·牙髓干细胞专栏·综述·

支架机械特征介导Yes相关蛋白信号调节干细胞生物行为的研究进展

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【摘要】 干细胞可感知局部微环境理化特征,传递并转导机械或化学信号以调控黏附、增殖、分化、代谢和免疫等生物行为。组织工程常通过设计人工支架模拟体内微环境机械特征对干细胞进行仿生调控,研究发现从细胞感知外界机械刺激到启动生物行为发生变化的过程中,Yes相关蛋白(YAP)发挥了重要作用。本文旨在对支架机械特征的功能,及其介导YAP调控干细胞生物行为作用机制的研究进展进行综述。

【关键词】 Yes相关蛋白; 干细胞; 支架; 机械特征; 生物行为
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Research progress of regulation of stem cell biological behavior by scaffold mechanical properties through Yes-associated protein signaling

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【Abstract】 Stem cells can sense the physical or chemical signals of the local microenvironment to regulate biological behaviors including adhesion, proliferation, differentiation, metabolism, and immunity. A common strategy of designing artificial scaffolds in tissue engineering is to simulate the mechanical properties of the microenvironment *in vivo*. Growing evidence suggests that Yes-associated protein (YAP) plays an important role in the process by which stem cells recognize external mechanical cues and transform the information into cellular responses. In this review, we summarized the research progress on the mechanical properties of scaffolds and the mechanism of YAP in regulating stem cell biological behavior.

【Key words】 Yes-associated protein; Stem cells; Scaffold; Mechanical properties; Biological behavior

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干细胞聚集的微环境常称为“干细胞生态位”,该微环境因细胞类型而异,包含多种生化和机械信号协同调节干细胞的增殖及分化[1]。多年来,生化信号如生长因子一直备受关注,然而机械信号对干细胞的作用尚不明确[2]。在器官发育过程中,细胞与细胞外基质(extracellular matrix,ECM)成分接触[3-4],后者具备微米/纳米孔和纤维结构,其硬度和形貌等通过机械信号转导途径影响细胞生物行为[5-7]。因此,众多学者尝试通过调控生物支架的机械特征模拟体内机械微环境,以促进干细胞的定向分化。

细胞从感知外环境机械刺激到发生基因转录水平变化称为机械信号转导,该过程涉及肌动蛋白细胞骨架的快速重构并激活特定基因,从而影响细胞生物行为[8-9]。近年来研究发现,Yes相关蛋白(Yes-associated protein,YAP)是机械信号转导过程中的关键基因[10-11]。本文对支架材料机械特征介导YAP信号调节干细胞生物行为的作用和机制进行归纳总结。

一、组织工程支架的机械特征

组织工程支架的主要作用是提供利于细胞黏附、增殖及分化等细胞生物行为的微环境;其次是运输营养物质,排泄代谢物;再次是基于力学性能引导组织按预定形态生长。支架的类型常分为生物提取、人工合成和复合型三种,可通过设计特殊机械特征调节干细胞生物行为。支架机械特征包括物理特征及拓扑结构。前者包括硬度及亲疏水性等,后者包括材料孔径及孔隙率、表面形貌等,其中表面形貌也可区分为微观形貌即表面微米纳米形貌或粗糙度,以及宏观形貌即表面图案等。通过不同加工技术或合成复合材料可改变支架的机械特征,如冷冻和交联技术可以合成硬度、孔隙度不同的胶原蛋白培养支架[12],静电纺丝技术、相分离技术、溶剂浇铸技术、褶皱基底表面作为模具或与生物提取材料组成复合支架可精准控制人工合成的有机聚合物纤维排列方向、孔径、孔隙率、硬度及空间形态[13-25]。部分拓扑结构的设计会对硬度产生一定的影响,如过大孔隙率会降低材料的机械强度[26]。

二、支架机械特征对干细胞生物行为的影响

1. 支架物理特征对干细胞生物行为的影响:支架的硬度

设计需依据干细胞定向分化的类别[20]。间充质干细胞(mesenchymal stem cell,MSC)倾向于在与自身ECM硬度相近的材料上增殖及分化为特定表型[27]。角膜缘上皮干细胞在15 kPa较软的Ⅰ型胶原(collagen type Ⅰ,COL Ⅰ)水凝胶中表现为迁移速度减慢,增殖率增高[12]。MSC在软(0.1~1 kPa)、中间(20~25 kPa)或硬(30~45 kPa)基质中分别向神经源性、软骨源性或成骨源性谱系分化[28]。当海藻酸盐聚合物3D水凝胶支架硬度为2.5~5 kPa,MSC可分化为成脂肪细胞[29]。在6~135 kPa范围内,随底物硬度的增加,牙周膜干细胞(periodontal ligament stem cell,PDLSC)的增殖与成骨分化能力增加[30]。支架表面亲疏水性也是决定细胞黏附行为的重要因素之一,在亲水表面上,细胞通常表现出良好的黏附、铺展、增殖和分化[31],如亲水性静电纺丝聚己内酯/明胶(PCL/Gel)三维支架利于人PDLSC的黏附、增殖及牙周再生[32]。

