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NK细胞免疫耗竭的特征及免疫治疗潜力

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[**摘　要**]　NK细胞是固有免疫系统核心成员,通过直接杀伤和辅助其他免疫细胞参与抗肿瘤和抗感染免疫应答。而肿瘤和慢性感染常导致NK细胞免疫耗竭,从而使其效应功能下降,限制其控制肿瘤和感染的能力。NK细胞耗竭导致表面受体、细胞因子和转录因子等多方面改变。深入研究NK细胞耗竭的特征不仅有助于理解NK细胞的基础生物学特性,还可以开发基于NK细胞的新型免疫治疗靶点。本文总结了现有的NK细胞耗竭特征及相关知识,并讨论其在免疫治疗方面的潜力。

[**关键词**]　NK细胞;NK细胞耗竭;NK细胞功能障碍;免疫治疗

Characteristics of NK cell immune exhaustion and immunotherapeutic potentia

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[**Abstract**]　NK cells are essential components of innate immune system and play crucial roles in combating tumors and infections by directly eliminating target cells and supporting other immune cells. However, tumors and chronic infections often result in exhaustion of NK cells, which diminishes their effector functions and hampers their ability to control progression of tumors and infections. NK cell exhaustion is accompanied by alterations in surface receptors, cytokines and transcription factors. A comprehensive investigation into characteristics of NK cell exhaustion not only enhances our understanding of fundamental biological properties of NK cells but also facilitates development of novel immunotherapy approaches utilizing NK cells. This article provides an overview of current understanding of NK cell exhaustion, including its characterization and relevant knowledge, and explores its potential applications in immunotherapy.

[**Key words**]　NK cell;NK cell exhaustion;NK cell dysfunction;Immunotherapy

机体免疫系统有两大分支,即适应性免疫系统(由T和B细胞构成)和固有免疫系统(由NK细胞、巨噬细胞等构成)。NK细胞是固有免疫系统的重要成员,能够直接杀伤靶细胞,且不会对健康细胞造成损伤[1]。NK细胞在血液和其他组织部位的淋巴细胞中相对丰富,其表型为$CD3^-CD56^+$,占总淋巴细胞的5%~20%,在控制感染方面起重要作用,能够杀伤肿瘤细胞并防止其转移[2-3]。NK细胞还在免疫介导的保护和稳态维持中起重要作用[4]。而在肿瘤和慢性感染环境中,NK细胞表现出与T细胞相似的耗竭状态,其效应功能较差,并降低了基于NK细胞的治疗效果[5]。与T细胞耗竭相比,NK细胞耗竭的定义尚不够精确。基本延续了T细胞耗竭的定义,被描述为在慢性且持续的抗原刺激下,NK细胞表现出功能低下状态,并伴随一系列特征性变化[6-7]。NK细胞耗竭的主要特征包括细胞毒性损害、细胞因子分泌减少、抑制性受体表达上调、激活受体表达下调、增殖失调、代谢功能障碍以及相关转录因子表达改变[7-8]。近年对NK细胞耗竭的研究已广泛进行,但仍存在许多争议和理解不足。既往研究并未考虑到传统NK细胞与适应性NK细胞的差异。适应性NK细胞表现出的表观遗传特征更类似于效应$CD8^+$T细胞,并具有免疫记忆特性和一定抗原特异性。传统NK细胞功能低下是否与稳定的表观遗传和转录组变化有关仍需进一步确定[9-10]。因此,适应性NK细胞可能是真正意义上的NK细胞耗竭群体。此外,相关研究还推动了NK细胞耗竭相关的免疫治疗发展。本文将总结目前对NK细胞耗竭的理解,并探讨其在免疫治疗方面的前景。

