

机械门控TRPV4在材料诱导骨形成中的作用 机制研究进展

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摘要

具有特定理化性质的骨诱导生物材料无需外源细胞或生长因子可在远离宿主骨部位诱导成骨, 在大段骨缺损修复中极具应用前景。然而, 材料诱导成骨机制尚未阐明, 限制了材料的优化。随着学科之间的交叉融合, 近年来机械转导被广泛关注。机械转导是细胞感知材料表面微结构等介导的机械应力刺激并将其转化为生物化学信号的过程, 而细胞微环境中机械应力信号的感知主要通过机械敏感离子通道介导。瞬时受体电位香草素受体4型通道蛋白(Transient Receptor Potential Vanilloid 4, TRPV4)作为机械敏感通道是细胞感知微环境力学信号的核心分子, 在骨诱导过程中扮演重要角色。本文系统综述了TRPV4的结构、功能及其在生理性骨改建和材料诱导成骨中的作用, 并探讨了靶向TRPV4通道优化骨诱导生物材料的设计策略, 以期为新一代骨诱导材料的优化设计提供理论参考。

关键词

瞬时受体电位香草素受体4型通道蛋白, 骨诱导, 生物材料, 机械转导

Research Progress on the Mechanism of TRPV4 in Material-Induced Bone Formation

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Abstract

Bone-inducing biomaterials with specific physicochemical properties can induce osteogenesis at sites far from the host bone without exogenous cells or growth factors, showing great application prospects in the repair of large bone defects. However, the mechanism of osteogenesis induced by materials remains unclear, which limits the optimization of materials. With the cross-integration of disciplines, mechanical transduction has attracted extensive attention in recent years. Mechanical transduction is the process by which cells sense mechanical stress stimuli mediated by material surface microstructures and convert them into biochemical signals, and the perception of mechanical stress signals in the cellular microenvironment is mainly mediated by mechanosensitive ion channels. Transient Receptor Potential Vanilloid 4 (TRPV4) channel protein, as a mechanosensitive channel, is a core molecule for cells to sense mechanical signals in the microenvironment and plays an important role in the process of bone induction. This article systematically reviews the structure, function of TRPV4 and its role in physiological bone remodeling and material-induced osteogenesis, and discusses the design strategies for optimizing bone-inducing biomaterials by targeting TRPV4 channels, with the aim of providing theoretical references for the optimized design of the next generation of bone-inducing materials.

Keywords

Transient Receptor Potential Vanilloid 4, Osteoinduction, Biomaterial, Mechanotransduction

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1. 引言

小面积骨缺损机体可以自我完成修复，但对于肿瘤切除、外伤等造成的大面积骨缺损，因缺损部位远离宿主骨，其自我修复能力有限，难以实现缺损修复[1]。目前，骨缺损的临床疗法主要包括自体骨、生物衍生骨与人工合成材料移植。其中，自体骨因其无抗原性，以及具有卓越的骨传导性和骨诱导性，被奉为治疗金标准[2]。然而，自体骨移植受限于供区并发症与骨量不足，生物衍生骨存在免疫原性与安全隐患，而人工合成骨替代材料缺乏骨诱导性，即使引入生长因子也受成本与并发症制约[3]。在此背景下，具有骨诱导性的生物材料应运而生。骨诱导生物材料能够在不添加任何生长因子及种子细胞的前提下，于非骨部位(如肌肉、皮下等组织)诱导新骨形成[4]，这一特性使其在大面积骨缺损修复领域展现出广阔的应用前景。然而，驱动此过程的生物学机制仍有待阐明[5]。

随着多学科交叉融合的深入，机械转导在骨再生中的作用被广泛关注，为揭示相关机制提供了新的视角[6] [7]。机械转导是细胞将胞外机械刺激转化为胞内生化信号的过程，其起始于细胞膜上的黏附分子与机械敏感性离子通道对机械刺激的感知[8]。其中，瞬时受体电位香草素受体 4 型通道蛋白(Transient

Receptor Potential Vanilloid 4, TRPV4)作为机械敏感性钙离子(Ca^{2+})通道,在多种细胞中广泛表达,能够感知材料物理特性(如刚度、表面结构等)介导的机械应力,并调控 Ca^{2+} 内流启动下游信号转导,在骨再生中发挥重要作用[9]-[11]。本文旨在系统综述材料物理特性通过 TRPV4 通道调控骨诱导效应的分子机制与研究进展,以期对骨修复材料的创新设计与优化提供新的视角和理论依据。