2. 支架拓扑结构对干细胞生物行为的影响:支架的拓扑结构通过影响细胞黏附与迁移诱导下游信号级联调节细胞分化。一般认为,孔径和孔隙率大小以模仿ECM结构为宜。以成骨细胞为例,孔径>600 μm的支架因降低材料总表面积不利于细胞黏附,而孔径<100 μm的支架因阻止细胞迁移至材料内部难以形成血管,不利于为成骨提供足够的营养[33]。超过60%孔隙率的支架材料可以增加材料的总表面积和连接性,促进成骨细胞黏附[34],如孔隙率为90%左右的聚乳-共-己内酯[Poly(L-Lactide-co-caprolactone),PLCL]海绵支架可刺激MSC的旁分泌作用促进成骨分化[35]。此外,粗糙度较高的材料可促进细胞黏附,由于其具有更好地吸附黏附蛋白能力。如粗糙度约为2 μm的羟基磷灰石(HA)支架较粗糙度约为1 μm的支架更促进成骨细胞黏附[36]。还可通过改变纤维排列方向及直径而调整一些支架的拓扑结构,促进干细胞平行排列且延展,如纤维方向对齐的聚氨酯丙烯酸酯(potentially unwanted applications,PUA)支架可促进MSC平行排列及延展从而促进成骨分化[25],纤维直径为2.76 μm较直径为0.5 μm左右的聚氨酯[poly(ether carbonate urethane)urea,PECUU]支架更能促进纤维环干细胞(annulus fibrosus-derived stem cell,AFSC)平行排列及成纤维细胞向分化[37]。

在口腔医学领域,已有利用拓扑结构对细胞生物行为影响设计的支架投入临床使用。例如应用于牙周组织再生引导术的Bio-Gide®是一种双面胶原膜,分为光滑面和粗糙面,成纤维细胞在光滑面沿着胶原纤维生长,起到物理阻隔作用,而成骨细胞可在生物膜粗糙面附着、伸长并长入膜内部,利于细胞成骨向分化[38-39]。

三、Yes相关蛋白响应支架机械信号的分子机制和功能

1. 支架机械信号激活YAP的分子机制:大量研究显示,YAP是机械信号转导过程的核心蛋白。YAP是Hippo通路的转录共激活因子和重要的下游效应子。Hippo通路能感知机械环境并通过蛋白激酶链的激活直接磷酸化YAP/Tafazzin蛋白(Tafazzin,TAZ)[10-11,40-41]。当Hippo信号通路被激活时,大肿瘤抑制因子1/2(large tumor suppressor 1/2,LATS1/2)磷酸化激活YAP/TAZ,使YAP/TAZ滞留在细胞质中被泛素化降解,从而阻碍下游靶基因的表达[42-43],Hippo信号关闭时,YAP处于激活状态进入细胞核内与转录因子TEAD(TEA domain)结合,诱导一系列与细胞增殖等相关的基因表达[44]。

机械信号转导过程中,细胞首先感知并传递机械信号于胞膜表面的整合素受体(integrins),影响黏着斑(focal adhesion,FA)形成,继而促进细胞骨架重构调节YAP活性。FA由整合素、黏着斑激酶(focal adhesion kinase,FAK)和肉瘤基因(sarcoma gene,Src)组成,是细胞黏附的重要组分并影响F-actin细胞骨架排列。在机械刺激作用下,整合素结合的踝蛋白(Talin)展开暴露黏着斑蛋白(vinculin)的结合区域,以促进FA成熟、细胞骨架重构和YAP/TAZ激活入核,触发一系列转录因子的表达,最终影响细胞的增殖和分化[37,45-48]。另外,RAS同源基因家族成员A(ras homolog family member A,RhoA)/Rho激酶(Rho-associated kinase,ROCK)信号通路也可通过重塑细胞骨架调节YAP/TAZ活性[40,49]。Hippo信号通路中的LATS1/2激酶活性也可以由F-actin调节,并有助于YAP/TAZ机制转导[50]。YAP参与机械信号传导的信号通路模式图见图1。

