骨 科 学

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关节软骨微环境的物质输运研究进展

窦霄云,裴启霖,饶习耘,王 彬
(重庆医科大学生命科学研究院医学实验技术教研室,重庆 400016)

【摘 要】关节软骨是最常见且研究最多的一种透明软骨;其软骨细胞的物质输运主要由扩散和对流 2 种方式完成。在关节软骨的胞外基质内,生物活性分子的扩散和对流输运在组织生理调节和细胞生物学响应中起到极为重要的作用。近年来,关节软骨与软骨下骨的交互作用备受关注;其交互作用在骨关节炎的发生发展中不容忽视。本文主要对关节软骨内、关节软骨与软骨下骨间物质输运的实验研究进展进行综述,旨在为研究关节软骨微环境的生理病理作用提供一定参考,并为临床治疗骨关节炎提供一定的新思路。

【关键词】关节软骨;软骨细胞;软骨下骨;钙化软骨;物质输运
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Research progress of solute transport in the microenvironment of articular cartilage

Dou Xiaoyun, Pei Qilin, Rao Xiyun, Wang Bin
(*Teaching and Research Section of Medical Laboratory Technology, Institute of Life Sciences, Chongqing Medical University*)

【**Abstract**】Articular cartilage is the most common hyaline cartilage which has been studied the most. The solute transport of chondrocytes includes diffusion and convection. In the extracellular matrix, diffusion and convection of bioactive molecule plays an important role in physiologic adjustment and cytobiological response. For the last few decades, the interaction of subchondral bone and articular cartilage has been investigated, which is considered as an important aspect in the etiology of osteoarthritis. In this paper, we have reviewed studies of solute transport in articular cartilage and the interface of cartilage and subchondral bone, aiming to provide references to environmental pathophysiological function of articular cartilage and provide new thoughts for treating clinical osteoarthritis.

【**Key words**】articular cartilage; chondrocytes; subchondral bone; calcified cartilage; solute transport

1 关节软骨与软骨细胞

关节软骨是最常见且研究最多的一种透明软骨,是骨骼系统的重要结构之一;其表面光滑、富有弹性,保证了关节的光滑[1]。关节软骨主要作用之一为分散机械应力,为关节活动提供低摩擦表面。与其他多数组织不同,关节软骨不具有血管、神经和淋巴系统等;正常的关节软骨是由软骨细胞组成,包封于细胞外基质内。关节软骨的胞外基质主要由Ⅱ型胶原组成,是软骨组织力学性质的关键因素[2]。胶原是关节软骨组织中决定张力的因素。在力学刺激下,通过自身聚集效应,形成定向排列的密集纤维结构以维持软骨组织的稳定性[3-4]。

软骨细胞是关节软骨中唯一存在的细胞类型,占关节软骨体积的 2%~10%,可合成和组装胞外基质[5]。依据胶原纤维超微结构和胞外基质,软骨细胞被分布于不同的亚群或区域。依据与软骨表面的距离,关节软骨大致分为浅层(表层,与滑膜液靠近)、中层、深层和钙化软骨层(与软骨下骨相邻)。软骨下骨(从软骨下到松质骨组织)毗邻深部软骨处为钙化软骨区;钙化软骨区是软骨到软骨下骨的过渡,将非钙化软骨固定于骨上[6]。与胞外基质的组分与组成相似,软骨细胞的大小、形状、排列方向和生物合成活动在不同区域具有显著

作者介绍:窦霄云,Email:yunyuexiaoyu@163.com,
研究方向:骨关节生物力学与组织修复。
通信作者:王 彬,Email:bwang@cqmu.edu.cn。
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差别[7-11]。不同区域软骨细胞的合成与分解代谢受关节胞外基质、机械载荷和可溶性介质（如生长因子、细胞因子）的影响差异明显。随着年龄和关节异常的出现，软骨细胞对这些环境因素的响应也可以发生很大的改变，并可能导致关节退化等。

