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Hans汉斯

基于NK细胞的恶性疾病免疫治疗

訾萌萌[1]，吴春涛[2*]，吴　庆[1]，许雅贤[1]，张　祎[1]

[1]华北理工大学临床医学院，河北　唐山
[2]华北理工大学附属医院肿瘤外科，河北　唐山

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摘　要

自然杀伤(NK)细胞是先天性淋巴细胞，具有识别和杀死肿瘤细胞的能力，在抗癌免疫中发挥着重要作用。肿瘤患者的NK细胞具有不同的表型和功能特性，这些特性可能是由肿瘤微环境决定的。控制NK细胞活性的人类白细胞抗原I类特异性抑制性受体的发现，为调节由一系列抑制性受体调节的免疫反应的基本概念铺平了道路，并强调了探索NK细胞在癌症治疗中潜力的重要性。尽管目前正在开发一系列基于NK细胞的方法，但为了提高这些疗法的疗效，仍然需要克服重大挑战。这些包括肿瘤细胞由于表达抑制分子而逃避NK细胞识别、NK细胞的免疫抑制信号、肿瘤的NK细胞浸润减少、免疫抑制微环境和NK细胞在体内的持久性有限。这篇综述将概述NK细胞生物学、NK细胞激活和抑制受体、在实体瘤免疫监视中的作用、导致NK细胞免疫逃逸或免疫监视的肿瘤微环境，以及NK细胞的来源，为以后临床上设计使用NK细胞提供有效策略，提高治疗效果。

关键词

NK细胞，肿瘤细胞，过继细胞移植

NK Cell-Based Immunotherapy for Malignant Diseases

Mengmeng Zi[1], Chuntao Wu[2*], Qing Wu[1], Yaxian Xu[1], Yi Zhang[1]

[1]Clinical Medical College of North China University of Science and Technology, Tangshan Hebei
[2]Department of Surgical Oncology, Affiliated Hospital of North China University of Science and Technology, Tangshan Hebei

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Abstract

Natural killer (NK) cells are innate lymphocytes with the ability to recognize and kill tumor cells

*通讯作者。

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and play an important role in anti-cancer immunity. NK cells from tumor patients have different phenotypic and functional properties that may be determined by the tumor microenvironment. The discovery of human leukocyte antigen class I-specific inhibitory receptors controlling NK cell activity has paved the way for the fundamental concept of modulating immune responses regulated by a range of inhibitory receptors and underscores the importance of exploring the potential of NK cells in cancer therapy. Although a range of NK cell-based approaches are currently being developed, significant challenges still need to be overcome in order to improve the efficacy of these therapies. These include tumor cells evading NK cell recognition due to the expression of inhibitory molecules, immunosuppressive signaling by NK cells, reduced NK cell infiltration of tumors, an immunosuppressive microenvironment, and limited persistence of NK cells in vivo. This review will provide an overview of NK cell biology, NK cell cytosolic activation and inhibitory receptors, their role in immunosurveillance in solid tumors, the tumor microenvironment leading to immune escape or immunosurveillance of NK cells, and the sources of NK cells, to provide an effective strategy for designing the use of NK cells in the future clinic and to improve therapeutic outcomes.

Keywords

NK Cells, Tumor Cells, Transplantation of Relayed Cells

1. NK 细胞的一般特征

自然杀伤细胞是在 20 世纪 70 年代被发现的，是对肿瘤细胞表现出自发反应的大颗粒淋巴细胞[1] [2] [3] [4]。与 T 细胞相反，NK 细胞的抗肿瘤活性不需要与 MHC 复合物中的抗原识别；相反，它是在缺乏对肿瘤细胞上“自身”标志物的识别后被激活的，再加上竞争性激活和抑制性受体的组合。NK 细胞有两种主要的细胞毒性机制，穿孔素和颗粒酶介导的粒细胞凋亡和抗体依赖性细胞介导的细胞毒性(Antibody-dependent cell-mediated cytotoxicity, ADCC)。NK 细胞能够形成含有穿孔素和颗粒酶的细胞质溶解颗粒，并产生大量细胞因子，特别是干扰素(IFN)，但也产生促炎和免疫抑制细胞因子，例如肿瘤坏死因子(TNF)，白细胞介素(IL)-10、趋化因子和各种生长因子，如粒细胞巨噬细胞刺激因子(GM-CSF)、粒细胞刺激因子(G-CSF)和 IL-3。它们通过不同的机制发挥细胞毒活性，包括颗粒酶和穿孔素的释放、IFN 和 TNF 的分泌、FasL/Fas 或 TNF 相关凋亡诱导配体(TRAIL)/TRAIL 受体的表达和 ADCC 通过 Fc 受体(CD16)识别与抗原包被的(肿瘤)细胞结合的抗体[5] [6] [7]。基于其溶细胞功能，NK 细胞在第一道免疫防御中发挥着关键作用，能够直接消除肿瘤或病原体感染的细胞。在这种情况下，值得注意的是 NK 细胞具有安全特性，很少引发自身免疫并促进免疫稳态。

