T细胞抑制性受体及其免疫调节作用

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摘要 T淋巴细胞在免疫系统中发挥细胞免疫、免疫调节等功能。然而,T细胞的过度激活会导致疾病(如哮喘、系统性红斑狼疮等)的发生,抑制T细胞的过度激活是免疫治疗的重要研究方向。T细胞抑制性受体可通过与其配体结合调控T细胞增殖或功能发挥,并在过敏性疾病、移植排斥等治疗中作为治疗靶点。因此,进一步解析T细胞抑制性受体的三维结构、配体-受体复合物组分及其下信游号通路将有助于免疫治疗的发展。本综述总结了GITR、CTLA-4、BTLA、PD-1、LAIR-1、TIM-3、TIGIT等T细胞抑制性受体的生理生化特性、与其配体结合后对T细胞免疫功能的调节以及抗体药物的研究进展。

关键词 T细胞;抑制性受体;免疫调节

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Immune regulatory function of T cell-inhibitory receptors

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Abstract T lymphocytes play a fundamental role in cellular immune and immune regulation in immune system. However, the over-activation of T cells may induce many diseases including asthma, systemic lupus-erythematosus. It is crucial to control the T cell over-activation in the immunotherapy field. The inhibitory receptors of T cells can regulate proliferation and function of T cells by contacting with their ligands. Latest studies have indicated that T cell inhibitory receptors targeting therapy can attenuate the symptoms of diseases and graft rejection. Intensive study on the regulation of T cells would provide effective strategies for preventing and treating immune diseases.

Keywords T lymphocyte; inhibitory receptor; immune regulation

T细胞是淋巴细胞的重要组成部分,具有多种免疫学功能,如激活细胞免疫应答、直接杀伤靶细胞、释放淋巴因子、辅助B细胞产生抗体等。然而,T细胞的过度激活会导致多种疾病的发生,如哮喘、系统性红斑狼疮、移植排斥等。T细胞抑制性受体通过与其配体结合从而调节T细胞的增殖或功能发挥,在过敏性疾病、移植排斥等免疫疾病的治疗中将其作为治疗靶点是有效的[1-4],因此,其免疫调节功能受到广泛关注。深入研究T细胞抑制性受体的免疫调节功能,将会为免疫疾病的预防与临床治疗提供积极有效的策略。本文着重介绍已被确定的T细胞抑制性受体GITR、CTLA-4、BTLA、PD-1、LAIR-1、TIM-3、TIGIT(图1)在重大免疫疾病免疫调节方面的作用。

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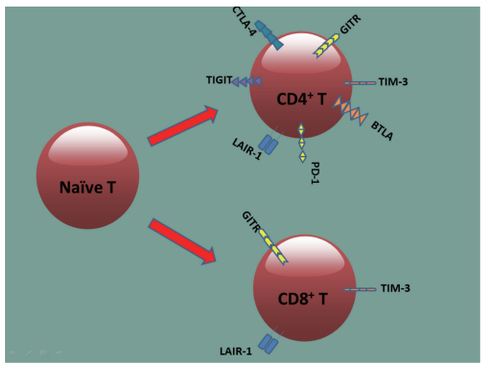


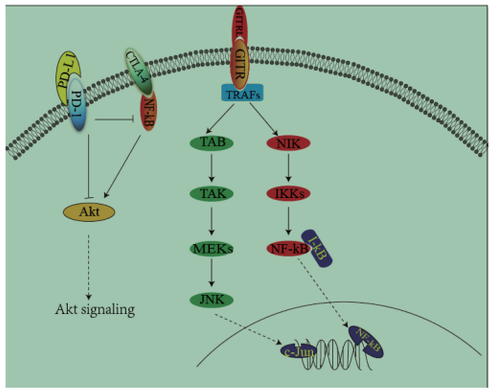
CD4⁺T细胞表面表达的7种抑制性受体分别为PD-1、CTLA-4、BTLA、GITR、TIGIT、TIM-3、LAIR-1;CD8⁺T细胞表达的3种抑制性受体,即GITR、TIM-3、LAIR-1

