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儿童难治性肺炎支原体肺炎生物标志物研究进展

邓如玉[1,2,3,4]，罗征秀[1,2,3,4*]

[1]重庆医科大学附属儿童医院呼吸科，重庆
[2]国家儿童健康与疾病临床医学研究中心，重庆
[3]儿童发育疾病研究教育部重点实验室，重庆
[4]儿科学重庆市重点实验室，重庆

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摘　要

肺炎支原体肺炎是儿童社区获得性肺炎重要组成部分，近年难治性肺炎支原体肺炎(refractory *Mycoplasma pneumoniae* pneumonia, RMPP)发病率升高，肺炎支原体感染导致过度免疫炎症反应是RMPP发病的重要原因之一，因此检测免疫相关标志物有可能是早期预测RMPP的重要方法。本文就近年来儿童RMPP中新型免疫相关生物标志物及其预测作用进行综述。

关键词

难治性肺炎支原体肺炎，生物标志物

Research Progress on Biomarkers of Refractory *Mycoplasma pneumoniae* Pneumonia in Children

Ruyu Deng[1,2,3,4], Zhengxiu Luo[1,2,3,4*]

[1]Department of Respiratory, Children's Hospital of Chongqing Medical University, Chongqing
[2]National Clinical Research Center for Child Health and Disorders, Chongqing
[3]Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing
[4]Chongqing Key Laboratory of Pediatrics, Chongqing

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*通讯作者。

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Abstract

Mycoplasma pneumoniae is an important pathogen of community-acquired pneumonia in children. The incidence of refractory _Mycoplasma pneumoniae_ pneumonia (RMPP) increased in recent years. It is accepted that the excessive immune inflammatory response caused by _Mycoplasma pneumoniae_ infection is one of the important causes of RMPP. To measure the immune-related biomarkers could be an important method for early prediction of RMPP. We aim to review the novel immune-related biomarkers and their predictive roles in children with RMPP in this article.

Keywords

Refractory _Mycoplasma pneumoniae_ Pneumonia, Biomarkers

1. 前言

肺炎支原体(*Mycoplasma pneumonia*, MP)是儿童社区获得性肺炎(community-acquired pneumonia, CAP)重要病原体之一，占儿童 CAP 的 10%~40%，在 5 岁以上 CAP 患儿中甚至超过 50% [1]。部分肺炎支原体肺炎(*Mycoplasma pneumoniae* pneumonia, MPP)可进展为难治性肺炎支原体肺炎(Refractory *Mycoplasma pneumoniae* pneumonia, RMPP)，伴发肺不张、坏死性肺炎、塑型性支气管炎、闭塞性支气管炎、肺栓塞等肺内并发症及肺外损害，为 MPP 诊治带来了新的挑战[2] [3] [4] [5]。目前，国内外对于 RMPP 的定义尚未统一，引用最多的是 Tamura 等[6] 2008 年研究中的标准：合理使用抗菌药物治疗 7 天或以上，仍持续发热并伴随影像学征象继续进展者。我国儿童肺炎支原体肺炎诊疗指南(2023 年版) [7]指出，RMPP 指 MPP 患儿使用大环内酯类抗菌药物正规治疗 7 天及以上，仍持续发热、临床征象及肺部影像学所见加重、出现肺外并发症者。如何早期识别儿童 RMPP 仍是临床工作中的重点及难点。目前 RMPP 发病机制尚未完全明确，可能与 MP 对大环内酯类药物耐药、机体对 MP 过度免疫炎症反应、混合感染、高凝状态等因素相关[8]，其中免疫相关生物标志物是近年研究热点。既往研究表明，乳酸脱氢酶(LDH)、C-反应蛋白(CRP)、白细胞介素(IL)-17、肿瘤坏死因子(TNF)-α、IL-6、D-二聚体等对 RMPP 具有较好预测价值[9]-[14]，随着 RMPP 发病率上升，国内外学者亦在不断探索新的 RMPP 预测生物标志物，因此本文对近年报道的新型免疫相关生物标志物在 RMPP 中的研究进展进行综述，以期为临床提供新思路。