2. NK 细胞激活和抑制受体

人们普遍认为，NK 细胞的激活是激活信号和抑制信号之间平衡的结果。为了防止 NK 细胞激活，肿瘤细胞进化为表达 NK 细胞抑制配体模式，例如经典和非经典 MHC-I [8]，并下调 NK 细胞激活配体的表达。

NKG2D 是一种识别细胞表面糖蛋白 MHC I 类多肽相关序列 A (MICA)和 B (MICB)以及 UL16 结合蛋白(ULBP 1-6)的激活受体，这些糖蛋白由 DNA 损伤、基因毒性或氧化应激诱导[9]。Guerra 等人使用

NKG2D 缺陷小鼠证明，NKG2D 是预防自发性和可移植肿瘤模型的发生和发作所必需的[10]。然而，为了逃避 NK 细胞识别并减少 NKG2D 介导的 NK 细胞激活，肿瘤细胞从其表面脱落 MICA 和 MICB [11]。肿瘤细胞脱落的 NKG2D 配体确实导致 NK 细胞和 T 细胞表面的 NKG2D 下调，进一步抑制抗肿瘤免疫[12] [13]。与 NKG2D 配体 MICA 和 MICB 类似，NKp30 配体 B7-H6 可以从肿瘤细胞表面裂解并以可溶性 B7-H6 形式释放，从而阻止 NKp30 介导的肿瘤细胞识别[14] [15]。

NKG2D 和 NKp30 并不是唯一在癌症中发挥作用的 NK 细胞受体。已经证明，NKp46 的缺失会导致 NK 细胞转移负担增加并减少 IFNγ 和 TNFα 的产生[16]。通过使用 NKp46-Fc 抗体，已证明某些肿瘤细胞系和原发肿瘤表达 NKp46 配体[16] [17]。这些发现证明了 NKp46 在肿瘤监测中的潜在意义。然而，还需要进一步的研究来鉴定诱导 NKp46 依赖性 NK 细胞抗肿瘤功能激活的肿瘤相关分子。尽管最近的数据表明 MHC II 类变体 HLA-DP 可以结合 NKp44，并可能在病毒感染时影响 NK 细胞激活[18]；没有证据表明 NKp44 在癌症中发挥作用。

DNAM-1 是 NK 细胞表达的细胞表面糖蛋白，参与肿瘤识别。DNAM-1 的配体是 CD112 和 CD155，这两种脊髓灰质炎病毒受体(PVR)在病原体感染或恶性细胞上表达[19]。由于这些分子具有结合 DNAM-1 和 TIGIT (NK 细胞上的一种抑制性受体)的独特特征，肿瘤细胞表达的 CD112 和 CD155 可能通过触发或抑制 NK 细胞效应功能发挥双重作用。最近的证据表明，小鼠 DNAM-1 缺乏或阻断并不影响免疫细胞对同基因肿瘤的控制[9] [20]。相反，在几种癌症的临床前模型中，TIGIT 的阻断可防止 NK 细胞耗竭并促进 NK 细胞依赖性肿瘤免疫[9] [20]。这些发现表明，肿瘤细胞表达的 CD112 和 CD155 作为 TIGIT 的抑制性配体可能比 DNAM-1 的激活配体更好地发挥作用。

在乳腺癌和胰腺癌中，已观察到 NKp30、NKG2D、NKp46 和 DNAM-1 的下调伴随着抑制性受体 NKG2A 的上调，与 NK 细胞的细胞毒性受损相关。阻断 TGFβ 部分挽救了这些 NK 细胞激活受体的表达[21]，这表明肿瘤微环境中的可溶性分子可能负责 NK 细胞受体库的调节。值得注意的是，TGFβ 不仅影响激活受体的表达，还影响趋化因子受体的表达，从而阻止 NK 细胞募集到肿瘤部位。这些证据表明 TGFβ 在支持 NK 细胞逃逸机制方面具有双重作用[22]。

3. NK 细胞在实体瘤免疫监视中的作用

NK 细胞对肿瘤细胞的免疫监视功能最早是 20 世纪 80 年代发现的：由于某些家族遗传病(如 Chédiak-Higashi 综合征、X 性连锁淋巴组织增生综合征等)会导致患者 NK 细胞功能丧失，继而使得这些患者往往更容易罹患肿瘤[23]。NK 细胞的主要作用是识别和消除肿瘤细胞或病毒/病原体感染的细胞，作为防止肿瘤形成和病原体入侵的第一道防线，无需事先致敏[24]。这一假设的证据是 NK 细胞功能受损的人类和实验模型中肿瘤发病率增加[25]。NK 细胞在控制原发肿瘤发生以及肿瘤转移方面发挥着积极的免疫监视作用，且主要通过以下几种方式发挥对肿瘤细胞的杀伤作用：NK 细胞通过溶细胞作用直接杀伤肿瘤细胞；活化的 NK 细胞通过分泌多种细胞因子发挥抗肿瘤效应，并促进抗原提呈细胞成熟，进而诱导适应性免疫应答的发生[26]。