图1　T细胞表面表达的抑制性受体

Fig. 1　Inhibitory recptors expressed on the surface of T cells

1　糖皮质激素诱导的肿瘤坏死因子受体

糖皮质激素诱导的肿瘤坏死因子受体(glucocorticoid-induced TNF receptor family-related protein,GITR)是TNF受体超家族的一员,其在调节天然免疫和获得性免疫反应中均起作用[5,6]。人源GITR编码基因位于第1号染色体,包含5个外显子,在B细胞、单核细胞、巨噬细胞、树突状细胞、调节性T细胞(regulatory T cells,Treg)及肥大细胞均表达[6~10]。其配体GITRL(glucocorticoid-induced TNF receptor family-related protein ligand, GITRL)在多种细胞,如巨噬细胞、树突状细胞、B细胞等均表达[10~12]。NF-1介导受刺激的抗原提成细胞(antigen presenting cell,APC)短暂表达GITRL,在炎症反应中起主要作用。促进剂单克隆抗体和GTIRL在体外能刺激T细胞增殖[5,8,10,13],而Treg具有抑制T细胞增殖的功能,这说明GITR可能会加强Treg的抑制功能。近年来,鼠源GITR(mouse GITR,mGITR)受到很大关注,mGITR在CD4⁺T细胞和CD8⁺T细胞低水平表达,只有通过T细胞抗原受体(T cell receptor,TCR)途径刺激后表达才能上调,然而在CD4⁺CD25⁺T细胞中可持续高表达[7~9],Yukiko等[11]发现,在Treg中叉头蛋白P3(forkhead box p3,Foxp3)与核因子κB(nuclear factor κB,NF-κB)共同作用调节Gitr的表达。在小鼠疾病模型研究中发现,GITR被GITRL或抗GITR抗体结合后能够下调Treg的抑制功能,进而增强机体对肿瘤和病毒的免疫反应,但同时也会导致自身免疫疾病的恶化[6,7,10,14~17]。因此,构建GITRL低聚物在治疗由免疫紊乱引起的疾病方面应该具有潜在价值。Kim等[14]研究发现皮肤移植手术1周内,引流淋巴结内的树突状细胞中GITRL表达上调,并认为该表达的上调会导致Treg处于非活性状态。而且他们发现阻止GITR与GITRL相互作用有利于维持Treg的功能,从而提高移植率[10]。GITRL与GITR的结合能够通过激活丝裂原活化蛋白激酶(Mitogen-activated protein kinase,MAPK)、NF-κB[18]、c-Jun氨基末端激酶(c-Jun N-terminal kinase,JNK)等途径调节T细胞的功能(图2)。在肿瘤模型中,抗体DTA-1与GITR结合后抑制Treg中Foxp3的表达,而效应CD8⁺T细胞活性增强[10]。



PD-1与PD-L1相互作用抑制Akt信号通路与NF-κB功能;GITR与GITRL相互作用激活NF-κB转移至核内;GITR与GITRL相互作用诱导JNK磷酸化

图2　抑制性受体PD-1、CTLA-4、GITR介导的信号通路

Fig. 2　Signal pathway mediated by PD-1, CTLA-4 and GITR

虽然目前已有针对恶性肿瘤的GITR抗体药物进入临床试验阶段,但是GITR/GITRL参与调控免疫系统的机制仍待进一步研究,GITR与抗体结合后下调Treg中Foxp3表达的原因还不清楚,因此,深入研究GITR/GITRL信号通路及其作用机制,不仅有助于在基础研究上加深免疫系统调控机制的理解,还有可为药物研发提供潜在分子靶点以利于抗体药物在免疫治疗中的应用。