2. 高迁移率群盒蛋白 1 (High Mobility Group Box Protein 1, HMGB1)

HMGB1 是介导感染、损伤和炎症反应的一种关键细胞因子，几乎在所有细胞中都有表达[15]。在细胞内，HMGB1 是一种高度保守的核蛋白。HMGB1 可通过免疫活性细胞主动分泌或由凋亡或坏死细胞被动释放到细胞外。在细胞外，HMGB1 属典型损伤相关分子模式，可通过与晚期糖基化终产物受体(RAGE)、Toll 样受体(TLR)2、TLR4 等受体结合，激活髓样分化因子依赖的 NF-κB 通路，促进免疫细胞成熟、激活以及细胞因子产生[15] [16] [17] [18]。研究表明表面活性剂蛋白 A 可抑制免疫细胞释放 HMGB1，进而抑制肺炎支原体诱导的树突状细胞成熟，从而减轻肺部炎症[19]。Ding 等[16]指出 RMPP 患者外周血 HMGB1 水平较非 RMPP 患者显著增高，外周血 HMGB1 较 TNF-α 与 IL-6 对 RMPP 具有更好预测价值(AUC

为0.876，当诊断阈值为5.25×10^{-3}时，灵敏度为83.3%，特异度为82.4%)。徐迎春等[20]研究发现RMPP组支气管肺泡灌洗液(BALF)中HMGB1较非RMPP组明显升高，HMGB1是MPP患儿进展为RMPP的独立危险因素(AUC = 0.666)，也是RMPP合并肺外损伤的独立危险因素(AUC = 0.814)。由此可见，外周血及BALF中HMGB1水平对RMPP均有一定预测价值，尚需对HMGB1诱导的免疫炎症反应机制进行深入研究，以开发新的治疗策略抑制HMGB1通路，从而防止其在RMPP中发挥的过度炎症作用。

3. 中性粒细胞与淋巴细胞比值(Neutrophil to Lymphocyte Ratio, NLR)

NLR是外周血中中性粒细胞与淋巴细胞计数之间的简单比值，是一种结合固有免疫反应(主要由中性粒细胞引起)和适应性免疫(由淋巴细胞支持)的生物标志物，是一种新的系统性炎症生物标志物，已用于预测多种感染性疾病不良预后[21]。中性粒细胞作为抵抗感染的第一道防线，在MPP发生发展中起关键作用。MP感染后，中性粒细胞在外周血[22]、BALF [23]和肺组织[24]中增加，发挥局部杀伤、吞噬病原体作用。然而，中性粒细胞过度聚集和激活会导致炎症瀑布效应及免疫失衡，引起组织损伤[25]。同时，过度炎症可诱导淋巴细胞凋亡，导致淋巴细胞数量减少，国内研究发现22.3%患儿入院时存在外周血淋巴细胞数量下降[26]。有研究发现[27]，6岁以上RMPP患儿中性粒细胞、NLR均显著高于非RMPP组，且NLR较CRP对RMPP有更高预测价值。Li等[28]研究发现RMPP组患儿NLR水平明显高于非RMPP组，NLR是RMPP独立预测因子，高NLR (≥1.9)患儿较低NLR (<1.9)患儿更易发生坏死性肺炎、总热程及住院时间更长、入住ICU比例及住院费用更高。高NLR是中性粒细胞计数增加和淋巴细胞计数减少的共同结果，能更好地反应机体全身性炎症状态。NLR作为一种价格低廉、容易获取的生物标志物，与RMPP发生发展可能相关，未来尚需进行前瞻性、多中心队列研究来证实其在RMPP中的预测价值。

