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中性粒细胞明胶酶相关载脂蛋白与慢性肾脏病

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[摘要] 慢性肾脏病(chronic kidney disease, CKD)在普通人群的发病率约为10%~16%,死亡率及心血管疾病发生风险高,带来沉重的医疗负担。近期研究发现,中性粒细胞明胶酶相关载脂蛋白(neutrophil gelatinase-associated lipocalin, NGAL)与CKD有紧密联系,提示其在慢性肾脏病的诊断、治疗和监测等多方面具有重要价值。本文就NGAL的生物学功能、来源、结构形式及其在CKD中作用的相关研究进展作一综述。

[关键词] 慢性肾疾病;中性粒细胞明胶酶相关载脂蛋白;急性肾损伤

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Neutrophil gelatinase-associated lipocalin and chronic kidney disease: a literature review

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[Abstract] Chronic kidney disease (CKD) is a common disease with an estimated prevalence of 10%-16% in the general population. With high mortality and high risk of cardiovascular disease, CKD imposes substantial cost burden. Recent studies have shown that neutrophil gelatinase-associated lipocalin (NGAL) is tightly associated with CKD, suggesting that it has an important role in the diagnosis, treatment and monitoring of CKD. This paper reviewed the progress in the biological function, originality, structure, and role in CKD of NGAL.

[Key words] chronic kidney diseases; neutrophil gelatinase-associated lipocalin; acute kidney injury

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根据2012年KDIGO慢性肾脏病(chronic kidney disease, CKD)评估及管理临床实践指南,慢性肾脏病定义为:对健康有潜在危害的肾脏结构或功能改变,持续时间大于3个月。CKD在普通人群的发病率大约在10%~16%^[1],死亡率及心血管疾病发生风险高,带来沉重的医疗负担^[2]。目前对于CKD的诊断主要还是依据估算肾小球滤过率(eGFR)和蛋白尿等传统指标,由于肌酐和尿蛋白影响因素较多,其对CKD的评价具有一定局限性。

中性粒细胞明胶酶相关载脂蛋白(neutrophil gelatinase-associated lipocalin, NGAL)作为急性肾损伤(acute kidney injury, AKI)的早期诊断标记物已得到大量研究的证实^[3]。近期研究发现,NGAL与CKD也有紧密联系,本文拟对NGAL在CKD中作用的相关研究进展作一综述。

1 NGAL的生物学功能

NGAL为Lipocalin超家族成员,是从中性粒细胞继发颗粒中分离出来的新型蛋白分子,相对分子质量为25 000,可共价结合于源于中性粒细胞的明胶酶^[4]。NGAL mRNA可在正常人的多种组织中表达,如骨髓、输尿管、前列腺、胃、大肠、气管、肺脏、肝脏和肾脏等^[5]。NGAL基因的启动子序列中存在包括NF- κ B在内的多种转录因子的结合位点,因此某些组织(肝脏、肾脏、大肠、肺)上皮细胞损伤时可释放NF- κ B,从而诱导产生NGAL^[6]。NGAL参与铁代谢,在细胞内可以结合铁元素,导致细胞内铁耗竭,从而发挥抗菌、促进凋亡及抑制增殖的作用;其还具有转铁蛋白的功能,可结合细胞外铁,进入细胞内,激活细胞内的铁依赖基因调节通路,促进

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上皮化和刺激增生^[3]。同时,NGAL可抵消金属蛋白酶-1组织抑制剂对基质金属蛋白酶9(MMP-9)的抑制效应,从而促进MMP-9降解细胞外基质,可能参与肿瘤细胞的转移过程^[7]。

2 NGAL的来源

2.1 血液 NGAL 来源 正常人体液中所含的NGAL浓度值较低,血液中浓度在20 ng/mL左右,大部分来源于中性粒细胞分泌,较少的一部分来源于肝脏、脾脏和肾脏的分泌,肾脏的滤过清除作用使血液NGAL水平保持稳定^[8]。动物研究发现,夹闭单侧肾动脉建立肾缺血再灌注模型,从同侧肾静脉采血测得的NGAL浓度不如预期高,而从同侧输尿管中收集尿液测得的NGAL浓度较高,这提示AKI时血液NGAL水平升高的主要来源可能并不是肾脏,而是由于AKI导致远隔器官(尤其是肝脏和肺脏)产生系统效应的结果^[9]。有研究^[10]认为,CKD患者血液中NGAL浓度升高是由肾小管慢性损伤而非肾功能下降导致的NGAL滤过减少造成的。但近期Rau等^[11]研究发现,无肾脏透析者和肾脏透析者血液中NGAL浓度差异没有统计学意义,提示在透析患者中,血液中NGAL的主要来源并非肾脏,慢性炎症反应可能是血液NGAL水平升高的主要因素。