2. TRPV4 通道的概述

2.1. TRPV4 通道的发现

TRPV4 是一种主要对 Ca^{2+} 具有渗透性的非选择性阳离子通道,隶属于瞬时受体电位香草素(Transient Receptor Potential Vanilloid, TRPV)阳离子通道亚家族[12]。TRPV4 于 2000 年首次被报道,因其在不同实验室呈现出的不同关键特征,被赋予多个名称,如 VR-OAC [13], TRP12 [14], OTRPC4 [15]和 VRL-2 [16]。直至 2002 年,学界才确认这些实为同一通道,并明确了其具有“混杂门控”的特性,这一特性使其能够整合多种物理及化学刺激,从而被广泛激活[17]。

2.2. TRPV4 通道的结构与功能

TRPV4 离子通道是一种由四个相同的亚基(各含 871 个氨基酸)构成的同源四聚体跨膜蛋白。每个亚基包含 6 个跨膜 α 螺旋(S1~S6),其中 S5 与 S6 之间的袢环在四聚体中心共同构成了一个允许 Ca^{2+} 通过的中央孔道[12] [18]。该通道的 N 端与 C 端均位于胞内,其上分布有多种功能结构域。其中 N 端包含富含脯氨酸的结构域(PRD),锚蛋白重复结构域(ARD)以及具有结构特征的连接域;C 端包含 TRP 结构域,钙调蛋白结合结构域(CAM)以及 PDZ 结构域。这些结构域共同参与通道的调控与相互作用[18] [19]。

作为机械敏感性离子通道,TRPV4 能够响应表面拓扑结构、基质刚度与流体剪切应力等多种物理刺激[20]。目前,其机械转导机制主要存在两种理论模型:直接激活与间接激活。在直接激活模型中,机械力引起细胞膜的形变与张力变化,从而直接诱导 TRPV4 发生构象变化并开启通道。在间接激活模型中,机械信号则通过整合素 β 1、细胞骨架蛋白或钙调蛋白等中间分子传递至 TRPV4,间接调控其开放状态[19] [21]。TRPV4 被激活后,其介导的 Ca^{2+} 内流能触发一系列下游信号通路,进而参与多种生理过程的调控,包括引导骨骼发育[22]、调节免疫相关基因[11]以及维持血管张力与力学平衡[23]。

2.3. TRPV4 在生理性骨改建中的作用

骨改建是通过成骨与破骨活动的平衡来维持骨稳态的动态过程[24]。探索骨骼细胞如何通过机械转导感知并响应力学微环境是当前的研究热点,而机械敏感离子通道正是此信号转导的首要环节[25]。TRPV4 作为一种 Ca^{2+} 可渗透的机械敏感通道,是细胞感知和转导力学信号的关键媒介。研究表明,TRPV4 可通过响应力学刺激和启动胞内 Ca^{2+} 信号来维系骨代谢稳态[26],并对成骨细胞、破骨细胞与骨细胞这三大骨骼核心功能细胞具有直接或间接的调控作用。

在成骨细胞中,TRPV4 通过感知机械刺激并将其转化为电化学信号以调控骨形成。该通道的表达随成骨细胞的分化而上调,是响应机械应力诱导钙振荡的关键通道[27]。TRPV4 激活后促进细胞 Ca^{2+} 内流,一方面直接驱动成骨细胞分化与矿化基因(如 Runx2、Col1)的表达[27];另一方面,通过激活 Rho/ROCK 通路调控应力纤维、黏着斑和细胞极性,最终影响成骨细胞的迁移[28]。反之,有研究指出,高渗应激可通过抑制 TRPV4 介导的 Ca^{2+} 内流与 Runx2 核转位,破坏骨代谢平衡[29]。以上证据均提示 TRPV4 在骨改建的机械传导中发挥重要作用。

TRPV4 在破骨细胞分化与功能调节中的作用已从多个层面得到证实。在破骨细胞分化过程中,TRPV4 基因表达显著上调,其 mRNA 水平可升高至未诱导状态的数百倍,远超其他 TRP 通道成员,提示其在破

骨细胞分化程序中的关键作用[30]。功能上, 激活 TRPV4 可显著促进破骨细胞形成, 而抑制其活性则明显减少破骨细胞数量[31]。并且 TRPV4 对成熟破骨细胞的存活至关重要, 其激动剂可在 RANKL 缺失时通过维持 Ca^{2+} 信号提升细胞存活率[32]。因此, TRPV4 是调控破骨细胞分化和存活的重要因子。

