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膜性肾病的免疫学及遗传学相关研究

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[摘要] 膜性肾病(membranous nephropathy, MN)是一种以自身抗体攻击其自身抗原并在肾小球上沉积形成的免疫复合物的病理特点而命名的疾病。为延缓MN患者进入肾脏替代治疗时期的时间,明确其发病机制是首要问题。近年来国内外学者发现免疫学及遗传学机制在MN的发生中占据重要位置。本文主要对免疫学及遗传学与MN的相关性作一综述,旨在为MN机制的研究提供新思路。

[关键词] 特发性膜性肾病; M型磷脂酶A2受体1; 人类白细胞抗原; 血小板反应素1型结构域7A

Study on immunological and genetic mechanism of membranous nephropathy

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Abstract Membranous nephropathy (MN) is a disease named after the pathological characteristics of autoantibodies attacking its own antigen and forming immune complexes deposited on the glomerulus. In order to delay the time of MN patients entering the period of renal replacement therapy, it is the most important problem to clarify the pathogenesis of renal replacement therapy. In recent years, scholars at home and abroad have found that its immunological and genetic mechanisms play an important role in the occurrence of MN. This paper mainly reviews the correlation between immunology, genetics and MN, in order to provide new ideas for the study of the mechanism of MN.

Keywords idiopathic membranous nephropathy; M type phospholipase A2 receptor 1; human leucocyte antigen; thrombospondin type-1 domain-containing 7A

目前,膜性肾病(membranous nephropathy, MN)的高发病率已逐渐引起国内外学者的关注,且男性发病率高于女性,60岁以上的MN患者已上升至40%^[1],而儿童MN患者也并不少见^[2]。2017年来自我国山东的一项对MN的横断面研究^[3]显示:53.5%的原发性肾小球疾病为MN,已经超过了IgA肾病的发病率。而特发性膜性肾病(idiopathic

membranous nephropathy, IMN)占比高达80%^[4],因此IMN是近些年来研究的热点。MN患者预后较差且复发率高,未经治疗的MN患者中40%将需要肾脏替代治疗,其中肾脏替代治疗的肾移植患者中复发率高达30%~50%,且10年后50%的患者移植将发生丢失^[5]。由此看来,IMN对人类健康的危害不可忽视,进一步对IMN的发病机制研究是我

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们的首要任务。

1 IMN与免疫学

IMN的发病机制复杂, 由多种因素共同参与, 目前对其与免疫学、遗传学、环境及饮食方面的相关性均有研究^[6-7]。而其中免疫学及遗传学的相关机制研究有较大进展。研究^[8]表明: IMN相关的主要抗原为M型磷脂酶A2受体1(M type phospholipase A2 receptor 1, PLA2R1)及血小板反应素1型结构域7A(thrombospondin type-1 domain-containing 7A, THSD7A), 在90%的IMN患者中, 二者分别占70%~85%和3%~5%。因此明确IMN的发病机制对临床治疗具有里程碑式的意义。

1.1 PLA2R1

PLA2R1是一种I型跨膜受体, 是经过高糖基化的跨膜糖蛋白, 分子质量为185 kD, 属于哺乳类动物甘露糖受体家族, 在肾小球足细胞中高度表达^[9]。2009年, Beck等^[10]发现M型PLA2R1参与IMN的发生, 且抗PLA2R1抗体或肾小球PLA2R1颗粒染色强度可作为判断IMN的疾病活动性、治疗效果及预测肾移植后疾病复发的新型标志物^[11-13]。不同种族抗PLA2R1抗体的检出率不同, 但其诊断MN的特异性近100%^[14]。因此, 有学者^[15]提出将IMN分为PLA2R1相关性MN及PLA2R1无关性MN。PLA2R1相关性MN会在PLA2R1分子结构发生改变时暴露其抗原表位, 通过二硫键与抗体结合, 而氧化的细胞外环境可能会导致PLA2R1形成或保存二硫键, 致使病原性表位的长期表达而与循环中抗体结合^[16-17]。PLA2R1具有多个抗原表位, 其中主要表位有CYS-R, CTLD1和CTLD7^[9,18], 且这些表位随着疾病的进展而扩散^[19]。由于PLA2R1是细胞表面的膜结合分子, 且CysR位于N末端, 因此它在疾病早期更容易被抗体识别, 约占PLA2R1抗体中的90%^[20-21]。随着疾病的进展, 细胞内部的表位也产生了相应的抗体, 即CTLD1与CTLD7表位, 且具有上述表位结合的抗体的患者往往年龄较大, 对治疗更具抵抗力^[22]。

1.2 THSD7A

THSD7A是导致IMN的第二大抗原^[23]。有趣的是, 其多在PLA2R抗体阴性的MN患者中被发现, 而几乎不存在于PLA2R阳性的患者中, 仅有少数研究^[24]表明MN患者中存在PLA2R1及THSD7A抗

体双阳性。不同种族的MN患者对THSD7A的检出率不尽相同。Larsen等^[24]研究发现: 在美国MN患者肾小球组织THSD7A染色增强的发生率为3%; Iwakura等^[25]发现9.1%的日本IMN患者THSD7A颗粒表达增强, 而在抗PLA2R1抗体阴性的MN中, 抗THSD7A抗体的检出率约8%~14%。但其与MN患者发病机制的相关性尚未明确, 这将是未来我们需要攻克的难题。