2.2 尿液 NGAL 来源 血液中NGAL经肾小球滤过后大部分由近端小管经细胞内吞作用重吸收,故正常人尿液中NGAL浓度也较低,维持在20 ng/mL左右。研究表明,当发生AKI时,远端肾单位(特别是Henle's袢的升支粗段和集合管)会快速大量表达NGAL并分泌到尿液中,成为AKI患者尿液NGAL的主要来源^[9]。存在蛋白尿而肾功能未恶化的CKD患者,其尿液中NGAL来源可能是一个系统变化的过程^[10]:蛋白尿初期,由肾小球滤过的大量蛋白导致近端小管蛋白转运能力饱和,从而使近端小管对NGAL重吸收相对减少,造成尿液中NGAL水平增加;随着蛋白尿对肾小管损伤持续加重,肾小管上皮细胞不断凋亡的同时也激活肾小管上皮细胞分泌大量NGAL来对抗蛋白尿的损伤效应,从而进一步导致尿液中NGAL水平升高;随着CKD病情不断进展,肾小管间质不断损伤和修复,导致大量NGAL由肾小管分泌到尿液中,成为尿液NGAL的主要来源。

3 NGAL的结构形式

NGAL主要存在以下3种结构形式:单体型

(25 000),同二聚体型(45 000),异二聚体型(135 000)^[12]。Cai等^[13]发现,AKI患者尿液中的NGAL主要为单体型,来源于肾小管上皮细胞,而尿路感染患者尿液中NGAL主要为二聚体型,来源于中性粒细胞。Nickolas等^[14]研究发现,单体型NGAL与CKD患者肾小管间质的损伤密切相关。由此推断,针对不同结构形式的NGAL进行检测,可能更有利于提高其对肾脏疾病诊断的特异性。然而目前上市的试剂盒尚不能对NGAL的来源加以区分(中性粒细胞来源或小管上皮细胞来源),尽管目前针对二聚体型NGAL的检测方法已有所进展,但对单体型NGAL的检测仍然面临较大挑战^[12]。

4 NGAL与AKI

发生AKI时,血液和尿液中的NGAL浓度会增高。NGAL被认为是新一代AKI早期诊断生物标记物^[10],这在多种类型的AKI临床研究中已得到证实,如:心脏手术后AKI^[15]、造影剂诱导AKI(CI-AKI)^[16]、脓毒症导致的AKI^[17]及梗阻性肾病导致的AKI^[18]。NGAL在评价AKI的发生风险、严重程度、持续时间及病情预后等方面也有重要意义^[19-21]。AKI是发生CKD的危险因素之一,Ko等^[22]研究发现,AKI后的持续炎症和免疫反应可导致CKD的发生,在AKI向CKD转变的这一过程中,NGAL基因处于高表达状态,可能提示AKI后NGAL的持续高表达有预测AKI向CKD转变的作用。

5 NGAL与CKD

NGAL不仅可作为AKI的早期诊断生物标记物,而且在CKD中也具有重要的临床意义。NGAL可在多种病因导致的CKD患者血液或尿液中高表达,其中包括IgA肾病、狼疮性肾炎、多囊肾病和多发性骨髓瘤相关性肾病等^[23-26],提示NGAL与CKD的联系紧密。

5.1 NGAL评估CKD发病风险 Bhavsar等^[27]以社区动脉粥样硬化风险(ARIC)研究人群为基础进行1:1巢式病例对照研究发现,尿液NGAL高基线水平与进入CKD3期的发病风险相关。与之不同的是,Peralta等^[28]以多种族动脉粥样硬化(MESA)研究人群为基础同样进行1:1巢式病例对照研究发现,尿液NGAL高水平与进入CKD3期的发病风险无关。对于以上两项研究结论的差异,基线尿蛋白水平可能做出部分解释。尿蛋白水

平与CKD发生发展密切相关,而蛋白尿程度与尿液NGAL水平也同样密切相关^[10]。Bhavsar等^[27]纳入病例的基线尿蛋白肌酐比 ≤ 30 mg/g,而在Peralta等^[28]的研究中,尿蛋白肌酐比 ≥ 30 mg/g的病例占到17%,这可能是导致二者研究结果之间差异的因素之一。因此,在限定既往研究已认同CKD危险因素(高血压、糖尿病、蛋白尿等)后,再评价NGAL与CKD发生风险的相关性可能更有意义。

5.2 NGAL早期诊断CKD 多项横断面研究发现^[29-30],尿液中NGAL水平与肾小球滤过率(GFR)及肾实质损伤的严重程度相关。近期Stelmach-Goldys等^[31]开展的一项纳入46例意义不明的单克隆巨球蛋白血症(MGUS)患者的研究发现,虽然没有临床和实验室表现,但MGUS患者的肾功能已经受损,MGUS患者尿液中的NGAL浓度较对照组高,可以考虑作为肾脏损伤的早期标记物。当然,NGAL可否用于CKD的早期诊断还有待进一步的研究。