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1　NK细胞的起源和功能

1.1　NK细胞的发育与成熟　人类NK细胞源自骨髓中的多能造血干细胞(hematopoietic stem cells, HSCs)。NK细胞发育通过一系列不连续步骤进行,每个步骤通过特定的表面标志物定义NK细胞在淋巴细胞谱系中的定位[11]。第一阶段是在骨髓中的$CD34^+CD45RA^+$HSCs;第二阶段发生在NK细胞发育的主要部位,如胸腺、脾脏和扁桃体,通过表达CD56、CD117和IL-1受体1(IL-1 receptor 1,IL-1R1)确定;第三阶段是CD34丧失;第四阶段是CD117下调并伴随CD94的获得,CD94标志$CD56^{bright}$NK细胞定型[12-14]。这个阶段NK细胞开始高水平表达T盒转录因子Eome(T-box transcription factors eomesodermin, Eomes)和T细胞表达的T盒(T-box expressed in T cells, T-bet)[15]。第四阶段又分为A和B两个阶段,后者特征为通过NKp80表达形成穿孔素和颗粒酶,从而获得细胞毒能力[16]。随后,CD16和杀伤细胞免疫球蛋白样受体(killer cell immunoglobulin-like receptor, KIR)表达标志第五阶段,即$CD56^{dim}$NK细胞。最后,CD57表达标志终末分化的NK细胞,即第六阶段[17]。与成熟的$CD56^{dim}CD16^+$亚群相比,外周血中$CD56^{bright}CD16^-$NK细胞丰度较低,细胞毒性较差。另外,暴露于环境刺激时,它们产生大量NK细胞标志细胞因子IFN-γ和TNF-α[15]。

1.2　NK细胞的功能　NK细胞在细胞毒性作用和免疫调节中发挥作用,是固有免疫中的两个重要功能[18]。$CD56^{dim}$NK细胞主要存在于外周血,可表达颗粒酶和穿孔素,直接杀伤肿瘤细胞和病原体[1,19]。$CD56^{bright}$NK细胞主要存在于淋巴器官,不表达穿孔素,但会产生大量细胞因子,如IFN-γ、TNF-α、IL-12、IL-15和IL-18,具有重要的免疫调节功能[20]。活化的NK细胞还可介导TNF-α、自杀相关因子(factor associated suicide, Fas)配体(Fas ligand, FasL)、TNF相关凋亡诱导配体(TNF-related apoptosis-inducing ligand, TRAIL)结合,从而启动凋亡途径[21]。外周组织中有足够数量的NK细胞对保持正常的免疫监视功能至关重要[22]。另有研究表明,NK细胞还可通过树突状细胞编辑和成熟增强适应性免疫应答[8]。

2　NK细胞耗竭特征

2.1　NK细胞耗竭概述　免疫耗竭指慢性感染或肿瘤引起的持续抗原刺激导致细胞功能逐渐丧失以及增殖能力下降,最早发现于慢性淋巴细胞性脉络脑膜炎病毒感染的T细胞[9,23]。耗竭的T细胞表现出一系列变化,包括细胞因子生成减少、趋化因子生成增多、增殖能力下降、抑制性受体高表达、转录程序改变和独特的表观遗传特征[24]。慢性感染和肿瘤环境中,NK细胞也表现出类似于耗竭T细胞的效应功能减退和表型变化[7]。尽管导致NK细胞在肿瘤和慢性感染中耗竭的机制尚不明确,但已发现越来越多与NK细胞耗竭相关的因素[8]。

2.2　适应性NK细胞与耗竭　NK细胞是固有淋巴样细胞(innate lymphoid cells, ILCs),ILCs不表达抗原特异性受体。然而已证实NK细胞在巨细胞病毒(cytomegalovirus, CMV)感染条件下可产生获得性免疫特性[25]。固有免疫细胞能够快速感知病原体及其产物,并做出相应反应,还能够提高对再次接触相同病原体时的反应能力,即训练免疫或固有免疫记忆,这种训练性免疫通常不具备抗原特异性。显然,CMV对NK细胞的调控超出了训练性免疫应答范畴[26]。事实上,CMV感染后,NK细胞会发生明显重组,表达人类白细胞抗原分子E(human leukocyte antigen-E, HLA-E)特异性激活性受体CD94/NKG2C,导致NK细胞扩张,同时表现出高度分化的表面特征,即$self^-KIR^+NKG2A^-LILRB1^+CD57^+CD328^-$[27]。这种由CMV驱动的NK细胞群体被称为适应性NK细胞,并具有记忆样特性。多种证据表明,适应性NK细胞与传统NK细胞不同。适应性NK细胞对IL-12、IL-18的反应性较差,且NKp30和NKp46表达较低[28]。适应性NK细胞寿命更长,即使在没有检测到CMV的情况下,也能保持高水平数年。此外,适应性NK细胞表现出与效应$CD8^+$T细胞相似的表观遗传特征,并具有独特的代谢特点。研究证实,适应性NK细胞和$CD8^+$T细胞具有共同导致耗竭的分子途径[26,29]。适应性NK细胞更易发生耗竭,比传统NK细胞耗竭更有研究意义,并得到多种观点的支持[7,9]。从某种意义上说,适应性NK细胞可能是真正的NK细胞耗竭群体。