4. 肿瘤微环境(TME)和 NK 细胞

免疫反应是免疫细胞之间联网的结果。肿瘤微环境中免疫抑制细胞的存在危及免疫网络，从而影响肿瘤免疫反应的成功。NK 细胞是天然细胞，其抗肿瘤功能主要由髓系细胞触发。反过来，NK 细胞通过产生免疫调节因子，如干扰素 γ、肿瘤坏死因子 α 和 CCL5 来协调髓系免疫和适应性抗肿瘤免疫。了解肿瘤微环境中 NK 细胞联网成功或失败的细胞和分子机制，对于识别潜在靶点，不仅释放自然杀伤的力量，而且释放整个抗肿瘤免疫反应的效率是至关重要的。目前大量研究显示，以下因素可诱导肿瘤逃逸 NK

细胞的免疫监视作用：血小板[27]、腺苷酸[28]、白细胞介素-10 (IL-10) [29] [30]、转化生长因子 β (transforming growth factor β, TGF-β) [31]以及吲哚胺 2,3 双加氧酶(indoleamine 2,3-dioxygenase, IDO) [32]，这些免疫抑制因素不仅会影响 NK 细胞的功能，还会影响 NK 细胞的成熟过程。在多方因素的共同作用下，使肿瘤细胞可以在肿瘤微环境中存活下来。

5. 过继细胞移植

NK 细胞可以从患者或健康捐赠者体内的多种来源获得。虽然成熟的 NK 细胞可以从血液中分离出来，但它们也可以与干细胞分化，包括从脐带血中分离的干细胞、胚胎干细胞和诱导多能干细胞。NK 细胞约占外周血淋巴细胞的 10%~15%。为了获得临床级 NK 细胞，首先对白细胞分离产品进行 CD3− CD56+细胞群分类，然后进行扩增通过细胞因子治疗，最常见的是 IL-2 和 IL-15 [33] [34]。除了扩大 NK 细胞群外，这些细胞因子还激活 NK 细胞，导致细胞毒性增加[35]。分离的 NK 细胞与经过辐照的饲养细胞群的共培养也被证明是有效的，并且在晚期消化癌的 I 期临床试验中被证明是安全的，因此可能是快速 NK 细胞扩增的更有效的方法[36]。从干细胞中分离的 NK 细胞受益于更易于储存和纯度的提高；然而，已有报道称 NK 细胞与外周血单核细胞(PBMC)来源的 NK 细胞存在功能差异。值得注意的是，与 PBMC 衍生的 NK 细胞相比，脐带血 NK 细胞缺乏激活标记 CD57 的表达，抑制性受体 NKG2A 的表达较高，并且表达较少的抑制性 KIR [37]，从而导致细胞毒性降低。然而，与 PBMC 分离的 NK 细胞类似，IL-2、IL-15、IL-7 或饲养细胞的处理已被证明可以增加其细胞毒性[38]，这表明脐带血 NK 细胞仍然是一个可行的选择[39]。同样，存在多种将 NK 细胞从胚胎或多能干细胞中分化出来的方案，这些方案依赖于细胞因子或饲养细胞的处理[40] [41]。干细胞衍生的 NK 细胞可能比脐带血细胞更有优势，因为与从 PBMC 中分离的细胞相比，它们的细胞毒性特征相似[42]，并且能够作为可再生的细胞来源进行维护[43]。在临床上，NK 细胞的过继细胞移植可以使用从患者自身血液或干细胞中分离或产生的自体 NK 细胞，也可以使用从健康供体获得的同种异体 NK 细胞。

6. 结论

NK 细胞活性的增强是控制癌症生长的重要途径。对 NK 细胞生物学的日益了解导致了基于 NK 细胞的控制肿瘤策略的发展。由于 NK 细胞在免疫抑制性 TME 中变得功能失调，因此需要新的方法来增强 NK 细胞的靶向性、活化和细胞溶解功能。尽管基于 NK 细胞的治疗具有潜力，但很明显，为了在临床上设计使用 NK 细胞的有效策略，需要对 NK 有详细的了解。一些临床前和临床研究表明，在使用联合疗法治疗癌症患者时，实施 NK 细胞有多方面的机会，这将导致进一步的临床进展。

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