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文献综述 REVIEW

自然杀伤细胞功能与维生素信号调节在免疫性肝病中的研究进展

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Role of natural killer cells and vitamin signaling in autoimmune liver disease

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Abstract

Natural killer (NK) cells are a major group of human hepatic lymphocytes. Their precursors undergo a maturation process that leads to the acquisition of their effecter functions to regulate the innate and acquired immune responses. With the changes in the expression of chemotactic receptors and adhesion molecules, NK cells migrate to the target organ, leading to the immune-related liver diseases. The discovery of the vitamin signaling and vitamin receptor expression in NK cell lineage, particularly the interaction with nuclear receptors, suggests a novel role for vitamin signaling in modulating immunological function and in the development or prevention of autoimmune diseases.

Key Words: Natural killer cell; Liver; Vitamin

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摘要

自然杀伤细胞(natural killer cell, NK细胞)在肝脏中占有很大比例, 通过分泌细胞因子和细胞间接触调节天然免疫和获得性免疫反应. NK细胞表达趋化因子受体迁移到炎症部位作用, 与免疫性肝病发病相关. 维生素相关代谢产物信号对NK细胞分化的调节是近年来受关注的热点, 通过与细胞核受体相互作用实现功能调控, 是自身免疫疾病治疗的新靶点.

关键词: 自然杀伤细胞; 肝脏; 维生素

核心提示: 自然杀伤细胞(natural killer cell, NK细胞)是免疫性肝病发病的重要机制. NK细胞的分化受到维生素信号调节, 提示自身免疫性疾病的发生和治疗都可能与肠源性因素相关.

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0 引言

自然杀伤细胞(natural killer cell, NK细胞)在不同的免疫器官中所起的作用各异[1],与环境中的不同炎症调控因子有关[2]. 以往根据其产生细胞因子的效应不同, NK细胞经典分类为NK1, 产生干扰素-γ(interferon-γ, IFN-γ)和白介素-10(interleukin-10, IL-10), 表达高水平的IL-12β2受体; NK2产生IL-5/IL-13, IL-12β2受体表达水平相对较低[3]. NKT细胞属于T细胞群体, 表达T细胞

■背景资料
自然杀伤细胞(natural killer cell, NK细胞)是肝脏内重要的免疫调节细胞. 肝脏具有独特的免疫耐受环境. NK细胞在免疫性肝病中的作用受到关注, 其功能和分化受到维生素信号的调节.

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■研发前沿
研究热点是在肝脏的特殊免疫环境下, NK细胞的功能与分化调节-其与多种细胞外信号相关. 维生素相关代谢产物对肝脏内NK细胞分化的调节是未来研究的方向.

(抗原)受体(T cell receptor, TCR)和NK1.1, 分为Ⅰ型(经典, CD1d依赖)、Ⅱ型(其他CD1d依赖的T细胞)和NKT样细胞(非CD1d, 表达NK1.1的T细胞[4]).

近来的研究[5]发现由于在不同器官中的免疫环境不同, 因此对NK细胞动态分化产生影响. 目前根据CD56和CD16的表达分群[6]: 循环中为$CD56^{low}CD16^{+}$ NK细胞, 可以杀伤靶细胞并产生细胞因子. $CD56^{hi}CD16^{-}$ NK细胞多存在于外周淋巴器官, 产生IFN-γ, 肿瘤坏死因子以及粒细胞集落刺激因子, 并可以分化成$CD56^{low}CD16^{+}$ NK细胞. 10%的NK细胞为对细胞因子高反应的$CD56^{bright}$, 90%为杀伤性的$CD56^{dim}$.

1 肝脏中的NK细胞亚群

NK细胞来源于$CD34^{+}$造血干细胞, 在脾脏、肝脏和外周血中占有5%-20%, 而在骨髓、胸腺和淋巴结中占有比例较低, 在中枢和外周免疫器官中有不同的分化模式[7]. 肠道NK细胞与其他有所不同, 称为“辅助”NK细胞, 维持肠道上皮完整, 与肠道内T细胞相同, 需要诸如IFN-γ、IL-15和IL-18的激活[8].

NK细胞是肝脏内重要的免疫调节细胞. 肝脏具有独特的免疫环境, 存在大量来自于肠道的抗原却不产生显著的炎症, 与免疫细胞诱导的免疫耐受有关[9]. 人类30%-50%的肝脏淋巴细胞是NK细胞及NKT细胞[10], 主要存在于肝窦并黏附于内皮细胞[11], 分为不同的亚群, 参与肝脏微环境的免疫调控[12]. NKT细胞促进肝内黏附分子的表达和趋化因子的产生, 促进Th1细胞的分化和调节T细胞在肝脏内浸润, 因此参与调节炎症反应平衡及介导肝脏损伤[13].