5.3 NGAL评价CKD病情进展 在纳入63例1型糖尿病患者的研究中,Nielsen等^[32]发现尿液NGAL高水平组的GFR下降速度比对照组更快,但在校正其他CKD进展因素后,高NGAL水平不是CKD进展的独立危险因素。而Nielsen等^[33]在另外一项纳入78例1型糖尿病患者的队列研究中发现,尿液NGAL水平与GFR下降无关,在未校正其他进展因素的情况下,NGAL水平与终末期肾病(ESRD)的发生风险相关。Parikh等^[25]在针对多囊肾病患者的研究中发现,尿液NGAL水平与肾脏体积和肾功能的改变均不相关。近期,Liu等^[34]以CRIC研究人群为基础研究发现,尿液NGAL水平与CKD进展(GFR下降一半或发生ESRD)密切相关,尿液NGAL水平是评价多种病因CKD患者病情进展的独立危险因素。Donadio等^[30]开展的一项包括310例CKD患者(CKD 1~5期)的横断面研究发现,血浆NGAL水平从CKD 2期患者开始显著增高,并随着CKD分期的进展而不断升高,而尿液中NGAL水平在CKD 4期才开始显著增高。这些研究提示在评价CKD进展方面,NGAL可能存在重要检测意义,但还有待多中心大样本的临床研究来加以验证。

5.4 NGAL评价CKD患者并发症 心血管事件是CKD患者的常见并发症^[35],研究表明NGAL在动脉粥样硬化和腹主动脉瘤的患者中有较高的表达,NGAL是否对CKD患者心血管并发症有预测

作用,这一点值得关注。Hasegawa等^[36]开展的一项透析前CKD患者的队列研究发现,尿液NGAL水平对CKD患者心血管事件的发生有预测作用。Liu等^[37]以CRIC研究人群为基础研究发现,尿液NGAL水平与成人CKD患者缺血性动脉粥样硬化事件发生率相关,但与心力衰竭和全因死亡事件的发生无关。提示NGAL对CKD患者心血管事件的发生有预测作用,可以作为评价CKD心血管事件发生的生物学指标。

5.5 NGAL监测CKD治疗效果 Ding等^[23]研究发现,对雷公藤和贝那普利治疗反应较好的IgA肾病,治疗后其尿液NGAL浓度会下降,而治疗反应较差的IgA肾病,尿液NGAL水平下降不明显。Kuwabara等^[38]研究发现,微小病变、狼疮性肾炎(V型)、新月体肾炎和间质性肾炎的患者给予激素和免疫抑制剂治疗后,尿液中NGAL和蛋白尿水平显著下降。这些研究提示尿液NGAL在监测疾病活动和治疗效果方面可能具有临床意义,但NGAL在监测CKD治疗效果方面的意义还有待多中心大样本的临床研究来加以验证。

5.6 NGAL与CKD基础上AKI的发生 一般人群AKI罹患率较低,而CKD患者因其存在肾脏病变基础,发生AKI的风险要高于普通人群。CKD患者发生AKI,临床上称之为CKD基础上AKI。目前,NGAL在AKI和CKD患者中的临床意义已得到大量研究的证实,但NGAL对于CKD基础上AKI的临床意义还不十分明确。近期,Doi等^[39]开展了一项心脏大手术后发生AKI的研究发现,CKD患者术前高血浆NGAL水平是术后发生AKI的独立危险因素,CKD患者术后发生AKI,其NGAL值会在CKD的基础之上进一步升高,可能对CKD基础上AKI的诊断有一定的指导意义。Tasanarong等^[40]研究表明,当CKD患者造影术后发生对比剂诱发的AKI(CI-AKI)时,其尿液NGAL水平及造影前后尿液NGAL的差值都要显著高于非CI-AKI组,造影后6h尿液NGAL取117 ng/mL为cut-off界值时,诊断CI-AKI的敏感性为94%,特异性为78%,当取264 ng/mL为cut-off界值时,其诊断II期CI-AKI的敏感性为100%,特异性为87%。结果表明尿液NGAL水平不仅可用来早期监测CKD患者CI-AKI的发生,并且对CKD患者发生CI-AKI严重程度的评定也具有预测意义。但是目前针对NGAL在CKD基础上AKI中的研究还较少,NGAL在这一类疾病中的临床意义也不十分明确,

有待大量的临床研究加以验证。

综上所述,NGAL 具有多种生物学效应,在肾脏病的发生、发展中发挥着重要作用。近 20 年的研究发现,NGAL 对于 AKI 患者具有重要的临床检测意义。近期研究表明,NGAL 与 CKD 关系密切,提示其在 CKD 的诊断、治疗和监测等多方面具有重要价值,但目前此方面研究的质量还不尽如人意,NGAL 在 CKD 中的应用价值还需要更多的大样本临床研究来加以论证。

6 利益冲突

所有作者声明本文不涉及任何利益冲突。

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