THSD7A与PLA2R1的结构相似, 都表达于足细胞膜表面^[26]。其结构是由1个小的胞质结构域、1个相对较短的跨膜结构域和1个包含21个血小板反应蛋白的大的细胞外结构域组。在这21个结构域中, 18个具有表位结合位点。THSD7A是一种细胞外基质糖蛋白, 参与组织再生过程和细胞黏附到胶质母细胞瘤(glioblastoma multiforme, GBM)的静电机理^[27]。最近在小鼠模型中进行的一项研究^[27]发现THSD7A可能参与钙/钙调蛋白裂解, 可以将足突与GBM分离, 破坏肾小球滤过膜; 此外, THSD7A抗体参与蛋白尿的产生, 抗体水平的降低和识别表位数量的减少与蛋白尿的缓解有关。虽然THSD7A主要参与IMN的发生, 但其介导的MN患者的癌症患病率很高, 为20%~33%, PLA2R1介导的MN患者的癌症发病率较少, 约5%^[28]。这提示应增加对抗THSD7A抗体阳性的MN患者的恶性肿瘤筛查^[29], 然而是否能发现早期肿瘤有待进一步研究。

2 基因多态性

2.1 HLA的基因多态性

1979年有研究^[30]首次报道了人类白细胞抗原(human leucocyte antigen, HLA)基因与MN的关系。其中HLA II类基因是目前研究最多的HLA类基因之一。来自2011年的一项全基因组关联分析研究^[31]显示: 在白种人和南亚人种族中携带PLA2R1和HLA-DQA1风险基因的患者发生IMN的概率很高, 且当PLA2R1结合HLA-DQA1纯合性时风险增加80倍。此后, 又有学者探讨了不同种族人群携带不同HLA-DQA1 SNP位点的IMN的发生率有何不同, 一项关于西班牙人群的研究^[32](包括89名IMN和286名健康人)发现: 在显性模型下, 携带HLA-DQA1的rs2187668和PLA2R1的rs4664308的人群高度易感IMN。该研究成果首次设想了HLA-DQA1和PLA2R1的SNP可以预测IMN对免疫抑制剂治疗的反应, 且免疫抑制剂治疗对携带IMN易感性基因型的患者更加有效。还有研究^[33]提出: HLA-DQA1 SNP rs2187668及rs28383345与中国汉族人

群IMN强关联。HLA-DRB基因也是目前研究的热点基因之一。据报道^[34-35], HLA-DRB1*15:01和HLA-DQB1*06:02与中国汉族及日本人的IMN都有关。HLA III类基因 TNF- α 的-308A位点与IMN相关^[36]。

2.2 PLA2R1的基因多态性

IMN与PLA2R1的不同位点具有不同的相关性, 且与不同种族存在相关性。日本一项招募183例IMN患者和811例健康对照的研究^[35]发现: PLA2R1的 rs3749119, rs2715928, rs35771982和rs16844715位点与日本的IMN患者具有较强的关联性。但在日本的一项小样本研究^[37]中, rs3749119与日本的IMN患者无关。不能确定这是否与两项研究的样本量不同有关。Ramachandran等^[11]对印度人群的rs3749117研究结果与之相反: rs35771982与抗PLA2R1抗体阳性的非裔美国IMN患者之间也无相关性^[38]。上述研究结果与日本研究结果有所不同, 不能排除研究的样本量不同、环境不同、饮食习惯不同等问题对实验结果的干扰。

有研究^[39]指出: 携带高风险基因的IMN患者血清中抗PLA2R1抗体出现率较高, 肾小球中表达PLA2R1也较高。在英国的一项横断面研究^[40]中, HLA-DQA1*05:01和HLA-DQB1*02:01与PLA2R-Ab的高水平相关。在一项中国的研究中(IMN患者1112例, 1020例健康者作为对照), PLA2R1的SNPs位点rs35771982, rs3749117和rs4664308具有IMN易感性。在携带高风险基因的人群中, 这种抗PLA2R抗体存在于73%的人群, 75%的患者的肾小球表达PLA2R。更有趣的是, 有研究^[39]发现: 在一些携带这两种基因保护性基因型的人群中, 并未发现有人具有抗PLA2R抗体, 而且肾小球中PLA2R的表达较弱或无PLA2R的表达。

有研究^[38]证实PLA2R1的基因变异主要与PLA2R1抗体阳性的IMN患者有关, 而与PLA2R1抗体阴性的IMN患者几乎无关, 此研究为我们提供了一个新的研究方向, 即在PLA2R1抗体阴性的IMN患者中可能存在某些新的基因变异。对HLA的风险基因与PLA2R1无关性MN的相关性也有一些研究。PLA2R1相关的MN和PLA2R无关的MN之间存在不同的HLA风险等位基因。HLA-DRB1*15:01和HLA-DRB3*02:02。这2个等位基因与PLA2R相关MN的风险增加密切相关。PLA2R无关的MN与HLA-DRB1*15:01无关, 与HLA-DRB3*02:02相关^[41]。未来也许可以进一步探

讨PLA2R相关及无关性MN在基因多态性上有什么不同。

3 结语

近些年来, 对IMN的发病机制的研究有了较大进展。本文主要介绍参与IMN发生的主要抗原及基因。首先, PLA2R1及THSD7A抗体有助于IMN患者的预后、治疗等, 这具有突破性的临床意义, 但实际上其参与的发病机制尚未完全明确, MN的发病机制仍然是人类的未解之谜; 其次, 对基因多态性也有了初步认识, 相信基于上述免疫学及遗传学基础, 可以找到新的治疗方法及进一步了解IMN发病机制。

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