肝脏作为肠道和全身其他系统的屏障, 可以阻止细菌产物的暴露以及毒物和食物抗原的不良刺激, NK和NKT细胞在天然免疫反应中也是必不可缺的[14], 在肝损伤和肝纤维化的发展中起到作用[15].

NK细胞表达不同的受体识别不同来源的配体, 发挥激活或抑制性作用[16]. NK细胞的杀伤作用是通过穿孔素, 丝氨酸酯酶和肿瘤坏死因子(tumor necrosis factor, TNF)家族受体介导的. NK细胞通过分泌细胞因子和细胞间接触调节天然免疫和获得性免疫反应[17].

■相关报道
原发性硬化性胆管炎患者肝脏组织中NK细胞与自身免疫的激活有关. 维生素D通过抑制T细胞促炎因子的表达, 抑制NK细胞以及NKT细胞的发育成熟.

2 肝脏免疫性疾病中的NK细胞功能

NK细胞在疾病中发挥着促进疾病进展或者抑制的角色-NK细胞同时表达激活和抑制受体. NK细胞的抑制性受体结合主要组织相容性复合体(major histocompatibility complex, MHC)Ⅰ类分子时, 其产生细胞毒性和细胞因子的作用被阻断, 与激活受体的信号的效应拮抗[18].

骨髓来源的NK前体细胞在成熟过程中表达趋化因子受体和黏附分子, 迁移定居至脾脏、肝脏、肺和其他器官并动态循环, 其表达趋化因子受体包括CCR2、CCR5、CXCR3和CX3CR1等[19]. 目前为止对NK细胞的循环模式并不十分清楚, 不同的脏器表达不同的趋化因子募集不同的NK细胞. 肝脏内产生的CCL2、CCL3、CXCL10诱导表达相应受体的NK细胞到达病变处; 表达抑制性细胞受体NKG2A的NK细胞参与诱导肝脏免疫耐受[20]. 高表达CX3CR1的NK细胞表达Th2类细胞因子, 促进NK细胞的成熟和迁移[21]. 肝脏内存在的IFN-α、IFN-γ、IL-2、IL-6、IL-12和IL-18激活NK细胞, IL-15和IL-2维持细胞存活.

NK细胞表达Toll样受体(Toll-like receptor, TLR), 激活后产生IFN-γ等参与炎症反应[22]. 研究[23]表明, poly I:C诱导的肝病模型中NK细胞在肝脏中大量积累. NK细胞通过细胞间相互作用诱导肝脏免疫耐受. NK细胞调节树突细胞(dendritic cell, DC)功能. 肝脏和肠道内的$CLEC9A^{+}$/$BDCA3^{+}$(CD141)DC和其他亚群在IL-12、IL-15等细胞因子作用下, 参与介导NK细胞激活[24]. Kupffer细胞产生IL-10抑制NKT细胞的杀伤功能, 减少肝脏炎症破坏[25].

NK以及NKT细胞在免疫性肝病中可扮演多种“角色”-具有促炎作用和抗炎作用, 参与其他免疫调节细胞向肝脏内募集的过程[26]. NK细胞受体基因多态性与原发性硬化性胆管炎(primary sclerosing cholangitis, PSC)发生及其癌变相关[27]. 原发性胆汁性肝硬化(primary biliary disease, PBC)患者肝脏组织中NK细胞与自身免疫的激活有关[28].

在PBC中, NK细胞起到了极为关键的调节免疫耐受的作用. 在PBC动物模型的胆管损伤中, 人们发现, NK细胞在早期打破免疫耐受方面起到重要作用, 并且诱导该疾病特异性的自身抗体产生[29], 参与激活下游免疫细胞导致胆管损伤. 也有研究发现PBC早期肝内的NK细胞数目减少, 但$CD56^{+}$ NKT细胞在进展期PBC中明显增多, 并表达FasL参与胆管上皮损伤, 由于TLR4配体激活的NK细胞联合TLR3配体激活的单核细胞可以攻击破坏胆管上皮细胞, 加速了PBC的进展[30].

CD1d-α-GalCer活化的NKT细胞在PBC患者体内明显升高, 加重了胆管损伤和肝脏纤维化程度. 在缺失NK细胞和NKT细胞动物体内, 会发现抗线粒体抗体滴度的降低, 而胆管炎症没有明显改善. 因此认为, NK细胞和NKT细胞在PBC早期免疫耐受的失衡中发挥作用[31].

3 维生素信号参与NK细胞功能调节

维生素与细胞免疫功能相关, 近年来发现维生素A、D和维生素E信号通路与免疫功能基因相互作用, 在免疫性疾病的发生、发展中起到作用[32,33]. 维生素相关代谢产物对免疫细胞, 特别是NK细胞分化的调节是最近几年来受关注的热点之一[34], 由于受到“肝-肠”循环的影响, 肠道对于维生素的吸收和利用可能与肝脏内NK细胞的功能状态密不可分[35], 也是未来研究的方向.