2　细胞毒T淋巴细胞相关抗原4

细胞毒T淋巴细胞相关抗原4(cytotoxic T lymphocyte associated antigen-4,CTLA-4)属于T细胞跨膜蛋白,人源CTLA-4编码基因位于第2号染色体,包含4个外显子,在激活的T淋巴细胞中表达[19],在FOXP3⁺Treg中,FOXP3可以直接上调Treg中CTLA-4的表达[20,21]。细胞表面分子间的相互作用介导T细胞免疫反应的起始、调节与终止,T细胞抗原受体(T cell receptor,TCR)决定了T细胞识别的特异性[16,17],除此之外,T细胞免疫活动的维持与增强还需要其他信号途径的参与,其中最重要的是T细胞的CD28与抗原提呈细胞的B7-1、B7-2的结合[22,23],而B7同系物与CTLA-4结合却能够导致该反应的下调[24]。CTLA-4与CD28虽是同系物,但CD28能在静息状态下的T细胞中表达,而CTLA-4只有在T细胞被激活24 h后才能被检测到[19],CTLA-4对B7同系物的亲和力是CD28的10~100倍[24]。基于表达水平和亲和能力的差异,CTLA-4、CD28与B7竞争性结合,参与调控抑制或激活信号复合物的组装[25],从而在调控T细胞的静息状态或激活状态中起重要作用,蛋白激酶C-η(protein kinase C-η, PKC-η)与CTLA-4复合物调控Treg的免疫抑制作用,PKC-η的缺失引

起Treg抑制功能的失调[26],这暗示PKC-η-CTLA-4信号通路可能是免疫治疗的新靶点。

由于在调节T细胞活动中的重要作用,CTLA-4在免疫治疗领域受到很大关注。溶解状态的CTLA-4-Ig融合蛋白可抑制CD28-B7的共刺激作用,在动物疾病模型中,如移植排斥、哮喘及过敏反应等其抑制作用已得到证明[2,27,28]。在临床试验中,CTLA-4-Ig融合蛋白可有效治疗寻常性银屑病。目前,经FDA批准的CTLA-4单克隆抗体包括Yervoy、tremelimumab,tremelimumab适用于间皮瘤的治疗,而Yervoy则用于晚期转移性黑色素瘤的治疗。

3 程序性死亡受体

程序性死亡受体(programmed death 1,PD-1)是一种重要的免疫抑制分子,人源PD-1编码基因位于第2号染色体,包含6个外显子,在T淋巴细胞、激活的自然杀伤细胞(NKT)、B淋巴细胞、单核细胞以及一些树突状细胞亚群中均表达[29]。虽然中枢耐受的形成使识别自身抗原的T细胞经阴性选择而被清除或处于无活性状态,然而一些自身抗原特异性T淋巴细胞能够逃脱此机制而分散在外周[30],因此外周耐受对于免疫系统稳态的维持非常重要,外周耐受包含多种机制,包括克隆清除、克隆无能、免疫忽视以及Treg细胞的抑制作用等[31]。一种包括PD-1及其配体PD-L1、PD-L2的B7-CD28家族通路能调节激活与抑制信号之间的平衡,该平衡对自身耐受、T细胞功能稳定的维持及T细胞的激活非常重要[32]。PD-1的配体PD-L1(即B7-H1)、PD-L2(即B7-DC)有不同的表达模式[33~36],抗原提呈细胞(树突状细胞、巨噬细胞、B细胞等)持续低表达PD-L1,被激活后表达上调,PD-L1在激活的T细胞中表达[33~37],并且PD-L1也会在多种非造血细胞中表达,包括血管内皮细胞、胰岛细胞以及免疫赦免部位,如胎盘、睾丸、眼睛等。相比之下,PD-L2主要在激活的树突状细胞和巨噬细胞中被诱导表达。虽然PD-L1与PD-L2在生发中心B细胞与树突状细胞中均表达,但PD-L1比PD-L2表达水平高[38]。在自身反应性T细胞激活和增殖的初始阶段,PD-1可抑制自身反应性T细胞对自身抗原的识别[39,40],同时PD-1能抑制自身反应T细胞对非造血组织的作用,也能通过抑制自身反应性T细胞而介导组织耐受以保护组织免受免疫损伤[41,42]。未成熟的树突状细胞、转化生长因子β(TGF-β)、IL-10等可诱导外周$CD4^+CD25^-$T淋巴细胞转变为iTreg细胞,PD-1能通过促进iTreg的诱导与维持抑制T细胞免疫反应[43]。PD-1通过与恶性肿瘤细胞表面表达的配体结合介导抑制信号,从而阻止效应T细胞的增殖,这不利于抗肿瘤特异性免疫反应[44~47]。病毒特异性T细胞表达PD-1能阻止病毒特异性效应T细胞的增殖与病毒的清除[48~51]。