2. 支架机械信号介导YAP的相关交互通路:YAP在机械信号转导过程中的功能与转化生长因子β(transforming growth factor-β,TGF-β)、经典WNT信号通路及机械敏感性离子通道PIEZO相关。然而,有关上述通路响应机械刺激的功能研究结果尚存在差异。

全转录组RNA测序揭示明胶/透明质酸混合水凝胶的机械微环境促进MSC分化与TGF-β/Smad信号通路和Integrins/YAP/TAZ信号通路相关[51]。2.4 GPa硬度的PUA纳米图案支架可促进血管平滑肌细胞(vascular smooth muscle cell,VSMC)的YAP/TAZ和TGF-β下游信号Smad2/3的核定位,而同时抑制YAP/TAZ时Smad2/3的核定位减少[52]。在杨氏模量分别为1.0 kPa和75 kPa的聚丙烯酰胺水凝胶支架对NIH3T3成纤维细胞作用的实验中,发现硬度低的水凝胶可增强*TGF-βI/TAZ*促进*COL* Ⅰ表达[53]。

在三维PDMS支架额外施加静态压缩力,发现WNT经典信号的主要效应物*β-catenin*表达减少而*YAP/TAZ*表达增加,ESC发生软骨向分化[49]。纳米拓扑结构钛板可诱导鼠前成骨细胞胞质YAP降解,增加β-catenin在胞核中运输和积累,激活TCF/LEF转录因子,导致更强的成骨分化,提示YAP与*β-catenin*表达呈负相关[54]。而增加纳米矿化胶原糖胺聚糖MC-GAG支架的硬度可以同时激活YAP和β-catenin通路诱导成骨分化[55]。

此外,孔径逐渐缩小的沸石咪唑骨架-8改性纤维蛋白生物支架可介导PIEZO1(piezo type mechanosensitive ion channel component 1)和YAP信号促进MSC成骨分化[56]。使用聚D,L-乳酸/聚乙二醇和聚乙二醇/聚己内酯材料制作软骨样水凝胶培养软骨细胞,在附加压缩应力后第3天YAP和RhoA的表达达到峰值,而且随着培养时间的延长,细胞内PIEZO1和瞬时感受器电位离子通道V4(transient receptor potential cation channel subfamily V member 4,TRPV4)蛋白水平逐渐

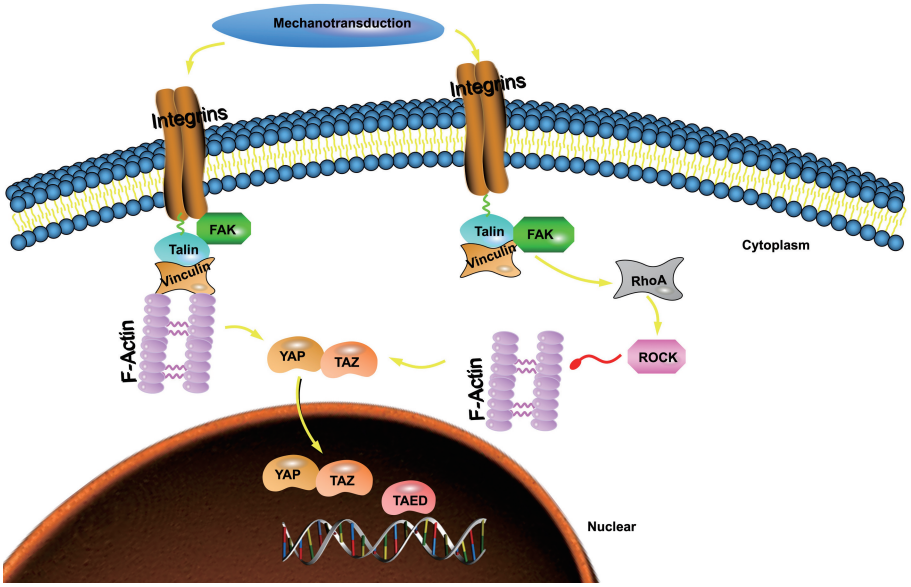

图1 Yes相关蛋白(YAP)参与机械信号传导的信号通路模式图 Integrins:整合素受体;Talin:踝蛋白;Vinculin:黏着斑蛋白;Src:肉瘤基因;FAK:黏着斑激酶;F-actin:F-肌动蛋白;RhoA:RAS同源基因家族成员A;ROCK:Rho激酶;LATS1/2:大肿瘤抑制因子1/2;TAZ:Tafazzin蛋白;TEAD:转录因子TEAD。

