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急性肾损伤的生物学标记物的研究进展

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摘 要

急性肾损伤(acute kidney injury, AKI)在重症监护病房(intensive care unit, ICU)中是一种常见的疾病，大多患者预后不良。早期的诊断和及时治疗对于患者来说非常重要。近期有大量的研究已经表明，相对于传统的实验室指标如尿量的减少以及血肌酐值的上升来说，有很多的生物学标记物对于AKI的早期诊断具有一定的意义，本文将对这些生物学标记物的研究进展进行一篇综述，旨在对AKI的早期诊断和护理有一定的作用。

关键词

急性肾损伤，重症监护病房，生物学标记物，早期诊断

Research Progress of Biological Markers of Acute Kidney Injury

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Abstract

Acute kidney injury (AKI) is a common disease in the intensive care unit (ICU), and most patients have a poor prognosis. Early diagnosis and timely treatment are very important for patients. A large number of recent studies have shown that compared with traditional laboratory indicators such as reduced urine volume and increased serum creatinine value, there are many biological markers that have certain significance for the early diagnosis of AKI. This article will review the research

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progress of these biological markers, aiming to have a certain role in the early diagnosis and care of AKI.

Keywords

Acute Kidney Injury, Intensive Care Unit, Biological Markers, Early Diagnosis

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1. 引言

急性肾损伤(acute kidney injury, AKI)在重症监护病房(intensive care unit, ICU)中是一种常见的疾病，大多患者预后不良[1]。早期的诊断和及时治疗对于患者来说非常重要。2012 年改善全球肾脏病预后组织(Kidney Disease: Improving Global Outcomes, KIDGO)指南[2]推荐使用尿量和血肌酐来诊断并对 AKI 进行分级。但是研究表明尿量和血肌酐的变化会受到很多因素的干扰，并不能完全反映肾小球滤过率和肾脏损伤的程度[3] [4]，而且尿量和血肌酐的变化总是滞后于病情的变化，不能及时地识别 AKI。

因此寻找可以早期预测 AKI 和持续性肾脏损坏的生物学标记物对于临床工作的开展和对疾病的预防和治疗来说非常重要。目前有些生物学标记物已经可以在早期 AKI 患者和持续性肾脏损坏的患者的尿液和血液中被发现，其中包括：中性粒细胞明胶酶相关脂质运载蛋白(neutrophil gelatinase-associated lipocalin, NGAL)，胱抑素 C (cystatin C)，肾损伤分子-1 (kidney injury moleculer-1, KIM-1)，肝脂肪酸结合蛋白(liver-type fatty acid binding protein, L-FABP)，胰岛素样生长因子结合蛋白-7 (insulin-like growth factor binding protein-7, IGFBP-7)，金属蛋白酶抑制剂 2 (matrix metalloproteinase inhibitor-2, TIMP-2)，尿 C-C 基质趋化因子配体 14 (urinary c-c motif chemokine ligand 14, CCL14)等。本文将对这些生物学标记物的研究进展做一综述。

2. NGAL

中性粒细胞明胶酶相关脂质运载蛋白(neutrophil gelatinase-associated lipocalin, NGAL)是脂脂素家族的一种分子量为 25 KDa 的一种蛋白质[5]。它最初在人中性粒细胞中纯化，以单体和异质二聚体形式存在，后者作为与人中性粒细胞明胶酶的二聚体[6]。在正常的情况下，NGAL 可以在人体的几个组织中低度的表达，包括肾脏，肺，和胃肠道[7]。在手术后的相关肾损伤和肾小管上皮细胞损伤的过程中，肾小管上皮细胞中的 NGAL mRNA 表达上调，大量的 NGAL 的分泌，导致血，尿中的 NGAL 的浓度升高，从而可以去早期预测 AKI 和反应 AKI 的严重情况[8]。在近期的一些关于 NGAL 的研究中，研究者发现在心脏手术后 AKI、脓毒症 AKI 和肝硬化失代偿期 AKI 时，NGAL 对于早期预测 AKI 都有高度的敏感性[9]-[11]。尤其是在肝硬化失代偿期的 AKI 中，NAGL 不仅可以区分肝硬化引起的 AKI 的类型，而且可能改善对死亡率的预测。因此它有可能优化肝硬化引起 AKI 的管理[12]。

3. Cystatin C

胱抑素 C (Cystatin C)是一种非糖基化蛋白，属于半胱氨酸蛋白抑制剂，胱抑素超家族[13]。Cystatin C 是所有有核细胞中“管家基因”所表达的产物，并且这种产物会以一种恒定速率产生。由于其体积小，且在正常的 PH 值下带正电荷，所以能够很好地被肾小球自由过滤。Cystatin C 不在肾小管上皮细胞分泌，

但是会被肾小管上皮细胞重新吸收，并且分解吸收，不会再次进入循环[14]-[17]。研究证实，在早期预测和诊断 AKI 时，Cystatin C 的敏感性要比血清肌酐高。在最近的研究中，研究人员发现在肝硬化失代偿期引起的 AKI 中，Cystatin C 可以准确地预测这些患者的 AKI 的发生率和死亡率[18]-[20]。在 Priti Vijay 的研究中，他们发现血清胱抑素 C 是诊断小儿肝硬化 AKI 最佳的生物学标记物，以血清 Cystatin C 为基础的公式计算的估计肾小球滤过率(Estimated glomerular filtration rate, eGFR)要比以血清肌酐为基础的公式计算的 eGFR 要准确得多[21]。