饮食和皮肤来源的维生素D无活性, 经过肝脏和肾脏的两步代谢产生活性维生素D. 维生素D受体(vitamin D receptor, VDR)在细胞核内结合特定反应元件促进靶基因的表达[36]. 维生素D一直被认为与骨代谢有关, 越来越多的研究显示其参与免疫调节过程, 涉及单核细胞, 树突细胞和活化的T细胞, 维生素D摄入的减少增加免疫性疾病发生的几率, 维生素D水平与组织功能与炎症改变有关, 缺乏维生素D可以导致肝脏纤维化的进展[37].

维生素D的代谢产物, 其受体基因多态性及转录调节因子在免疫性肝病的发病和治疗中有重要意义[38]. VDR的多态性和转录调节参与T细胞和NK细胞的分化[39], 其在PBC发病中的意义还有争论[40,41]. 免疫性肝病患者多伴有维生素D的缺乏, 其参与调节患者体内磷酸化激酶信号通路活化[42], γδT细胞分化, IFN-γ, 一氧化氮合酶和氧自由基的表达水平.

维生素D受体在肝窦内皮细胞、Kupffer细胞、星状细胞和胆管细胞中均有表达, 其作为重要的核受体成为PBC胆汁淤积的治疗靶点. PBC患者常常缺乏维生素D, 维生素D具有抗增殖和抗纤维化作用, 其与MHC Ⅱ类分子, TLR信号有相互作用, 并调节基质金属蛋白酶、前列环素、活性氧自由基及转化生长因子的表达[43].

$1,25(OH)_2D_3$抑制Th1和Th17细胞产生IL-17和IFN-γ, 诱导调节T细胞和NKT细胞产生[44]. 维生素D缺失时iNKT细胞多进入凋亡, 使最终成熟iNKT数目减少, 而缺失VDR的iNKT细胞停滞在S_2阶段, 不能发育成熟[45]. 维生素D可以上调NK细胞毒性受体NKp30、NKp44和NKG2D, 阻断抑制性受体CD158的表达, 促进NK17/NK1的细胞溶解效应[46]. 维生素D抑制脐带来源的$CD34^+$细胞向NK细胞分化, 降低其毒性作用和细胞因子的表达, 但不影响成熟NK细胞上述功能[47].

维甲酸(retinoic acid, RA)是维生素A的代谢产物, 在黏膜免疫中被发现有重要作用[48]. RA可以抑制IL-1受体上调, 抑制IL-6R表达, 通过促进免疫抑制的机制治疗免疫性疾病. RA通过激活抗原提呈细胞表达CD1d激活NKT细胞, 减少IFN-γ和IL-4的产生, 通过RARα介导并减少MAPK信号磷酸化实现[49].

RA可以诱导DC免疫耐受, 减少Th1和Th2类细胞因子分泌, 视黄醇结合蛋白(retinoid binding protein, RBP)是从肝细胞到靶细胞的重要转运蛋白, 主要由肝脏合成, 其通过作用于DC-NK细胞, 促进IFN-γ的产生[50]. RA通过抑制NKT细胞产生IFN-γ和由TCR/CD28激活的下游信号的磷酸化减少肝脏内的炎症反应[51].

维生素E可以延缓免疫性疾病的进展, 减少IL-6、IL-10及TNF-α的水平. 维生素C和E可以降低NK细胞活性, 减轻炎症反应[52]. 维生素E可以降低肝脏内一氧化氮、肿瘤坏死因子、IL-6、C反应蛋白和IgG的水平, 从而起到肝脏保护作用[53].

4 结论

目前对于NK细胞的器官特异性分布和调节成为研究热点, NK细胞通过迁移, 与其他免疫细胞相互作用在自身免疫性疾病中发挥作用. 肝脏内具有特殊的免疫微环境, 肠道抗原参与了肝脏内免疫耐受环境的形成, NK细胞在炎症因子的诱导下参与免疫损伤, 维生素信号直接或间接的诱导不同亚群和功能的NK细胞分化, 未来可能成为免疫性肝病的治疗的新方向.

■创新盘点

NK细胞在肝脏免疫性疾病的发生中有重要作用. 该综述将目前最新的基础研究与临床研究进行分析、讨论及总结, 提出维生素信号直接或间接的诱导不同亚群和功能的NK细胞分化, 未来可能成为免疫性肝病的治疗的新方向.

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■应用要点

本综述对免疫性肝病环境中，NK细胞的亚群特征和功能研究的最新进展总结分析，提出肠道来源的维生素信号参与调节NK细胞分化，可能成为未来治疗的新途径.

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■同行评价
本文对NK细胞在免疫性肝病发病和治疗中的应用有重要的意义.

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