Patsoukis等[52]报道PD-1抑制Akt(v-akt murine thymoma viral oncogene homolog,Akt,蛋白激酶B)与Ras(rat saroma,Ras)信号通路,通过影响细胞循环组件成分而阻止效应T细胞的增殖。Nikolaos等[53]研究证明PD-1在G1期阻止细胞分裂,PD-1虽然不改变G1期细胞周期蛋白以及细胞周期蛋白依赖性激酶的表达,但是会抑制SKP2的转录,PD-1通过上调P27、P15和抑制Cdc25A从而抑制T细胞增殖。PD-1与PD-L1相互作用能抑制CD28介导的PI3K的激活(图2),从而抑制T细胞的活化[54]。肿瘤细胞表达的PD-L1结合激活的T细胞上的PD-1后能够抑制T细胞功能,其机制可能是T细胞胞质内磷酸酶向PD-1胞内域聚集,抑制磷脂酰肌醇3-激酶途径,致使T细胞分泌毒性颗粒的能力下降[55]。

无论是在基础研究还是临床研究中,PD-1与PD-L1的单克隆抗体都会阻断两者的相互作用,从而恢复T细胞的毒性功能,这通常会导致肿瘤快速大量的萎缩,且反应持久[56],该疗法能特异性增强抗肿瘤T细胞的免疫功能,而CTLA-4抗体会增强淋巴结内各种特异性T细胞的增殖,因此PD-1/PD-L1抗体在免疫治疗中具有更强的特异性。在癌症治疗领域,基于PD-1的免疫治疗研究已取得长足进展,经FDA批准的PD-1抗体药包括Keytruda、Opdvio、Ipilimumab、MP-DL3280A等,最新的临床疗效表明:PD-1抗体能治愈10%左右的皮肤癌病人,控制50%皮肤癌的癌症进展,也能控制24%具有顽固非小细胞肺癌的病人病情恶化。百时美施贵宝最新的临床试验显示Opdivo能使41%的患者存活超过一年。

4 B和T淋巴细胞衰减因子

B和T淋巴细胞衰减因子(B and T lymphocyte attenuator,BTLA,CD272),是一种跨膜蛋白,属于免疫球蛋白超家族成员,胞质区包含免疫受体酪氨酸转换基序(ITSM)和免疫受体酪氨酸抑制基序(ITIM),胞外区包含Ig结构域。人源BTLA编码基因位于第3号染色体,包含6个外显子,在$CD4^+$T细胞、$CD8^+$T细胞、B细胞、树突状细胞、巨噬细胞中均表达。T细胞的激活除需要TCR与MHC-肽复合物相互作用外,还需共刺激信号的参与,如CD28/B7途径、ICOS/B7RP-1途径等,$CD28^{-/-}$小鼠体内产生免疫耐受的T细胞中BTLA表达增高[57],这表明BTLA可能参与调控T细胞免疫耐受。静止期的T细胞被激活后,BTLA迅速富集于细胞膜区域,与其配体——疱疹病毒侵入介体(herpesvirus entry mediator,HVEM,TNFRSF14)相互作用[58,59]。HVEM结构中有3个富含半胱氨酸的区域,BTLA与HSVI型膜糖蛋白D竞争性结合在最重要的膜末梢区域——富含半胱氨酸的区域1的赖氨酸上[60,61]。

