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基质 Gla 蛋白对骨性关节炎的影响

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[摘 要] 基质Gla蛋白(matrix Gla protein，MGP)是一种维生素K依赖性蛋白，在人体内起抑制血管和软骨钙化的作用，对骨形成和软骨退变具有重要影响。骨性关节炎(osteoarthritis，OA)作为老年人常见的退行性关节疾病，其具体的病理生理机制至今仍不明确。了解MGP在OA病理生理学所发挥的作用影响对探讨OA发病机理有重要意义。

[关键词] 基质Gla蛋白；骨性关节炎；维生素K；生物标志物

Effect of matrix Gla protein on osteoarthritis

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Abstract Matrix Gla protein (MGP) is a kind of vitamin K-dependent protein, which inhibits the calcification of blood vessels and cartilage in the body and has an important effect on bone formation and cartilage degeneration. Osteoarthritis (OA) is a common degenerative joint disease in the elder. Its specific pathophysiology is still unclear. It is a great significance to understand the effect of MGP on the pathophysiology of osteoarthritis and to explore the pathogenesis of OA. In this review, MGP and osteoarthritis with its related signaling pathways and related factors are reviewed.

Keywords matrix Gla protein; osteoarthritis; vitamin K; biomarkers

骨性关节炎(osteoarthritis，OA)是一种中老年人关节慢性退行性异质性疾病，膝关节最常受累。全球范围内，10%男性和18%女性患有OA，其中60岁以上有临床症状的OA患者占60%~65%，80%OA患者存关节活动障碍[1]。随其病情的加重可引起关节肿胀、疼痛、僵硬、甚至不可逆性的关节功能丧失和畸形。目前OA的病因由多因素组成，包括遗传学、吸烟、生物力学损伤、生化代谢学等因素，并与骨质疏松有密切联系[2-3]。OA病理特征为关节软骨代谢异常、关节软骨退变，进而形成负重区软骨丢失、软骨下骨硬化、关节周围骨质增生形成骨赘、滑膜和滑液非特异性炎症[4]。目前对OA的诊断及评价其严重程度主要通过患者的临床症状和影像学表现。在血液和关节液中寻找一种新的生物学标志，以助于OA的早期诊断，评估OA病理进展及治疗效果目前已成为OA研究新方向，并对OA的发病机制提供指导作用[5]。

基质Gla蛋白(matrix Gla protein，MGP)是一

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种分子质量为14 kD(1 D=1 u)的维生素K依赖循环蛋白，最初在牛骨骼中被分离提取。Cancela等[6]应用DNA探针技术克隆人类MGP基因，发现其位于12号染色体短臂上，长度为3.9 kb，有4个外显子、3个长序列内含子。其具有5个可羧化的谷氨酸残基和多个可磷酸化的丝氨酸残基，在血清和滑液中以不同种分子形式存在，包括：磷酸化MGP、非磷酸化MGP、羧酸化MGP、非羧酸化MGP(ucMGP)[7]。非活性的MGP可通过维生素K2依赖转化酶：γ-羧化酶和磷酸化酶，转换非活性MGP蛋白残基，形成磷酸化或羧酸化MGP蛋白，从而调节其活性。MGP在软骨细胞和骨骼组织中可调节骨钙化和软骨分化[8]。在循环系统中，血管内皮细胞分泌MGP可抑制血管异位钙化[9]。Khan等[10]在乙二醇诱导大鼠肾草尿酸结石模型中发现：肾小管上皮细胞表达MGP显著增加。

1 MGP 和 OA 的关系

MGP可在患者的血清和膝关节滑液中以非活化的形式ucMGP定量检测[11]。Silaghi等[12]报道：在OA患者中，炎症组膝关节滑液中ucMGP明显高于非炎症组，并与ESR呈正相关，但OA患者血清和滑液中的ucMGP明显低于对照组。Bing等[13]报道：在178名OA患者中，膝关节滑液中的ucMGP含量与患者影像学严重程度(按Kellgren-Lawrence分级)呈明显负相关；血清ucMGP明显低于对照组，与影像学严重度无意义，可能因为样本数量少，或其他疾病对血清ucMGP浓度有所干扰。Misra等[14]研究表明：MGP基因多态性与手部OA密切相关。综上，血清MGP和滑液MGP浓度与OA临床诊断和OA进展程度密切相关，MGP也可以作为一种新的诊断OA并评价其严重程度的生物标志物。现未有患者治疗OA(手术、药物、安慰剂等)前后ucMGP浓度水平对照实验，尚需进一步研究验证。

2 MGP 对 OA 的调节作用

维生素K依赖性羧化酶可将未活化的MGP蛋白的γ-Gly残基转化为γ-Gla残基使其活化，从而发挥其抑制异位骨化的作用。γ-Gla残基与被磷酸化后的基团可在血管内皮表面与局部的钙离子螯合，降低局部钙离子浓度，抑制局部钙沉积[15]。研究[16]报道：MGP可以与骨形态蛋白-2(bone morphogenetic protein-2，BMP-2)螯合，从而降低局部BMP-2浓度，抑制其成骨钙化作用。MGP可以和纤维蛋白的特定位点III1-C结合，从而增强细胞黏附性，抑制局部病灶形成[17]。Wallin等[18]在膝关节软骨细胞和囊泡中发现：由肝合成的胎球蛋白与羧酸化的cMGP结合形成胎球蛋白-MGP络合物(fetuin-MGP complex，FMC)，并证明OA患者FMC的缺乏与OA软骨钙化密切相关。以上结果均说明MGP具有抑制钙盐沉积、抑制软骨钙化、调节软骨和软骨下骨分化的作用，可作为OA疾病的一种保护性蛋白。