骨细胞是骨骼中的关键调控细胞, 不仅通过分泌 RANKL、OPG 等因子影响破骨细胞的活性, 还可产生多种刺激来调节成骨细胞功能[33]。作为机械敏感细胞, TRPV4 介导的 Ca^{2+} 内流是骨细胞响应机械刺激的起始信号。这一过程主要通过两种结构实现: 初级纤毛和树突网络。在初级纤毛中, TRPV4 可被流体剪切力激活导致 Ca^{2+} 内流, 进而调节成骨相关信号通路[34]。在树突形成中, 低渗刺激可通过激活 TRPV4 以启动 CDC42 信号通路, 进而调控肌动蛋白与促进树突的形成和延伸, 从而扩展其力学感知网络和调节骨重塑[35]。这些研究结果揭示了 TRPV4 在骨细胞信号转导和结构适应方面协调骨改建的作用。

3. TRPV4 通道在材料诱导成骨中的作用

在骨诱导研究领域, 材料的物理特性发挥着与生化信号同等关键的作用。这些物理信号通过细胞表面的力学感受器(如离子通道)转化为细胞内生化信号, 进而调控成骨。研究表明, 钛基材料的特定表面结构可协同信号通路和诱导巨噬细胞 M2 极化以优化骨整合[36]; 多孔支架结构则能有效加速兔颅骨缺损的修复[37]。其中, TRPV4 通道作为关键传感器, 通过感知材料刚度与拓扑结构等多种物理刺激, 介导 Ca^{2+} 内流以驱动成骨分化。

3.1. TRPV4 通道在材料物理特性调控干细胞成骨向分化中的作用

骨组织工程的核心挑战在于精准调控间充质干细胞(MSC)的成骨分化。研究表明, 此过程高度依赖于胞外的机械信号[38]。TRPV4 可将机械刺激转化为胞内 Ca^{2+} 信号, 主导材料物理特性对 MSC 成骨分化的诱导过程。

多项研究从不同物理特性维度证实了 TRPV4 在材料诱导成骨中的重要作用。它不仅响应水凝胶的粘弹性, 启动 Ca^{2+} -Wnt/ β -catenin 信号轴促进骨髓间充质干细胞(BMSC)的成骨分化[10]; 其表达与活性也受到基质刚度的调控, 在高刚度基质上培养的 BMSC 促成骨作用显著增强[9]。而 Hou 等人[39]的研究揭示, 具有微纳米拓扑结构的钛表面同样可显著上调并激活 TRPV4 通道和引发 Ca^{2+} 内流, 并驱动 Wnt/ β -catenin 信号通路与 NFATc1 核易位促进 BMSC 成骨分化。这些发现共同确立了 TRPV4 在介导材料物理特性诱导的 MSC 成骨分化中的关键地位。

3.2. TRPV4 通道在材料物理特性调控免疫微环境进而促成骨中的作用

免疫微环境在骨组织的愈合、缺损修复与再生中起着主导性作用, 其动态平衡直接决定骨缺损处的修复结局[40]。研究表明, 骨诱导生物材料的物理特性是调控此免疫微环境的关键[41]。不仅纳米晶须结构与 3D 打印齿轮状有序微结构可通过诱导巨噬细胞 M2 极化和调控其空间分布以修复大段骨缺损[42][43], 研究还进一步揭示了 TRPV4 是介导此过程的核心分子。拓扑结构、基质刚度及左手手性等多种物理信号, 均可通过激活 TRPV4 这一共同通路调节免疫细胞, 从而促进材料的骨诱导进程[11][21][44]。这些结果明确了 TRPV4 在连接材料信号与免疫微环境中的重要作用。

4. 靶向 TRPV4 通道优化骨诱导生物材料设计策略

TRPV4 通道是连接材料物理信号与细胞生物学行为的桥梁, 既能直接促进间充质干细胞的成骨分化, 也可通过调节免疫微环境间接推动骨形成。然而, TRPV4 是否通过调控破骨细胞参与该过程, 目前尚缺乏相关报道。值得注意的是, 破骨细胞在材料诱导成骨中具有关键作用。研究指出, 破骨细胞可能通过分泌多种信号分子(如 CTHRC1、S1P)诱导 MSC 的成骨分化[45], 并且在材料植入早期抑制破骨细胞形成

