) Injectable Hydrogel Encapsulated with VEGF-Mimetic Peptide-Loaded Nanoliposomes Promotes Peripheral Nerve Repair *in Vivo*. *Acta Biomaterialia*, **160**, 225-238. https://doi.org/10.1016/j.actbio.2023.02.004

[47] Chen, Z., Wang, L., Guo, C., Qiu, M., Cheng, L., Chen, K., Qi, J., Deng, L., He, C., Li, X. and Yan, Y. (2023) Vascularized Polypeptide Hydrogel Modulates Macrophage Polarization for Wound Healing. *Acta Biomaterialia*, **155**, 218-234. https://doi.org/10.1016/j.actbio.2022.11.002

[48] Li, B., Li, Y., Chen, S., Wang, Y. and Zheng, Y. (2023) VEGF Mimetic Peptide-Conjugated Nanoparticles for Magnetic Resonance Imaging and Therapy of Myocardial Infarction. *Journal of Controlled Release*, **360**, 44-56. https://doi.org/10.1016/j.jconrel.2023.06.017

[49] Lacey, D.L., Timms, E., Tan, H.L., *et al*. (1998) Osteoprotegerin Ligand Is a Cytokine That Regulates Osteoclast Differentiation and Activation. *Cell*, **93**, 165-176. https://doi.org/10.1016/S0092-8674(00)81569-X

[50] De Leon-Oliva, D., Barrena-Blázquez, S., Jiménez-Álvarez, L., Fraile-Martinez, O., García-Montero, C., López-González, L., Torres-Carranza, D., García-Puente, L.M., Carranza, S.T., Álvarez-Mon, M.Á., Álvarez-Mon, M., Diaz, R. and Ortega, M.A. (2023) The RANK-RANKL-OPG System: A Multifaceted Regulator of Homeostasis, Immunity, and Cancer.

Medicina (*Kaunas*), **59**, Article No. 1752. https://doi.org/10.3390/medicina59101752

[51] Cheng, X., Kinosaki, M., Takami, M., Choi, Y., Zhang, H. and Murali, R. (2004) Disabling of Receptor Activator of Nuclear Factor-KappaB (RANK) Receptor Complex by Novel Osteoprotegerin-Like Peptidomimetics Restores Bone Loss *in Vivo*. *Journal of Biological Chemistry*, **279**, 8269-8277. https://doi.org/10.1074/jbc.M309690200

[52] Uehara, T., Mise-Omata, S., Matsui, M., Tabata, Y., Murali, R., Miyashin, M. and Aoki, K. (2016) Delivery of RANKL-Binding Peptide OP3-4 Promotes BMP-2-Induced Maxillary Bone Regeneration. *Journal of Dental Research*, **95**, 665-672. https://doi.org/10.1177/0022034516633170

[53] Luo, P., Fang, J., Yang, D., Yu, L., Chen, H., Jiang, C., Guo, R., Zhu, T. and Tang, S. (2023) OP3-4 Peptide Sustained-Release Hydrogel Inhibits Osteoclast Formation and Promotes Vascularization to Promote Bone Regeneration in a Rat Femoral Defect Model. *Bioengineering & Translational Medicine*, **8**, E10414. https://doi.org/10.1002/btm2.10414

[54] Xie, C., Satake-Ozawa, M., Rashed, F., Khan, M., Ikeda, M., Hayashi, S., Sawada, S., Sasaki, Y., Ikeda, T., Mori, Y., Akiyoshi, K. and Aoki, K. (2022) Perforated Hydrogels Consisting of Cholesterol-Bearing Pullulan (CHP) Nanogels: A Newly Designed Scaffold for Bone Regeneration Induced by RANKL-Binding Peptides and BMP-2. *International Journal of Molecular Sciences*, **23**, Article No. 7768. https://doi.org/10.3390/ijms23147768

[55] Aoki, K., Saito, H., Itzstein, C., Ishiguro, M., Shibata, T., Blanque, R., Mian, A.H., Takahashi, M., Suzuki, Y., Yoshimatsu, M., Yamaguchi, A., Deprez, P., Mollat, P., Murali, R., Ohya, K., Horne, W.C. and Baron, R. (2006) A TNF Receptor Loop Peptide Mimic Blocks RANK Ligand-Induced Signaling, Bone Resorption, and Bone Loss. *Journal of Clinical Investigation*, **116**, 1525-1534. https://doi.org/10.1172/JCI22513

[56] Rashed, F., Kamijyo, S., Shimizu, Y., Hirohashi, Y., Khan, M., Sugamori, Y., Murali, R. and Aoki, K. (2021) The Effects of Receptor Activator of NF-κB Ligand-Binding Peptides on Bone Resorption and Bone Formation. *Frontiers in Cell and Developmental Biology*, **9**, Article ID: 648084. https://doi.org/10.3389/fcell.2021.648084

[57] Li, Y., Zhang, J., Chen, L., Li, H. and Wang, J. (2023) Repair of Critical-Sized Rat Cranial Defects with RADA16-W9 Self-Assembled Peptide Hydrogel. *Biochemical and Biophysical Research Communications*, **652**, 68-75. https://doi.org/10.1016/j.bbrc.2023.02.028

[58] Furuya, Y., Inagaki, A., Khan, M., Mori, K., Penninger, J.M., Nakamura, M., Udagawa, N., Aoki, K., Ohya, K., Uchida, K. and Yasuda, H. (2013) Stimulation of Bone Formation in Cortical Bone of Mice Treated with a Receptor Activator of Nuclear Factor-κB Ligand (RANKL)-Binding Peptide That Possesses Osteoclastogenesis Inhibitory Activity. *Journal of Biological Chemistry*, **288**, 5562-5571. https://doi.org/10.1074/jbc.M112.426080

[59] Ma, S., Wang, C., Dong, Y., Jing, W., Wei, P., Peng, C., Liu, Z., Zhao, B. and Wang, Y. (2022) Microsphere-Gel Composite System with Mesenchymal Stem Cell Recruitment, Antibacterial, and Immunomodulatory Properties Promote Bone Regeneration via Sequential Release of LL37 and W9 Peptides. *ACS Applied Materials & Interfaces*, **14**, 38525-38540. https://doi.org/10.1021/acsami.2c10242

[60] Ornitz, D.M. and Marie, P.J. (2015) Fibroblast Growth Factor Signaling in Skeletal Development and Disease. *Genes & Development*, **29**, 1463-1486. https://doi.org/10.1101/gad.266551.115

[61] Presta, M., Dell'Era, P., Mitola, S., Moroni, E., Ronca, R. and Rusnati, M. (2005) Fibroblast Growth Factor/Fibroblast Growth Factor Receptor System in Angiogenesis. *Cytokine & Growth Factor Reviews*, **16**, 159-178. https://doi.org/10.1016/j.cytogfr.2005.01.004

[62] Lee, J.-Y., Choo, J.-E., Choi, Y.-S., *et al*. (2010) Characterization of the Surface Immobilized Synthetic Heparin Binding Domain Derived from Human Fibroblast Growth Factor-2 and Its Effect on Osteoblast Differentiation. *Journal of Biomedical Materials Research Part A*, **83**, 970-979.