3 OA 相关信号通路和调节因子与 MGP 的联系

Notch信号通路已被证实为膝关节炎的经典信号通路，其在健康成人膝关节软骨中几乎没有表达，但在退变或钙化的软骨细胞中大量表达，并参与软骨细胞的自我修复[19]。Yao等[20]发现：MGP缺乏可增强Notch信号通路中受体蛋白Jagged1和Jagged2活化，调控Notch信号通路的表达。此外White等[21]发现：Notch1可直接调节MGP表达，并通过特定的增强子与信号通路中CSL结合位点结合，调控MGP基因转录。

ERK1/2信号通路可调控软骨细胞增殖，细胞外基质合成，促进软骨钙化和关节缘骨赘形成，对OA骨代谢具有重大意义[22]。Julien等[23]研究发现：无机磷酸盐可通过ERK1/2信号通路使ATDC5软骨干细胞和生长板软骨细胞调节MGP表达升高。后续研究[24]发现：在Fra-1基因敲除的小鼠中，无机磷酸盐也可以通过ERK1/2信号通路调节成骨细胞表达MGP。随后Khoshniat等[25]证明：无机磷酸盐在钙离子调控下，通过ERK1/2信号通路促进成骨细胞分泌MGP和骨桥蛋白(osteopontin，OPN)。

Runx2是Wnt/B-catenin信号通路重要的转录因子之一，可调控间充质细胞向成骨细胞分化[26]，调控成骨相关因子(骨钙素、I型胶原、OPN等)表达，促进成骨细胞发育，并调控人OA软骨细胞MMP-13的表达，参与软骨退变，与OA疾病发展密不可分[27]。Fazenda等[28]通过体内和体外实验证实：Runx2也可激活MGP基因，调控MGP表达，并外源性使Runx2过度表达，上调MGP转录。Suttamanatwong等[29]研究证明：甲状旁腺激素通过调控Runx2从而调节成骨细胞MGP基因转录。

已有研究[30]证实：HtrA1是一种新的矿化调节因子，并与病理钙化相关。Polur等[31]发现：在OA基因敲除小鼠模型中，关节软骨中的Htra1 mRNA转录表达水平是野生型的8倍，且Htra1与盘状结构域受

体2(discoidin domain receptor 2，DDR2)在软骨表达上呈正相关，证明Htra1在OA软骨退变中起重要作用。研究[31]发现：HtrAl在软骨细胞中可剪切MGP蛋白，抑制MGP蛋白发挥作用，从而调节矿化。

肥胖是OA的最重要危险因素之一，不仅可使关节负重增加，其相关因子也可调节骨生成[32]。瘦素是一个由肥胖基因编码的小的脂肪细胞源性激素，可通过促进软骨细胞合成IL-1产物、MMP-9和MMP-13等炎性因子，对关节软骨和滑膜产生不利影响[33]。Zeadin等[34]发现：瘦素可通过抑制糖原合成酶激酶3β(GSK-3β)，下调MGP表达。

4 维生素 K 与老年 OA

临床上维生素K主要用以治疗新生儿维生素K缺乏症、辅助骨质疏松用药和防止血管钙化。Neogi等[35]研究发现：672名OA患者中，血清维生素K浓度处于低值，提示维生素K与膝OA密切相关。Oka等[36]对719名日本农村居民进行膳食营养素摄入量与OA疾病的调查，发现：在每日营养素摄入中，只有维生素K的摄入量与OA的患病率呈负相关，并与膝关节间隙狭窄程度呈负相关。Misra等[37]对1 180名美国社区居民进行调查，结果显示：血浆维生素K浓度与OA患病率相关。Ishii等[38]通过定量分析OA患者膝关节置换术后的股骨髁维生素K2，发现：与股骨外侧髁相比，股骨内侧髁OA程度严重，但维生素K2浓度却远远小于外侧髁。这与OA患者肢体重力线向内侧倾斜，内侧髁症状较严重吻合，从而推测维生素K2参与软骨退化、软骨下骨硬化。MGP作为维生素K依赖蛋白，在OA机制中发挥重要作用。由此推测维生素K对OA的防治可能具有重大意义。然而目前维生素K对OA的影响机制尚不明确，且维生素K每日治疗或预防剂量及代谢机制仍需进一步研究。

5 结语

MGP是一种维生素K依赖蛋白，在OA中主要起防止软骨钙化、调节骨代谢的作用，被视为OA的保护性蛋白，可作为诊断OA的生物标志物，并可预测OA影像学进展，为防治OA提供重要线索。MGP在OA数个重要的信号通路中均起重要的调节作用，但其机制尚待进一步研究明确。尽管目前临床上已有诸多药物和治疗可缓解OA患者疼痛，延缓其疾病进展，但真正做到防治OA仍遥不可及。因此未来仍需进一步研究OA的预防与治疗方法。

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