2.3　NK细胞功能障碍　NK细胞耗竭的直接表现是功能障碍。功能受损的NK细胞显示瞬时的脱颗粒标志溶酶体相关膜糖蛋白-1(LAMP-1,也称为CD107a)下调,且IFN-γ、TNF-α、细胞毒素穿孔素和颗粒酶产生减少[30]。NK细胞功能障碍需注意耗竭、衰老和抑制这3个概念存在相互关联和重叠。衰老是一种NK细胞功能障碍状态,与端粒缩短和DNA损伤有关,造成细胞周期停滞,从而限制寿命[23]。多数衰老细胞会产生多种促炎因子、趋化因子、生长因子和蛋白酶,即衰老相关分泌表型

(senescence-associated secretory phenotype, SASP)[31]。随着年龄增长,T细胞数量减少,而NK细胞数量增加[32]。NK细胞衰老可能是正常现象,仿佛在生命周期中具有进化保守作用[33]。另一种NK细胞功能障碍状态是外部因素导致的抑制。肿瘤微环境中的T调节细胞、肿瘤相关成纤维细胞和髓系抑制细胞会抑制NK细胞对肿瘤的杀伤能力[34]。另外,组织缺氧、血液高凝状态、糖皮质激素、前列腺素E2、IL-6、IL-10和TGF-β1也会抑制NK细胞功能[35]。这种抑制状态是可逆的,信号解除时可逆转,但耗竭会导致稳定的表型和表观遗传变化,而抑制和耗竭会相互重叠,不同刺激类型倾向于两种不同状态[9]。总的来说,耗竭是由抗原过度刺激引起的,抑制是外部非抗原因素的直接作用,而衰老则是NK细胞生命周期的必然终点。

2.4　NK细胞耗竭相关受体　NK细胞表面表达多种受体,这些受体的信号平衡和时空整合决定NK细胞的效应功能[36]。受体表达失衡是NK细胞耗竭的重要特征,包括激活性受体表达降低和抑制性受体表达升高,其中部分受体被称为NK细胞耗竭的关键表型[37]。需明确的是,NK细胞耗竭不是单一受体表达改变决定的,而是多个受体表达改变的共同结果。