升高[57]。大多数研究认为YAP是PIEZO1的下游,当细胞感受外界机械环境改变,细胞膜离子通道打开,PIEZO1表达增多,促进胞质YAP核易位[58]。利用硅胶材料制备硬度不同的支架培养神经干细胞时,发现0.7 kPa低硬度的支架相比750 kPa高硬度的支架可促进PIEZO1表达升高和YAP核易位,当敲低PIEZO1时,YAP核易位受抑制[59]。降低工程纳米管的弹性和增加黏度可激活肠上皮细胞PIEZO和下游p38蛋白激酶-YAP通路,促进细胞增殖分化[60]。

3. 支架机械特征介导YAP信号影响干细胞生理功能:支架的机械特征一般通过促进干细胞黏附,平行排列和形态延展,激活YAP信号调控细胞的增殖、迁移和分化。2.0 μm纤维直径的静电纺纳米纤维支架促进人类脐静脉内皮细胞(human umbilical vein endothelial cell,HUVEC)细胞骨架收缩性增加,YAP入核,利于细胞增殖和迁移,当添加YAP抑制剂时,HUVEC的增殖受限、迁移速度降低[61]。纤维对齐的PECUU静电纺丝纤维支架能促进AFSC黏着斑成熟,促进细胞黏附及平行排列且延展,通过刺激YAP核易位增加成纤维相关蛋白COLⅠ的表达,添加YAP抑制剂后COLⅠ蛋白表达降低[37]。支架孔径或硬度影响YAP信号调控干细胞分化的特点不一。大孔径聚-L-乳酸(poly-L-lactic acid,PLLA)支架利于维持MSC的细胞干性,促进MSC的YAP入核和成骨分化,添加YAP抑制剂后,成骨特异性转录因子(runt related transcription factor 2,*RUNX2*)及干细胞标记CD44表达降低[13]。低温沉积PLCL海绵支架在孔径为(15.7±6.3) μm时可促进黏着斑成熟,通过YAP信号通路刺激MSC的旁分泌,增强体外血管生成相关基因血管内皮生长因子(vascular endothelial growth factor,*VEGF*)的表达,添加YAP抑制剂后,*VEGF*基因表达水平大幅下调[35]。硬的支架常激活YAP信号诱导成骨分化,如杨氏模量为(525.5±67.2) kPa的矿化水凝胶激活骨髓MSC的细胞骨架组装,增强了YAP和RUNX2的表达和核共定位[62]。软的支架则抑制YAP功能促进脂肪分化,如压缩模量为0.5 kPa的较软明胶水凝胶支架材料通过降低YAP磷酸化介导骨髓MSC成脂肪相关基因脂蛋白脂肪酶(lipoprotein lipase,LPL)等生成[63]。

研究显示,支架机械特征还可介导YAP信号影响干细胞的自噬、代谢、免疫和释放细胞外囊泡等功能,为进一步分析YAP在机械转导信号中的角色提供了新思路。如纳米级拓扑结构较微米级钛支架更能诱导鼠前成骨细胞出现较强的自噬反应,降解细胞质YAP,促进细胞成骨[54]。与孔径为450 μm的多孔径HA支架相比,高密度MSC在孔径为250 μm的支架上培养时,细胞代谢需求增高,缺氧诱导因子1α(hypoxia inducible factor-1α,HIF-1α)信号和*YAP*表达增多,刺激血管形成,考虑支架机械特征通过影响细胞代谢调节Hippo通路[47]。此外,纤维方向对齐的PLLA静电纺丝支架及平均孔径为(15.7±6.3) μm的PLCL与HA多孔复合支架促进MSC产生免疫调节因子刺激巨噬细胞M2型极化,增加YAP表达及核定位,在此基础上添加YAP抑制剂降低免疫调节因子表达,表明该免疫调节特性可能部分由YAP/TAZ信号介导[16,41]。Guo等[64]发现,MSC在商用Fibra-Cel支架中培养附加流动力刺激可促进YAP核易位及细胞外囊泡(主要为外泌体)的产生,认为细胞外囊泡的释放显著增加可能由YAP机械感受性介导。

四、总结展望

组织再生一直是近年来的研究热点,但目前可真正应用于临床的人工支架仍不多见,推测与支架种类繁杂多样、分子机制复杂、体内外研究差异等多种因素有关。YAP家族是

机械信号转导中的核心蛋白,受支架硬度或拓扑结构激活后对细胞增殖、免疫、代谢等发挥重要影响。深入探讨YAP信号通路响应机械调控的分子机制将为提升支架性能和实现支架同一化提供可靠分子依据。

利益冲突 所有作者均声明不存在利益冲突

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