



# 中国病原生物学杂志

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中国病原生物学杂志

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# 中国科学引文数据库(CSCD)来源期刊

## 收录证书

### 中国病原微生物学杂志

依据文献计量学的理论和方法,通过定量与定性相结合的综合评审,贵刊被收录为中国科学引文数据库(CSCD)来源期刊,特颁发此证书。

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表达水平下调<sup>[25]</sup>,IL-12活性下降,影响了NK和CTL细胞的增殖和活化,进而导致HBV的清除障碍。

以上研究表明,由HBV感染诱导产生的外泌体miRNA通过影响相关细胞因子的产生及其介导的信号通路,影响免疫细胞的活化,使机体对HBV的识别和清除障碍,进一步加重HBV诱导的慢性炎症,最终导致HBV的持续感染。

#### 3 外泌体与HBV感染的诊断

大量研究发现,健康人群和HBV感染者外泌体的组成存在定性和定量差异,其中,血清外泌体miRNA表达谱随疾病进展而发生变化,外泌体miRNA的种类及水平变化可反映HBV感染所致疾病及其进展的不同阶段<sup>[26-27]</sup>。

有文献报道,HBV感染的PXB嵌合小鼠肝细胞外泌体相关miRNA水平增加2倍以上<sup>[24]</sup>。HBV感染者血清外泌体miR-21、miR-221和miR-222水平均显著升高<sup>[26]</sup>,Wang等<sup>[28]</sup>也证明HCC和CHB患者血清外泌体富含miR-21,且具有比血清miRNA更高的检测灵敏度。miR-122是肝脏特异性miRNA之一,能够直接靶向病毒RNA或调节宿主基因的表达,通过与HBV靶序列的相互作用抑制HBV基因的表达和复制,是HBV复制的重要调控因子<sup>[29]</sup>。研究发现,与健康人群相比,HBV感染者血清外泌体miR-122-5p水平显著升高<sup>[30]</sup>,且CHB患者血清外泌体中miR-122与HBVDNA、ALT和HBsAg水平呈负相关,提示血清外泌体miR-122水平可以反映CHB患者体内HBV病毒复制及肝脏损伤的程度<sup>[29]</sup>。另有研究发现,血清外泌体miR-130、miR-183、miR-196、miR-209和miR-96的水平能够区分不同阶段的肝炎和肝损伤<sup>[31]</sup>。

血清外泌体miRNA可以反映HBV相关HCC。有研究分析了HBV相关HCC血清外泌体miRNA的整体表达谱,发现包括miR-150和miR-342-3p在内的多种miRNA的水平发生了改变<sup>[32]</sup>,且miR-122增加近4倍<sup>[33]</sup>。另有研究发现,血清外泌体异型核糖核蛋白H1mRNA(heterogeneous nuclear ribonucleoprotein H1,hnRNPH1mRNA)可作为HBV高发地区HCC的有效标志物<sup>[34]</sup>。文献报道,HCC的患者血清外泌体miR-212的表达水平显著升高,其敏感性和特异性均优于AFP,CA125和HBx蛋白<sup>[35]</sup>。

上述研究表明,不同类型的HBV患者和健康人群血清外泌体miRNA的表达谱不同,且水平随着疾病进程而变化,能够指示不同的生理或病理状态,因此,血清外泌体miRNA的检测能够明显提高HBV感染不同临床阶段的诊断准确,有利于HBV相关HCC的早期诊断和识别,从而提高患者的疗效及预后。

#### 4 外泌体与抗HBV治疗

尽管目前有多种抗HBV药物可供选择,但由HBV感染引发的相关疾病仍在严重威胁着人类的健康,研究人员一直在寻找新的抗HBV治疗方法。外泌体作为多种生物活性物质的天然载体,在抗HBV感染的治疗中具有广阔的应用前景。

来自免疫细胞的外泌体具有免疫刺激作用,能够诱导机体针对抗原特异性CTL的免疫应答,因此,外泌体可以作为疫苗佐剂用于增强机体对HBV的免疫应答,促进机体对HBV的清除。

Nef蛋白突变体(Nef<sup>mut</sup>)是一种与外泌体脂膜有高度融合性但其本身不具有生物活性的蛋白质,可以作为外泌体的良好载体,增强机体对外泌体抗原成分的免疫应答<sup>[36]</sup>。研究发现,将经过体外抗原改造的外泌体与Nef<sup>mut</sup>外泌体锚定蛋白融合后接种小鼠,能够增强抗原特异性CTL的免疫应答效应<sup>[37]</sup>。HBcAg由于存在于HBV病毒颗粒的核心且其外被HBsAg所覆盖,因此不易在血液循环中检出,但大量存在于受HBV感染的肝细胞内<sup>[38]</sup>,是CTL免疫治疗的理想靶标。研究发现,全长的HBcAg与Nef<sup>mut</sup>融合后,其抗原信息可被有效整合到外泌体中,外泌体免疫原性增加,引发CTL免疫应答,进而促进HBV感染细胞被CTL清除<sup>[39]</sup>,提示将与Nef<sup>mut</sup>融合的改造外泌体诱导CTL免疫应答用于抗HBV治疗具有良好的可行性。Nef<sup>mut</sup>作为外泌体的载体。

此外,外泌体还可作为载体向体内递送特定分子。研究发现,将人单核细胞系(human monocytic cell line,THP-1)经脂多糖刺激后产生的外泌体注射于正常小鼠皮下,结果发现小鼠分泌细胞因子TNF- $\alpha$ 和IL-1 $\beta$ 增加;另外,小鼠皮下联合接种外泌体与重组HBsAg的混合溶液,结果显示外泌体触发了小鼠的免疫调节,增加了小鼠IFN- $\gamma$ 的分泌<sup>[40]</sup>,进而增强了小鼠对HBV的免疫应答,促进了小鼠对HBV的清除。

外泌体作为抗病毒治疗的载体和疫苗佐剂正在被不断探索,随着相关研究的逐渐深入,外泌体在抗HBV治疗领域的特殊临床应用价值将不断展现。

#### 5 展望

外泌体作为一种细胞间物质和信息传递的载体,是一种独特的细胞间沟通的工具。外泌体可以在细胞间传递HBV多种相关物质,在HBV感染、传播及相关疾病的发生发展过程中发挥重要作用。外泌体miRNA的种类及其水平变化可反映HBV相关疾病的不同阶段。此外,外泌体作为治疗性药物的天然内源性载体用于临床治疗具有独特的优势,为临床抗HBV治疗提供了新的方向。

目前,有关HBV与外泌体的相关研究仍处于早期阶段,深入研究外泌体在HBV致病、诊断和治疗中的作用,将有助于揭示HBV和宿主细胞的相互作用方式并进一步明确HBV的致病机制,有利于我们了解如何通过外泌体影响HBV感染的最终转归,以及进一步了解如何通过改变外泌体的成份来进行抗HBV的治疗。

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