抑制性受体一直是NK细胞耗竭研究重点,有些受体被认为是NK细胞耗竭的重要标志。程序性死亡蛋白1(programmed death 1, PD-1)作为经典的免疫检查点,最早发现与T细胞耗竭相关,后续研究证实其可能与NK细胞耗竭也相关。霍奇金淋巴瘤、鼻咽癌、卵巢癌和肾细胞癌等多种癌症中,NK细胞表达升高[38-40]。而关于PD-1存在很大争议,有观点认为其对NK细胞耗竭不如其他抑制性受体重要[7]。一项研究发现非小细胞肺癌患者NK细胞几乎无PD-1表达[41]。T细胞免疫球蛋白和免疫受体酪氨酸抑制结构域(T cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibition motif domains, TIGIT)和CD96为共抑制受体,已被证明是NK细胞重要的抑制靶点[42]。肠癌、卵巢癌和肝癌中,肿瘤内NK细胞TIGIT表达升高并与肿瘤进展相关[43-45]。事实上,高表达TIGIT的NK细胞功能明显受损,主要体现在TNF-α和IFN-γ分泌减少以及细胞毒性减弱[46-47]。此外发现CD96在肝癌的NK细胞中表达升高,且瘤内NK细胞产生的IFN-γ明显减少[48]。因此,TIGIT和CD96很可能与NK细胞耗竭相关。淋巴激活基因-3蛋白(lymphocyte activation gene-3, LAG-3)和T细胞免疫球蛋白黏蛋白3(T cell immunoglobulin domain and mucin domain-3, TIM-3)作为新兴的免疫检查点受体逐渐受到关注,某种意义上被认为是NK细胞耗竭的关键标志[49]。研究证实,阻断LAG-3后明显逆转了NK细胞的功能障碍[50]。TIM-3在不同类型肿瘤患者NK细胞上高表达,包括肺癌、胃癌、膀胱癌和晚期黑色素瘤,与NK细胞功能障碍和衰竭有关[51-53]。TIM-3还被认为是晚期肿瘤中NK细胞耗竭的标志[54]。另一个关键的NK细胞抑制性受体为NK细胞家族2成员A(natural-killer group 2 member A, NKG2A),研究发现非小细胞肺癌组织中NK细胞NKG2A表达高于外周血NK细胞[55]。另有研究观察到NK细胞耗竭过程中,NKG2A和杀伤细胞凝集素样物受体G1(killer cell lectin like receptor G1, KLRG1)表达升高[56]。除上述已报道与NK细胞耗竭相关的抑制性受体外,还可能存在其他相关的抑制性受体,包括细胞毒性T淋巴细胞抗原4(cytotoxic T-lymphocyte antigen 4, CTLA-4)[57]、唾液酸结合免疫球蛋白样凝集素7/9(sialic acid-binding immunoglobulin-like lectin 7/9, Siglecs7/9)[58-59]、Ig样转录本2(Ig-like transcript 2, ILT-2)[60]、白细胞免疫球蛋白样受体B4(leukocyte immunoglobulin like receptor B4, LILRB4)[61]、白细胞相关免疫球蛋白样受体-1(leukocyte-associated immunoglobulin-like receptor-1, LAIR-1)[62]、CD112R[63]、CD161[64]、CD200[65]、CD300a[66]以及部分抑制性杀伤性免疫球蛋白样受体(killer immunoglobulin-like receptor, KIR)[18],NK细胞耗竭相关抑制性受体信息见表1。

表1　NK细胞耗竭相关抑制性受体

Tab. 1　NK cell exhaustion-related inhibitory receptors

Name of receptors	Expressions	Receptor types	Reference
PD-1	Increased	Inhibitory receptor	[38-40]
TIGIT	Increased	Inhibitory receptor	[43-45]
CD96	Increased	Inhibitory receptor	[48]
LAG-3	Increased	Inhibitory receptor	[49]
TIM-3	Increased	Inhibitory receptor	[51-53]
NKG2A	Increased	Inhibitory receptor	[55]
KLRG-1	Increased	Inhibitory receptor	[56]
CTLA-4	Increased	Inhibitory receptor	[57]
Siglec-7/9	Increased	Inhibitory receptor	[58-59]
ILT2	Increased	Inhibitory receptor	[60]
LILRB4	Increased	Inhibitory receptor	[61]
LAIR-1	Increased	Inhibitory receptor	[62]
CD112R	Increased	Inhibitory receptor	[63]
CD161	Increased	Inhibitory receptor	[64]
CD200	Increased	Inhibitory receptor	[65]
CD300a	Increased	Inhibitory receptor	[66]
Inhibitory KIRs	Increased	Inhibitory receptor	[18]

激活性受体表达降低同样是NK细胞耗竭的重要特征。CD16a（IgGⅢ型Fcγ受体）是一种能与抗体Fc段结合的激活受体，能够介导抗体依赖性细胞毒作用，且能够单独激活NK细胞[67]。研究发现，乳腺癌患者NK细胞表达明显降低[68]。除CD16a外，NK细胞的主要激活性受体包括天然细胞毒性受体（natural cytotoxicity receptors，NCRs）、脱氧核糖核酸X辅助因子-1（deoxyribonucleic acid X accessory molecule-1，DNAM-1）和NKG2D，这些受体参与调节细胞毒作用的关键过程[67]。肿瘤和慢性肝炎患者的NK细胞中NKG2D、DNAM-1和NCRs中NKp30、NKp44、NKp46表达都有所降低[56,69]。其中，NKG2D表达降低被认为是NK细胞耗竭的关键表型[70]。其他可能的NK耗竭相关激活性受体包括CD49b[71]、CD160[72]、CD244[73]、NKG2C[74]、NKp80[75]、4-1BB[76]、信号淋巴细胞激活分子家族受体（signaling lymphocyte activating molecule-family receptors，SFRs）[77]以及部分激活性KIR[78]。NK细胞耗竭相关激活性受体信息见表2。

