• 综述 •

受体活性修饰蛋白1促进成骨作用的研究进展

张勤 宫苹
口腔疾病研究国家重点实验室 国家口腔疾病临床医学研究中心
四川大学华西口腔医院种植科 成都 610041

[摘要] 生理状态下，骨吸收与骨形成过程的动态平衡对维持骨组织功能至关重要。而在骨损伤状态下，如何通过促进骨形成，抑制骨吸收从而促进骨愈合过程一直是该领域研究的热点。近年来，受体活性修饰蛋白-1（RAMP1）在骨代谢过程中的调节作用已受到越来越多的关注。RAMP1广泛存在于骨组织中，它可以与不同的G蛋白偶联受体（GPCR）结合，修饰受体行为，调节相应的配体作用。此外，它还能进一步参与到受体介导的信号转导中，影响成骨相关细胞内蛋白的相互作用，从而影响成骨相关细胞增殖、迁移、分化等生物学特性。本文就近年来RAMP1促进成骨作用的研究作一综述。

[关键词] 受体活性修饰蛋白1；降钙素基因相关肽；成骨作用；G蛋白偶联受体；降钙素受体样受体
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Advancements in receptor activity-modifying protein-1 for osteogenesis *Zhang Qin, Gong Ping. (State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases & Dept. of Implantation, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China)*

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[Abstract] Under physiological conditions, the dynamic balance between bone resorption and bone formation is necessary to maintain bone tissue function. However, whether we can further accelerate or improve osteogenesis process during bone wound healing has been widely explored. Receptor activity-modifying protein-1 (RAMP1) has been extensively investigated because of its extensive biological activities, especially its effects on bone fracture repair. RAMP1 is commonly found in bone tissues and can interact with G-protein coupled receptors to modify their activities. RAMP1 also has a broader role in regulating receptor trafficking and signaling, affecting the biological characteristics of osteoblasts, such as proliferation, migration, and differentiation. Thus, this review summarizes recent studies about the effects of RAMP1 on osteogenesis.

[Key words] receptor activity-modifying protein-1; calcitonin gene-related peptide; osteogenesis; G-protein coupled receptor; calcitonin receptor-like receptor

据文献[1-3]报道：骨组织是一个持续活动性组织，骨代谢和改建过程的动态平衡对维持正常的生理功能至关重要。而在骨损伤状态下，骨改建平衡被打破，能否通过促进骨形成，抑制骨吸收，从而加速骨损伤的愈合一直是一个热点问题[4]。新近研究发现：受体活性修饰蛋白-1（receptor activity-modifying protein-1，RAMP1）在骨组织中广泛存在，提示RAMP1可能会参与骨代谢过程。进

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[作者简介] 张勤，硕士，Email：zhangq0312@hotmail.com
[通信作者] 宫苹，教授，博士，Email：dentistgong@hotmail.com

一步的研究显示：RAMP1能够促进成骨。有学者[5-7]认为：RAMP1是骨代谢和改建过程的潜在调节蛋白。

RAMP1属于单跨膜蛋白家族，它主要的生物学作用是通过与细胞表面的降钙素受体样受体（calcitonin receptor-like receptor，CLR）结合，协助CLR向细胞膜的转运，并形成降钙素基因相关肽（calcitonin gene-related peptide，CGRP）的特异性受体[8-9]。值得注意的是，CGRP作为骨组织中分布最广的一种感觉神经肽，在调控骨的生长和代谢方面至关重要[10-11]。本课题组前期研究[12]也发现：CGRP有望用作一类种植体表面的化学改性因子，以改善钛种植体的骨结合。而研究[13-16]发现：RAMP1能够通过影响机体骨组织对CGRP的应答，调节CGRP促进成骨的作用而参与骨代谢。此外，细胞表面的RAMP1/CLR复合体被CGRP激活后，RAMP1能直接参与到受体介导的信号转导中，影响成骨相关细胞内的蛋白相互作用以促进成骨[5-7]。本文就近年来RAMP1促进成骨作用的研究作一综述。

1 RAMP1的分子生物学特征

RAMP1肽链由148个氨基酸残基组成，可分为3个结构域：胞外N末端、单跨膜区域和胞内C末端[17]。其中，长N末端是与受体结合，决定受体表型的区域。单跨膜区域可稳定受体复合体，并影响受体介导的信号转导。短C末端的功能目前还存在争议，可能与RAMP1未转移至细胞表面时，在内质网的潴留相关。