BTLA具有抑制T细胞免疫应答反应的功能,BTLA可正向调控Foxp3的表达[62],增强Treg的抑制活性。$BTLA^{-/-}$小鼠产生自身免疫性脑炎,并表现出严重的过敏性呼吸道感染,而且不能接受局部组织相容性复合体不匹配的心脏移植,$HVEM^{-/-}$小鼠在刀豆蛋白A(Con A mitogen)诱导下,更易患T细胞依赖性自身免疫性肝炎[63]。

Tao等[63]发现在小鼠疾病模型中,TCR的激活能分别诱导效应T细胞上调表达BTLA和调节性T细胞上调表达HVEM,CTLA-4、GITR在激活的Treg和Teff细胞中均可表达,抑制性受体BTLA在激活的Teff细胞中表达上调,但是在Treg中表

达水平非常低,然而HVEM在激活的Treg中表达水平较高[64]。这种受体和配体在不同细胞中的表达方式为通过BTLA-HVEM信号通路调节T细胞免疫应答反应提供了新思路,BTLA-HVEM信号通路可能参与Treg调节的机体免疫耐受及调节T细胞免疫应答反应,这为Treg在免疫治疗中的应用提供了新思路,即HVEM可作为Treg效应分子的补充物以提高Treg在免疫治疗中的应用。

5　人白细胞相关免疫球蛋白受体1

人白细胞相关免疫球蛋白样受体1(human leukocyte-associated Ig-like receptor-1,LAIR-1,CD305),是一种跨膜糖蛋白,在胞外区含有单链免疫球蛋白样区域结构(Ig-like domain),胞质区含有两个免疫受体酪氨酸抑制基序(immunoreceptor tyrosine-based inhibition motifs,ITIMs)。人源LAIR-1编码基因位于第19号染色体,包含11个外显子,在外周T细胞中表达[65],但表达水平各不相同,初始$CD4^+$T细胞、$CD8^+$T细胞以及$CD8^+$效应T细胞均高表达LARI-1,记忆性T细胞表达水平较低[66]。并不是所有的T细胞都表达LAIR-1,70%~80%的$CD4^+$T细胞、80%~90%的$CD8^+$T细胞表达该受体[65],这说明LAIR-1在T细胞中的表达机制可能比较复杂。LAIR-1在羟脯氨酸(hydoxyproline)协助下通过识别胶原蛋白共有基序,然后与跨膜及胞内胶原蛋白相互作用,在体外条件下,胶原蛋白与LAIR-1相互作用能抑制免疫细胞功能[67]。因此,LAIR-1与胶原蛋白可能参与免疫反应调控,它们相互作用为免疫细胞的激活设定"阈值"。抗原提呈细胞、细胞因子以及病原体能提供较强的激活信号,当该激活信号大于"阈值"时,便会激活T细胞,另外通过下调LAIR-1的表达降低"阈值"也有利于T细胞的激活。初始T细胞中LAIR-1的高表达能抑制其对自身抗原的反应,有利于免疫耐受的维持,从而阻止自身免疫疾病的发生。这种由LAIR-1参与的免疫耐受机制也许能够解释低浓度的外来抗原能够激活T细胞的免疫应答,而自身抗原却不能激活T细胞[67]。记忆性T细胞在无抗原存在时增殖缓慢[68,69],而少量抗原存在时就可以表现出较强的增值能力,这是因为LAIR-1在记忆性T细胞中表达较少,阈值较低,进而容易激活。LAIR-1在效应T细胞高表达,Maasho等[70]进一步发现LAIR-1能够下调TCR信号通路,从而抑制非必需免疫应答反应的激活。

6　T细胞免疫球蛋白黏蛋白分子-3

T细胞免疫球蛋白黏蛋白分子-3(T-cell immunoglobulin and mucin-3,TIM-3)属于I型膜蛋白,胞外区包含黏蛋白区域和富含半胱氨酸的Ig样区域,于2002年在小鼠体内首次被发现表达于Th1型淋巴细胞和$CD8^+$T淋巴细胞[71]。后来被证实人类T细胞也表达TIM-3,含有302个氨基酸,人源TIM-3编码基因位于第5号染色体,包含7个外显子[72,73]。鼠源TIM-3含有282个氨基酸,编码基因位于第11号染色体,与人源TIM-3有63%的相似度[71]。有研究证明TIM-3是人类Th1淋巴细胞的负向调控分子[73~75]。在刚出生的或者尚未获得免疫能力的小鼠体内,TIM-3主要在树突状细胞高表达[76],只在少部分的$CD4^+$T淋巴细胞、$CD8^+$T淋巴细胞中表达[77]。在体外Th1过量存在的情况下,TIM-3增加至稳定的较高的水平才会停止表达[71,78]。