4. 铁蛋白

铁蛋白水平升高被认为是一种炎症标志物。在感染早期阶段，巨噬细胞受到刺激后合成并释放细胞因子，从而刺激铁蛋白合成。血清铁蛋白升高通过抑制淋巴细胞增殖发挥免疫抑制作用。过量的铁蛋白能反映TNF-α水平升高，以及细胞毒性标志物如天冬氨酸转氨酶、乳酸脱氢酶和肌酸激酶水平升高[29]。铁蛋白明显升高可反映机体铁代谢紊乱，可作为判断疾病严重程度的指标[30]。Choi 等[22]研究显示，RMPP组血清铁蛋白明显高于非RMPP组，铁蛋白可作为RMPP早期预测标志物，当铁蛋白 ≥ 230 pg/mL，诊断RMPP的敏感性和特异性均为67%。Wen等[31]研究发现铁蛋白 ≥ 329.01 ng/mL，诊断RMPP的敏感性和特异性分别为67.09%及93.13%，AUC为0.90，其诊断价值高于CRP (AUC为0.81)，Logistic回归性分析显示铁蛋白是预测RMPP的独立危险因素，提示铁蛋白对RMPP具有较好预测作用。

5. 趋化因子

趋化因子和其受体相互作用，构成复杂的趋化因子调控网络，特异性控制免疫细胞活动，参与免疫和炎症反应[32]。研究表明，MP感染发病机制与MP通过TLR刺激巨噬细胞释放炎症细胞因子及趋化因子密切相关[33] [34]。MP产生的社区获得性呼吸窘迫综合征(CARDS)毒素可指数级地刺激Th2细胞因子和趋化因子CCL17、CCL22表达，导致气道过敏反应和高反应性[35] [36]。研究报道CCL11可募集并动员嗜酸性粒细胞至肺部，引起气道高反应性[37]。抑制CCL3可募集促炎T细胞，导致疾病加重[38]。抗菌治疗显著降低了MPP小鼠模型BALF中CXCL10水平[39]。Lee等[40]发现RMPP组患儿血浆CXCL10高于非RMPP组，血浆CCL3和CCL11低于非RMPP组。CCL2是一种重要的促炎症趋化因子，参与炎症、免疫、创伤等过程[41]。Zhu等[42]研究发现，RMPP组患儿BALF中CCL2水平高于非RMPP组，当BALF中CCL2截断值为0.645 ng/ml时，预测RMPP的AUC为0.94，敏感性为85%，特异性为94%，诊断价值优于血清CRP和LDH。

6. 其他

除 HMGB1、NLR、铁蛋白、趋化因子等新型生物标志物外，亦有研究报道血清可溶性 B7 树突状细胞(sB7-DC)、自分泌运动因子(autotoxin, ATX)可用于预测 RMPP。Zhang 等[43]研究指出，RMPP 患儿 sB7-DC 浓度明显高于非 RMPP 组，sB7-DC ≥ 1109.7 pg/ml 时，诊断 RMPP 的灵敏度和特异度分别为 86.7%及 62.9%，AUC 为 0.794，其诊断价值高于 IL-17 (AUC = 0.741)。ATX 是一种分泌型糖蛋白，与血管炎症、糖脂代谢及肺部炎症反应有关。付彬彬等[44]研究发现 RMPP 患儿血清及 BALF 中 ATX 水平均高于非 RMPP 组，对 RMPP 具有较好预测价值(AUC 分别为 0.874、0.862)，相关性分析显示，血清和 BALF 中 ATX 水平与 IL-6、IL-8 及 CRP 均呈正相关，提示 ATX 可能通过调节机体免疫炎症反应参与 RMPP 发病过程。目前 sBC-D7、ATX 对 RMPP 的预测研究较少，其预测价值尚需进一步验证。

7. 小结

RMPP 诊断滞后可影响患儿预后，给家庭及社会带来不同程度负担，探索早期预测 RMPP 的生物标志物及不同生物标志物在 RMPP 发生发展中的机制，为 RMPP 早期诊断提供高敏感性及高特异性生物标志物，将有助于减轻 RMPP 疾病负担。

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