2.5　NK细胞耗竭相关转录因子　研究发现多种转录因子参与NK细胞耗竭过程。转录因子Eomes和T-bet在NK细胞成熟、分化和功能发挥中起重要作用[79]。研究发现，NK细胞耗竭过程中，这两种转录因子表达降低[56]。此外，研究还证实肿瘤导致的NK细胞耗竭与Eomes和T-bet显著减少相关[71]。此外，还有一些可能与NK细胞耗竭相关的转录因子和表观遗传调节因子，包括叉头盒转录因子O1（forkhead box transcription factor O1，FOXO1）[80]、叉头盒蛋白1（forkhead box protein 1，FOXP1）[81]、特异性AT富集序列结合蛋白1（special AT-rich sequence-binding protein 1，SATB1）[82]、T细胞因子12（T-cell factor 12，TCF12）[83]、胸腺细胞选择相关高迁移率族蛋白（thymocyte selection-associated high mobility group box，TOX）[84]、Ikaros家族锌指基因3（Ikaros family zinc finger 3，IKZF3）[85]、活化T细胞核因子C（nuclear factor of activated T cells C，NFATC）[86]和含锌指和BTB结构域的38号基因（zinc finger and BTB domain containing 38，ZBTB38）[87]。

表2　NK细胞耗竭相关激活性受体

Tab. 2　NK cell exhaustion-related activating receptors

Name of receptors	Expressions	Receptor types	Reference
CD16a	Decreased	Activating receptors	[67-68]
CD49b	Decreased	Activating receptors	[71]
CD160	Decreased	Activating receptors	[72]
CD244	Decreased	Activating receptors	[73]
4-1BB	Decreased	Activating receptors	[76]
DNAM-1	Decreased	Activating receptors	[56,69]
NKG2D	Decreased	Activating receptors	[67]
NKG2C	Decreased	Activating receptors	[74]
NKp30	Decreased	Activating receptors	[56,69]
NKp44	Decreased	Activating receptors	[56,69]
NKp46	Decreased	Activating receptors	[56,69]
NKp80	Decreased	Activating receptors	[75]
SFRs	Decreased	Activating receptors	[77]
Activating KIRs	Decreased	Activating receptors	[78]

3　NK细胞耗竭与免疫治疗

鉴于NK细胞具有强大的清除病原体和杀伤肿瘤细胞的能力，克服NK细胞耗竭问题催生了一系列基于NK细胞的免疫治疗方法，为肿瘤临床治疗提供了新策略。

逆转T细胞耗竭的免疫检查点阻断疗法为免疫治疗带来了新策略，并取得了前所未有的成功[88-89]。深入研究NK细胞耗竭促进了基于NK细胞的免疫检查点阻断疗法发展[90]。PD-1抑制剂已被批准用于各种癌症临床治疗，如帕博利珠单抗、纳武利尤单抗和西米普利单抗等[91]。最近，一种靶向LAG-3的单克隆抗体也被FDA批准用于治疗黑色素瘤[92]。当下数十种针对其他免疫检查点的单克隆抗体，如KIR、TIGIT、TIM-3和NKG2A，正在开发和临床试验阶段[93-94]。奥西佩里单抗（BGB-A1217）是一种新型人源化单克隆抗体，可与TIGIT高亲和力特异性结合。最新的1期临床试验中，其单独使用或与PD-1抑制剂替雷利珠单抗联用在晚期实体瘤患者中展现出良好的抗肿瘤疗效。目前，奥西佩里单抗联合替雷利珠单抗的2期和3期临床试验正在一系列实体瘤中进行，包括非小细胞肺癌、小细胞肺癌、食管癌和头颈部鳞状细胞癌[95]。一种靶向TIM-3的单克隆抗体沙巴托利单抗（MBG453）在最新的临床试验中显示出其作为髓系恶性肿瘤免疫治疗靶点的潜力[96]。虽然免疫检查点抑制剂研发越来越多，但由于肿瘤的复杂机制和耐药性等原因使其治疗效果仍有待提升[97]。一项关于头颈部鳞癌的临床试验中，阻断NKG2A并未取得理想效果[98]。然而，后续试验显示NKG2A抑制剂和PD-1抑制剂联用显著提升了非小细胞肺癌治疗效果[99]。因此，对不同类型肿瘤、不同治疗方法、不同药物组合和治疗方案仍需进一步探索，以达到满意疗效。