Anderson等[78]发现TIM-3的表达受Th1特异性转录因子T-bet的调控,T-bet能直接与TIM-3启动子结合。但Szabo等[79]发现在Th1分化的早期阶段T-bet的表达量就会上调,这说明可能其他的转录因子也在调控TIM-3的表达。另外,$T\text{-}bet^{-/-}$细胞中也会有TIM-3表达[80],这更进一步说明了TIM-3的表达需要其他转录因子的参与,其机制问题有待进一步阐明。通过检测人类TIM-3基因的单核苷酸多态性(SNP)发现了外显子3编码区的SNP,该SNP的发生会导致氨基酸突变。通过对类风湿关节炎患者和健康人的TIM-3基因型及等位基因的对比分析发现,TIM-3的单核苷酸多态性易导致类风湿性关节炎的发生[81]。Graves等发现TIM-3启动子和编码区的单核苷酸多态性可能与特应性皮炎的发生有关[82]。

Sanchez-Fueyo等[77]证明半乳凝素-9(galectin-9)是TIM-3的配体。半乳凝素-9在多种类型细胞中表达,在IFN-γ刺激下表达上调[83]。它通过自身的糖类识别区域(carbohydrate recognition domain)识别TIM-3 IgV区域的寡糖。体外实验发现,半乳凝素-9能诱导表达TIM-3的Th1细胞的钙离子外流、细胞聚集和细胞的死亡,而TIM-3缺损的Th1细胞抵抗半乳凝素-9诱导的死亡。并且,在实验性自身免疫脑脊髓炎中,半乳凝素-9减弱T细胞引起的感染,从而减弱病情的恶化[77]。在对其他动物疾病模型的研究中发现半乳凝素-9与TIM-3的相互作用能减弱Th1和Th17的免疫应答反应,这表明了其在皮肤感染、实验性关节炎、HSV诱导的眼部炎症治疗中的潜力[77]。并且,半乳凝素-9诱导同种异体$TIM\text{-}3^+CD8^+$T细胞的死亡,从而降低皮肤移植产生的细胞毒性并得以延长存活时间[84]。

在小鼠EAE疾病模型中,发病初期浸入中枢神经系统的$CD4^+$T淋巴细胞、$CD8^+$T淋巴细胞均表达TIM-3,但随着病情的恶化,中枢神经系统中的$TIM\text{-}3^+$T淋巴细胞的数量减少,这表明TIM-3在抑制EAE发生过程中起着积极作用。多发性硬化症(multiple sclerosis,MS)患者体内TIM-3的表达下调,治愈之后TIM-3表达增高[74,75]。并且,在HIV和HCV感染中,TIM-3参与负性调控T淋巴细胞的免疫应答反应[85~87]。TM-3信号途径的阻断能部分修复T细胞功能。以上研究证明了TIM-3在负性调控T细胞免疫应答反应中的重要作用,阻断TIM-3信号通路有利于T细胞功能的激活。

7　含T细胞免疫球蛋白域和免疫受体酪氨酸抑制基序的蛋白

含T细胞免疫球蛋白域和免疫受体酪氨酸抑制基序的蛋白(T cell immunoglobulin and ITIM domain,TIGIT)属于I型跨膜蛋白,胞质区包含ITIM基序和PDZ结合结构域,胞外区