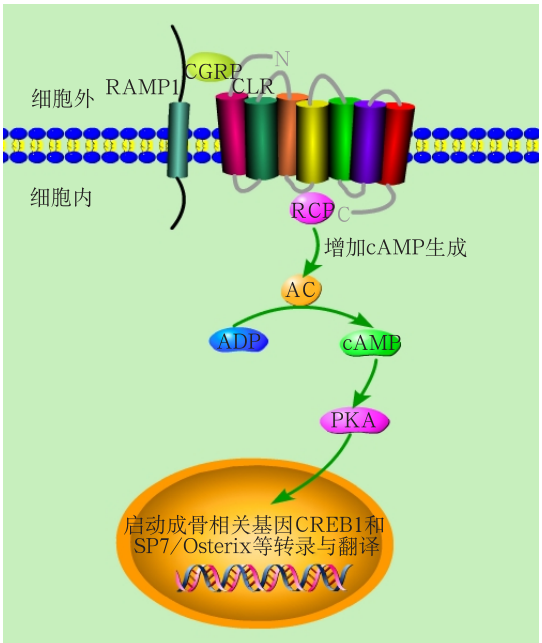
RAMP1具有广泛的生物学效应，它与CLR、降钙素受体（calcitonin receptor，CTR）、血管活性肠肽（vasoactive intestinal peptide，VPAC）受体等多种G蛋白偶联受体（G-protein coupled receptor，GPCR）均有一定的相互作用，从而形成不同的功能性受体，并进一步参与后续反应（表1）[18-22]。其中，RAMP1最主要的作用是作为CLR的分子伴侣蛋白，与CLR结合后，决定CLR的药理作用和末端糖基化状态，协助CLR转运至胞膜上，并选择性表达为CGRP受体表型[23]。此外，当CGRP激活功能性受体后，RAMP1能进一步通过修饰受体行为等，参与到受体介导的信号转导中，影响细胞内的蛋白相互作用，从而影响细胞增殖、迁移、分化等生物学特性[23-24]。基于上述的研究基础，RAMP1在促进成骨方面的作用逐渐受到关注。研究[7,22,25-28]发现：骨损伤状态下，RAMP1的表达会增加细胞内CGRP诱导的环腺苷酸（cyclic adenosine monophosphate，cAMP）产量，促进成骨相关细胞增殖、分化及成骨相关蛋白的产生，从而促进损伤组织愈合（图1）。

表 1 常见的RAMPs家族参与构成的受体

Tab 1 Summary of the receptors that RAMPs have been involved in

受体名称	受体主要分子组成
CGRP受体	CLR+RAMP1
AM1受体	CLR+RAMP2/3
AM2受体	CLR+RAMP1/2/3
AMY受体	CTR+RAMP1/2/3
VPAC受体	VPAC受体+RAMP1/2/3
PTH_1受体	PTH_1受体+RAMP2
PTH_2受体	PTH_2受体+RAMP3
CaSR	CaSR+RAMP1/2/3

注：AM为肾上腺髓质素（adrenomedullin），AMY为胰淀粉样酶（amylin），PTH为甲状旁腺素（parathyroid hormone），CaSR为钙敏感受体（calcium-sensing receptor）。



N：氮末端；C：碳末端；RCP：受体组分蛋白（receptor component protein）；AC：腺苷酸环化酶（adenylate cyclase）；ADP：二磷酸腺苷（adenosine diphosphate）；PKA：蛋白激酶A（protein kinase A）；CREB1：环磷酸腺苷应答元件结合蛋白1（cyclic adenosine monophosphate response element binding protein 1）；SP7/Osterix：锌指结构转录因子。

图 1 RAMP1参与CGRP促进成骨作用的机制

Fig 1 RAMP1 modulation of CGRP-mediated activities in osteogenesis

2 RAMP1调控CGRP促进成骨作用及其机制

2.1 RAMP1调控CGRP促进成骨作用

CGRP作为骨组织中分布最广的一种感觉神经肽，在调控骨的生长和代谢方面的作用已逐渐获得国内外学者[7,12,29-30]的认可。研究[31]发现：它的亚型之一——α-CGRP广泛分布于骨髓腔、干骺端和骨膜等骨代谢活跃程度较高的区域，在刺激骨形成过程中发挥着重要作用。另有研究[32]显示：局部过表达α-CGRP基因的小鼠，骨损伤部位新骨形成速度及质量较正常组明显增加；而α-CGRP基因敲除小鼠体内骨量明显减少，并常伴有骨质疏松症[12,33-34]。Zhang等[7]在大鼠股骨损伤部位局部抑制CGRP的产生后，新骨形成也明显减少。有文献[12]报道：α-CGRP在促进小鼠体内钛种植体骨结合过程中发挥着重要作用。Li等[35]也发现α-CGRP能够促进兔下颌骨损伤的愈合。进一步的研究显示：CGRP与RAMP1/CLR复合体结合后，会刺激cAMP的形成，从而增加成骨相关蛋白CREB1和SP7/Osterix等的表达以实现促进成骨的作用[7,22,25-28]。

早期的学者认为：CGRP促进成骨作用主要是由CLR调节[36]，但这个猜想在之后的实验中被推翻。研究[37-38]发现：仅仅增加CLR的表达，而RAMP1的表达不改变，机体对CGRP的应答并不会增加；反之，RAMP1则具有调节机体组织对CGRP敏感性等作用[39-43]。