2 关节软骨物质输运的主要形式

2.1 关节软骨的溶质扩散

物质输运在组织器官的生理调节和细胞生物学响应中起到了极为重要的作用。人们对软骨细胞的溶质输运已有一定了解，软骨细胞的物质输运通过扩散和对流 2 种方式完成[12]。关节软骨主要依靠扩散进行养分、排泄物、信号分子和氧的输运[13-14]。软骨内分子输运通过扩散系数和分配系数来衡量，扩散系数受到软骨内胶原和蛋白多糖结构组织的影响。关节软骨是无血管组织，其扩散行为主要通过化学势梯度趋动完成[15-17]。在猪软骨内，分子量 70 kD 的葡聚糖在浅层的扩散系数是中层内或深层内的 0.3 倍[18]。Quinn TM 等[19]研究发现，软骨内不带电荷的分子（如葡聚糖等）扩散系数与蛋白多糖含量成反比，且在静态压缩下会减小。在关节软骨内，胶原构成纤维网架的胞外基质结构，蛋白多糖则维持关节软骨的良好弹性。软骨胞外基质是软骨细胞汲取营养物质和传递信号的载体，其代谢平衡维持关节软骨的生物学性能。基质中的蛋白多糖作为分子筛，对溶质的扩散和分配具有决定性影响[20]。蛋白多糖的网状系统对中性小分子的扩散及分配影响相对较小；但对于蛋白质等大分子，由于空间相互作用较大，影响程度与溶质的形状与大小相关。就白蛋白而言，其软骨内的扩散率比自由扩散溶液内低一个量级，其分配系数甚至小于 0.01[21-22]。O'Hara BP 等[15]认为大分子主要通过软骨循环挤压载荷引发的对流输运进行传递；Torzilli PA 等[23]和 Quinn TM 等[24]研究均显示无对流存在的情况下，静态加载溶质转运率明显减小。

2.2 关节软骨的溶质对流

软骨对机械载荷的承载使人们不得不思考溶质对流在力传导中的重要作用。Salter RB 等[25]的体内研究和 Sah RL 等[26]的关节外植体研究均指出动态载荷影响细胞介导的重塑。动态挤压状态下软骨内溶质输运的机制较为复杂；流体流动可能提高软骨基质内的对流；而基质的压缩则可能导致分子扩散率的降低。因此，动态挤压下软骨溶质输运参数的研究对理解软骨细胞的生物学响应非常重要[27]。在软骨内的溶质扩散被广为认知的同时，动态挤压状态下软骨的溶质对流表征研究少之甚少。Kapur V[28]和 Johnston ST[29]等于 20 世纪末开始研究软骨状凝胶的溶质对流。Ferguson SJ[30]和 Mauck RL[31]等研究团队于 21 世纪初均建立动态挤压软骨对软骨溶质对流影响的模型；Evans RC 等[32]于 2006 年系统研究了动态挤压下软骨的溶质对流，其研究结果强调挤压引发的改变对扩散和对流均有重大影响，且溶质的形貌和溶质与基质的相互作用对整个溶质输运过程有明显的影响。

3 关节软骨与软骨下骨间的物质输运

3.1 软骨下骨力学载荷的变化参与骨关节炎的发生发展

关节软骨与软骨下骨在关节的载荷承重中起相辅相成的作用。骨关节通过钙化软骨层和软骨下骨将骨与软骨相互联系在一起，软骨与软骨下骨被认为是骨关节炎（osteoporosis，OA）发生发展的关键复合结构。关节软骨随着 OA 的不断加重，磨损会越来越严重，同时因为软骨的变化，软骨下骨也会发生相应力学变化，进一步导致关节软骨的力学缓冲下降，加重软骨的损伤[33]。研究显示当 OA 患者的关节载荷承载区受到影响后，软骨下骨会出现骨转换的增加和形貌上的改变（如硬化、囊肿和骨赘的产生）。Chiba K 等[34]研究发现，OA 软骨下骨髓病变的出现与微裂痕有关；在 OA 的发展阶段，微裂痕和骨髓病变主要继发于异常的力学负荷[35]。Stender ME 等[36]的研究结果表明，钙化组织的渗透性对软骨和软骨下骨的力学反应无明显影响，但在软骨下骨发生微骨折时可显著提高其力学反应，因此软骨下骨的微裂缝会导致对软骨的张力和剪切力负荷增加，最终导致关节退变[37]。