会阻断材料的成骨效应，而体外破骨细胞形成能力更是预测材料骨诱导潜能的重要指标[46] [47]。

鉴于 TRPV4 在机械转导和破骨细胞调控中的关键作用，我们推测材料物理特性可能通过激活该通道，精确调控破骨细胞的分化与功能，从而将其整合至由干细胞与免疫细胞共同构建的骨诱导调控网络。因此，以 TRPV4 为靶标设计新一代骨诱导材料，已成为一个极具前景的研究方向。其设计策略可以围绕两种路径展开。一是化学激活策略。在材料中负载 TRPV4 特异性激动剂并控制其在体内缓释，以直接激活 TRPV4 增强成骨。但该策略的核心问题在于药物的精准控释，剂量过低可能导致激活效果不足，而过高则易产生细胞毒性[9]。二是物理调控策略。通过优化材料的刚度、表面拓扑结构及粘弹性等物理特性，为 TRPV4 提供理想的力学刺激环境[9] [10] [39]，该方式能借助材料自身属性实现对通道天然和持续的激活，为安全高效的骨再生提供更具潜力的途径。

5. Piezo1 通道在材料诱导成骨中的作用

除了 TRPV4 通道，另一个备受关注的机械敏感离子通道——Piezo1，在材料诱导成骨过程中同样重要。Piezo1 能够直接感知细胞膜张力的变化，并通过其独特的三叶螺旋桨状结构将外部的机械信号转化为胞内的电化学信号，从而启动下游的生物学响应[48]。与 TRPV4 主要感知低强度机械信号(如基质刚度等细微变化)不同，Piezo1 主要负责响应快速、高强度的机械刺激[49]。正是这种对于刺激的差异化感知，使它们在组织中发挥多种作用，能够整合不同范围的机械信号，共同实现对复杂力学环境的应答[50]。

Piezo1 在骨细胞、成骨细胞及巨噬细胞等多种骨相关细胞中广泛表达，对骨稳态的维持至关重要。研究证实，Piezo1 对正常骨骼发育不可或缺，其功能缺失会导致骨骼结构异常和机械强度下降，从而增加骨折风险[48]。在骨免疫调节方面，机械刺激可上调巨噬细胞中 Piezo1 的表达，驱动其向特定亚型分化并分泌 TGF- β 1 等因子，从而募集骨祖细胞至成骨表面，直接增强成骨效能[51]。但该研究方法主要基于基因敲除和小分子抑制剂模型，鉴于 Piezo1 在各种细胞中的广泛表达，其在体内对其他免疫细胞亚群的影响，仍需在更复杂的动物模型中得到系统阐明。在生物材料诱导骨再生的领域，Piezo1 同样扮演着重要的角色。研究发现，二氧化钛纳米管可以通过激活 Yap 信号并上调 Piezo1 表达来促进骨再生[52]。然而，该研究更多地呈现了表型关联，即 YAP 激活与 Piezo1 上调及成骨增强同时发生，但其具体机制尚未被完全揭示，这限制了基于此结论的材料优化设计。而更具创新性的压电响应性水凝胶，能将材料自身的力学形变直接转化为特异性激活 Piezo1 的生物电信号，从而促进干细胞的软骨向分化，加速软骨修复，为骨-软骨复合再生提供了设计思路[53]。此外，与 TRPV4 可通过小分子激动剂(如 GSK1016790A)特异性激活相类似，Piezo1 的特异性激动剂 Yoda1 已被应用于骨再生研究，将其负载于微纤维支架能激活 Piezo1-F-actin-YAP 信号轴，促进巨噬细胞的 M2 极化，从而有效增强成骨分化与骨缺损修复[54]。这些研究共同表明，Piezo1 作为另一核心机械敏感离子通道，与 TRPV4 在功能上形成了重要的协同与互补，共同参与材料诱导的骨再生过程。研究二者在材料力学微环境中的交互作用将是推动该领域向精准治疗前进的关键。

6. 小结与展望

大面积骨缺损的修复是临床面临的重大挑战，其核心在于现有骨修复材料的骨诱导能力的不足。在影响材料骨诱导性能的诸多因素中，物理特性尤为关键。然而，其信号转导机制尚不明确。近年来，机械敏感性离子通道 TRPV4 已被证明能够响应材料物理特性并调控骨再生过程，提示其可能是连接材料物理性能与细胞生物学行为的关键分子。因此，未来研究的关键在于系统阐明 TRPV4 如何协同破骨细胞、免疫微环境及干细胞来调控材料诱导的骨形成过程。这不仅对理解骨诱导的生物学本质具有重要理论价值，也为设计开发新一代骨诱导材料提供了关键的靶点与策略依据。

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