Bohn等[44]发现：小鼠全身性过表达人RAMP1基因时，机体各组织对CGRP的敏感性明显增加。Zhang等[7]在研究镁促进成骨作用的机制时发现：CGRP和RAMP1参与其中，过表达RAMP1可以促进骨质疏松大鼠体内股骨骨折愈合的过程；反之，抑制RAMP1表达时，相关的成骨作用也会受到抑制。RAMP1的表达与CGRP促进骨膜来源干细胞成骨分化的作用呈正向相关[7]。另有研究[45]发现：RAMP1的过表达能够增加外源性CGRP的促MG-63增殖作用；干扰RAMP1的表达，其促MG-63增殖作用也受到抑制[46]。由此可见，RAMP1可能直接参与调节骨组织对CGRP的应答。此外，RAMP-1可以增加伤口愈合过程中CGRP诱导的血管和淋巴管生成[47-48]。进一步的研究[49]发现：CGRP与RAMP1/CLR复合体结合后可下调血管平滑肌细胞内的内源性Ca^{2+}释放，舒张血管，促进血液循环。Kawashima-Takeda等[50]发现：RAMP1也具有减轻小鼠大肠炎黏膜炎症反应的作用。在损伤状态下，骨组织与血管和炎症反应之间存在复杂的偶联关系，有学者[21,51-60]认为：RAMP1在促进损伤区血运重建、神经再生、抑制炎症反应方面的作用也可能有利于改善局部成骨的微环境，从而间接影响骨组织代谢过程。综上所述，RAMP1在调控CGRP促进成骨的过程中发挥着至关重要的作用，但其具体的作用机制还有待进一步的探究。

2.2 RAMP1调控CGRP促进成骨作用的机制

RAMP1的分子学研究为理解其调控CGRP促进成骨作用的机制提供了大量的理论线索和依据。Héroux等[61]发现：当过表达CLR时，一分子RAMP1可与两分子CLR结合形成功能型CGRP受体，但该受体只能与一分子的CGRP结合；而当RAMP1过表达时，一分子的CLR与两分子的RAMP1虽不能形成功能型的CGRP受体，但CLR竞争性与RAMP1结合，有更多的CLR从胞内转移至细胞表面，进而形成较多的CLR·RAMP1异源二聚体复合物。

另一方面，研究[18-20,22]发现：RAMP1在没有CLR蛋白的细胞也有大量分布，其与CTR、VPAC受体等多种GPCR均有一定的相互作用，其中与CTR的结合也可能形成CGRP受体[8,62-63]，进而增加机体对CGRP的应答。

亦有研究[23,64]表明：成骨细胞系RAMP1过表达时，能够将细胞表面的肾上腺髓质素受体（adrenomedullin，AM）——CLR/RAMP2复合体转化为CGRP受体，进而促进CGRP的生物学效应。

值得注意的是，有学者[44]认为：RAMP1增强机体对CGRP应答的机制在不同的组织中可能有差异，而其在骨组织中的作用机制还未有报道，其中涉及的分子信号通路研究也不完善，这些问题均有待进一步的探究。

3 展望

在口腔医学领域，患者骨组织代谢水平、骨损伤愈合情况一直是一个临床关注的重点。对外伤或肿瘤导致的颌骨缺损的重建、种植义齿修复等治疗，能否进一步促进成骨，抑制骨吸收直接影响着患者的预后。RAMP1的发现为调节骨代谢方面提供了新的思路。随着RAMP1基因敲除小鼠、转基因小鼠模型的发展以及RAMP1促进剂的

出现[21-22,65-67]，RAMP1的研究越来越深入，实现对RAMP1表达的调节逐渐成为可能。从调节RAMP1的表达入手，增加机体骨组织对CGRP的应答，进而促进机体骨损伤修复过程，为新药研制提供新的靶点，也为CGRP的临床应用提供新方向[23,68-69]。

综上所述，RAMP1具有广泛的生物学效应，对研究者进一步了解生命活动，疾病发展过程等也有着重要意义，其有望成为研究骨代谢调节的新的突破点。但目前RAMP1在成骨过程中发挥作用的具体机制及该过程中涉及的分子信号通路尚未明确，还有待于进一步的研究。

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（本文编辑 王姝）

《国际口腔医学杂志》入选2018学术类期刊数字影响力100强

2018年9月15日，由中国（武汉）期刊交易博览会组委会和中国期刊协会共同举办的“2018期刊数字影响力100强”遴选结果公布。遴选活动的目的在于鼓励勇于探索数字化创新发展的期刊媒体，同时也为了能够更客观地反映传统期刊媒体在数字阅读世界的影响力。遴选的办法主要是通过各个期刊数字版的发行量数据和它们在社交媒体的阅读数据，并且结合各学科学术期刊的影响因子等来综合考量各个期刊在各类数字终端和数字形态领域的影响力。经过初选、复选、专家评审、社会公示，最后得出了大众类期刊和学术类期刊各100强的遴选结果。《国际口腔医学杂志》作为唯一口腔医学类期刊入选100强。

此次获奖是社会各界对《国际口腔医学杂志》数字传播影响力的认可，对期刊办刊质量的肯定，同时也对期刊未来的发展提出了更高的要求，我们仍会不断紧跟时代步伐，在数字化出版的浪潮中砥砺前行，再创辉煌。

《国际口腔医学杂志》编辑部