3.2 软骨下骨在力学刺激下产生的信号分子或参与骨关节炎的发生发展

研究发现，对 OA 患者软骨下骨硬化区和非硬化区的成骨细胞施加周期性压应力，核因子-κB 受体活化因子配体（receptor activator of NF-κB ligand，RANKL）和基质金属蛋白酶（matrix metalloproteinases，MMPs）的表达均增加[38-39]。骨形成指标（胰岛素样生长因子 1）、骨吸收指标（RANKL、MMPs）、血管生成指标（血管内皮生长因子）及生化反应指标（白介素-6、白介素-8）的改变显示了机械压应力刺激对骨组织合成分解和代谢有显著影响，这些变化在软骨下骨重塑时释放细胞因子和生长因子，该因子可能转移进关节软骨。研究指出这些信号可能启动骨关节炎，并导致正反馈和负反馈的恶性循环，从而加剧骨关节炎的发展，但这些因子的性质和输运通路至今仍未得以界定。

3.3 软骨下骨与关节软骨间的物质输运参与骨关节炎发生发展的可能性

一般认为，连接关节软骨与软骨下骨的钙化软骨对于溶质或气体的输运是不可渗透的[40-42]；但近年的研究结果对此观点提出了挑战。首先直接传递途径已被发现。解剖学研究

发现了血管通道连接于软骨下骨与关节软骨之间，此血管通道侵入钙化软骨，且老龄化和骨关节炎关节内出现概率更大[43-45]；此外微裂痕和结构缺陷在成年关节内被发现，尤其在过度使用、创伤或骨关节炎引发的退化关节内[46-48]。近期研究通过罗丹明和荧光素等小分子灌流测量表明了这些通路的存在[49]。其次，在这些组织内产生的各种细胞间生物学相互作用已得以证实；这些相互作用揭示通信生物化学机制的存在。共培养研究显示，浅层表面软骨细胞的功能和表型受深层组织（包括钙化软骨层和软骨下骨成骨细胞）的调控[50-52]。Westacott CI[53]和 Martel-Pelletier J[54]等对这些通信信号的具体性质进行了研究。

目前对软骨物质输运的研究主要通过各种相应的荧光检测技术对扩散系数等进行测量。较常用的物质输运检测方法主要有荧光光漂白恢复法（fluorescence recovery after photobleaching，FRAP）[55]，光漂白荧光缺失法（fluorescence loss in photobleaching，FLIP）[56]，三维扫描显微法[57]、荧光关联谱法。Lee JI 等[58]采用荧光关联谱法直接测量了软骨胞外基质的扩散行为，此新型灵敏性检测技术可为检测扩散分子提供很大帮助。

本研究团队的前期研究对软骨下骨与关节软骨间的物质输运潜在性进行了探索。采用 FLIP 对正常成年小鼠的膝关节钙化软骨和骨-软骨接口小分子示踪剂（荧光素钠）的通透性进行了原位量化研究[56]。所测关节内的溶质输运结果对“软骨下骨和钙化软骨间不可透性”观点提出了挑战。研究证实骨关节炎可导致关节组织结构和材料性能的变化[59-63]；且骨关节炎关节的血管道[44-45]和微裂痕[48,64]可作为物质输运管道。然而骨关节炎关节基质性能和结构改变对骨-关节交互作用的影响研究甚少。

4 总结与展望

骨关节炎是一种退化性关节疾病，其特征为关节软骨和关节周围的软组织和硬组织（包括骨）流失[65]，而且软骨和软骨下骨之间的生物力学相互作用也是 OA 发生发展的一个重要因素[66]。骨关节炎是一种涉及整个关节疾病的这一观点越来越被肯定[67-68]。尤其是 OA 患者和动物模型软骨下骨的骨转换增加，使得人们产生一种假想：在软骨下骨骨转换过程中释放的各种细胞因子和生长因子可能传至上覆关节软骨，并激发软骨与引发 OA 骨修复过程间的正反馈循环[69]。近期此假想得到一定的实验数据支持。OPG 的使用不仅阻止骨小梁骨损失，还阻止手术 OA 模型的软骨退化[70]。聚合蛋白多糖 II 缺失型小鼠关节不稳定不会引发软骨退化；与野生型相比，软骨下骨变化不大[59]。在细胞水平，骨关节炎患者的成骨细胞诱导正常在体软骨细胞的肥大分化和基质矿化[71]。

总之，尽管以上研究为间接依据，但软骨下骨与关节软骨间的交互作用的观点在关节炎关节研究中已经确立；进一步对原位环境下 OA 软骨下骨与软骨间溶质输运进行研究将为两者的交互作用及其生理作用提供一定的参考价值。

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