4. KIM-1

肾损伤分子(kidney injury moleculer-1, KIM-1)是一种 38.7 KDa 的 I 型跨膜糖蛋白，胞外免疫球蛋白样结构域位于长黏蛋白样结构域之上，其在正常的肾脏组织和其他器官中的表达水平较低，但在肾脏受到损伤后尤其是在缺血－再灌注损伤后，在肾脏的近端小管处显著上调表达[22]。在肾损伤的早期，由于 KIM-1 介导小管的吞噬作用，所以它的表达对于 AKI 来说是抗炎的。在早期对大鼠以及人的研究中表明，KIM-1 相对于血清尿素氮和血清肌酐来说是更敏感和特异的标记物[23]。根据近期的研究，研究者发现 KIM-1 是脓毒症相关的急性肾损伤、成人急性肾损伤和手术引起的医院获得性急性肾损伤良好的预测性指标，并且有着相对较高的敏感性和特异性[24]-[26]。但是 KIM-1 能否运用于临床诊断，仍然需要大量的临床研究[25]。

5. L-FABP

肝脂肪酸结合蛋白(liver-type fatty acid binding protein, L-FABP)是脂肪酸结合蛋白(Fatty acid-binding proteins, FABPs)中的一员。FABPs 是一组分子量为 14 KDa 的低分子量的蛋白质家族，它们可以协调细胞内脂质反应，与细胞的代谢和炎症的途径密切相关。FABPs 具有组织特异性，在肾脏的近端小管上皮细胞表达着 L-FABP 的 mRNA，实验表明在受到了如肾小管缺血、毒素、盐敏型高血压等物理和化学的刺激下，L-FABP 的表达会上调并且排入尿液中，导致肾脏疾病的发展[27]-[30]。在肾小管损伤的早期，微量白蛋白尿未被检测出时，由于 L-FABP 的组织学特性，尿液中的 L-FABP 就已经升高[31]。在最新的研究中发现儿科患者的心脏手术后导致的 AKI 中，尿 L-FABP 的排泄在 4 小时内升高，相比而言血清肌酐在 24~48 小时内才升高，并且 uL-FABP 的敏感性与特异性均高[32]。在一项受试者工作特征(ROC)分析中，L-FABP 在成人先天性心脏病导致心力衰竭的患者在治疗中进展为 AKI 中，最大曲线下面积(AUC)为 0.769 ($p < 0.001$)，具有良好的预测作用[33]。接受顺铂治疗的过程中通常会导致患者发生 AKI，在发生 AKI 的患者中，尿 L-FABP 的排泄增加相比于血清肌酐值的升高提前了 2 天，并且肾功能稳定的患者并未发现尿 L-FABP 的升高，对于使用顺铂治疗的患者早期监测尿 L-FABP 能更好地预测 AKI 的发生[34]。

6. TIMP-2 & IGFBP-7

金属蛋白酶抑制剂 2 (matrix metalloproteinase inhibitor-2, TIMP-2)分子质量约为 24 KDa，胰岛素样生长因子结合蛋白 7 (insulin-like growth factor binding protein 7, IGFBP7)分子质量约为 29 KDa，其中 TIMP-2 优先在肾小管的远端小管起源的细胞表达分泌，IGFBP7 可以在不同类型肾小管中表达和分泌，但优先在近端小管起源的细胞表达分泌[35] [36]。他们是在肾小管细胞在受到应激或损伤期间所表达的细胞周期阻滞蛋白[37]。TIMP-2 可以刺激 p27 的表达，IGFBP7 可以直接增加 p53 和 p21 的表达。这些作用可以通过 TIMP-2 和 IGFBP7 的受体以自分泌和旁分泌的形式进行。这些 p53、p27、p21 可以阻断周期依赖性蛋白激酶复合物(CyID-CDK4 和 CycIE-CDK2)从而导致 G1 细胞周期停滞，这可能是为了避免细胞分裂可

能造成的损伤，直至损伤修复[38]。研究表明，在接受心脏手术后发生 AKI 的患者中，基于血清肌酐或者少尿来诊断需最少等到术后 3 天，而[TIMP-2]*[IGFBP7]在术后 4 小时就有了升高[39]。在预测重大非心脏手术后的 AKI 中，[TIMP-2]*[IGFBP7]同样有着良好表现[40]。有研究者在近期对儿童肝移植后急性肾损伤和造影剂诱导的儿童急性肾损伤的研究中发现，[TIMP-2]*[IGFBP7]同样有着优于其他生物学标记物的预测能力[41] [42]。

7. CCL14

尿 C-C 基质趋化因子配体 14 (urinary c-c motif chemokine ligand 14, CCL14)是小分子趋化因子家族中的一员，最初是被认为在白细胞的趋化作用中起作用。CCL14 可以被单核/巨噬细胞系统招募，巨噬细胞的招募和极化是被认为在肾细胞的损伤和持续性肾功能障碍的发展中发挥着重要作用，但是由于 CCL14 不在大鼠和小鼠中表达，所以它介导持续性严重 AKI 的机制尚不完全清楚，但是 RUBY 实验得出趋化因子信号通路和巨噬细胞转用似乎在肾脏的修复和恢复中起重要作用[22]。在近期关于 CCL14 与急性肾损伤的研究中，CCL14 展现出来极好地预测危重症患者持续严重 AKI 的能力[22] [43] [44]。CCL14 的发现和应用，可能对 AKI 的治疗和护理带来新的方向和思路[45]。

8. 小结

由于 AKI 在临床上的发病率仍然高居不下，早期发现，早期治疗对于患者来说非常重要，传统的生物学标记物并不能早期且准确地诊断 AKI，合理探索并且应用 AKI 的生物学标记物非常必要。目前探索出的各种 AKI 生物学标记物，各有长处和缺点，对于该如何将各种生物学标记物灵活地应用于各种临床场景，仍然需要进行大量的临床研究。

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