同时，NK细胞激活性受体激动剂开发和应用也取得了不错的进展。CD16a是目前最受欢迎的靶点之一，许多产品目前正处于临床前开发或临床试验阶段。如AFM13是一种双特异性抗CD30和CD16a的四价抗体，临床试验显示AFM13可有效治疗复发或难治性霍奇金淋巴瘤患者，且在连续治疗期间耐受性良好[76]。另一款产品AFM24专门设计用于治疗实体瘤，AFM24正在进行针对晚期实体癌的1/2a期临床试验（NCT04259450），同时还与阿替利珠单抗联合用于EGFR表达的晚期实体恶性肿瘤（NCT05109442）[100]。靶向NKG2D治疗已被证实可提高NK细胞免疫治疗的疗效[101]。一种靶向NKG2D和HER2的双特异性抗体正在临床试验中，用于治疗乳腺癌[102]；还有两种靶向NKp30的产品CTX-4419和CTX-8573正在接受临床前评估，以评估它们在多发性骨髓瘤治疗中的效果[76,103]。此外，包括靶向NKp80、NKG2C、4-1BB等其他治疗靶点的产品也在开发和进行临床试验[76]。

重组细胞因子药物目前正在开发以促进NK细胞活化。IL-12主要由抗原呈递细胞分泌，增强NK细胞增殖、存活和细胞毒性。目前有几种重组IL-2药物正在研究或批准用于治疗各种癌症，如肺癌、膀胱癌、卵巢癌和肾癌。一项正在进行的临床试验涉及重组IL-12与EGFR抑制剂西妥昔单抗联合治疗头颈癌[5,36,104]。IL-15具有与IL-2相似的功能，但不具有激活诱导细胞死亡的作用。IL-15超激动剂ALT-803目前正在临床试验中用于治疗多种类型癌症，包括非小细胞肺癌、头颈癌、肾细胞癌和黑色素瘤[43,105-106]。

NK细胞的过继性转移是癌症治疗的另一种策略。治疗性NK细胞可从外周血或脐带血中纯化，也可从诱导的多能干细胞中提取。一些NK细胞系，如NK-92也可用于输血[107-108]。输血前使用IL-2、IL-12、IL-15和IL-21等多种细胞因子和饲养细胞促进NK细胞活化和增殖[5,109]。生产嵌合抗原受体-NK细胞等基因工程NK细胞，以提高NK细胞杀伤能力和特异性[110]。如抗CD19 CAR-NK细胞已在临床试验中用于治疗淋巴样肿瘤[111]。合成生物学方法也在研究中，以帮助NK细胞克服免疫耗竭[112]。

4　小结与展望

目前，关于NK细胞耗竭的知识不断增加，但仍有许多问题和争议未解决。对NK细胞耗竭的准确定义尚未达成共识，常与其他NK细胞功能障碍状态混淆。因此，需进一步研究其机制和特征。T细胞和NK细胞都可能出现耗竭现象，存在多种淋巴细胞耗竭风险，这值得思考和注意。对NK细胞耗竭的持续研究可促进NK细胞免疫治疗相关进展。近年不断发现并尝试应用越来越多的NK细胞治疗靶点于临床实践，展现出NK细胞在免疫治疗方面十分具有前景。总之，通过不断研究NK细胞耗竭，不仅能增加对NK细胞基础研究的了解，也能推动NK细胞的实际应用。

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