域包含免疫球蛋白V样结构域,人源TIGIT编码基因位于第3号染色体,包含5个外显子,主要在NK细胞和T细胞表达,初始$CD4^+$T细胞被激活后表达上调。

Joller等[88]报道了TIGIT在自身免疫反应中负性调控T细胞的免疫应答反应。在TIGIT缺损小鼠模型中,T细胞具有更强的增殖能力,并且产生更多的促炎细胞因子。在胶原诱导性关节炎疾病模型(collagen-induced arthritis model)中,可溶性的TIGIT-Fc蛋白能显著地抑制疾病的恶化,阻断抗TIGIT的作用会加速疾病的发生[89]。因此,TIGIT可负性调控T细胞的免疫应答反应,从而参与自身免疫疾病的抑制。

类似于PD-1配体,TIGIT配体CD155、CD112在一些肿瘤细胞中过表达,如结直肠瘤、胃癌[90]、成神经细胞瘤[90]等。TIGIT与其配体结合后能抑制T细胞的免疫应答反应,从而导致肿瘤细胞逃逸,因此TIGIT抗体在抗肿瘤免疫治疗领域具有巨大应用价值。

Zhang等[91]报道在再生障碍性贫血(aplastic anemia,AA)患者体内$TIGIT^+CD4^+$T淋巴细胞数量减少,在小鼠模型中发现TIGIT的过表达能抑制$CD4^+$T细胞的功能并且缓解AA症状,而TIGIT编码基因被敲除后$CD4^+$T淋巴细胞功能增强。这可能为AA的病因提供理论依据,并可提供有效的AA治疗策略。

8 结论

虽然T细胞抑制性受体的研究进展很快,但仍有很多问题有待阐明,比如抑制性受体的转录与翻译是如何受到精确调控的,抑制性受体参与哪些信号通路,抑制性受体与其配体结合后如何调节下游信号通路等。目前,主要研究的是鼠源的T细胞抑制性受体,人源抑制性受体与鼠源抑制性受体在基因表达、蛋白组装、蛋白结构及功能等方面都有很大差异。且在体内外不同的条件下,抑制性受体的功能也会有所不同,处于体内免疫调控网络中的抑制性受体可能会受到多种蛋白分子的共同调控,体内复杂的免疫环境要求人们全面研究影响抑制性受体功能的信号通路,只有这样才可能深入地了解抑制性受体对T细胞免疫应答反应的调控机制。这为人们将基础免疫研究转化为临床研究提出了新的研究命题,也为研发针对人类重大疾病的免疫治疗提出了挑战。

针对T细胞抑制性受体的抗体药物目前已有上市,如PD-1/PD-L1抗体药、CTLA抗体药等,且在临床治疗中效果较好,应用潜力巨大,目前已获FDA批准的抑制性受体抗体药物主要多是单抗体药物,而免疫细胞的靶点是多向性的,如果研发出双特异性抗体药物、甚至是三抗体药物将会更有利于抑制性受体抗体药物药效的发挥。比如PD-1抗体与CTLA-4抗体的联合或者PD-1抗体与GITR抗体的联合等,双特异性抗体药物的应用可能会激发更强的免疫反应,更有利于对肿瘤细胞的杀伤作用。目前有不少双特异性抗体药物进入临床试验阶段,方法不尽相同,主要的做法包括两种:1)连接T细胞和肿瘤细胞的双靶向抗体,“双管齐下”增强免疫效果,临床试验较好。2)针对上皮细胞黏附因子(Epithelial cell adhesion molecule, EpCAM)与CD3的双靶向抗体,欧盟在2009年已经批准主要针对癌性腹水的相关药物上市。安进公司研发的BLINCYTO是一种双特异性T细胞CD3结合CD19靶向抗体药物,用于费城染色体阴性(Ph-)的复发性或难治性前B细胞急性淋巴细胞白血病(ALL)治疗,在临床上疗效显著,在2014年获得FDA批准,BLINCYTO的上市代表免疫治疗研究取得了重要的里程碑式的进步。

尽管基于抑制性受体抗体药物的研发已经取得较大进步,但其疗效、副作用及研发速度还有待改善。改善抗体药代动力学、改善抗体药学特性、缩短研发周期、降低生产成本、筛选高表达细胞株、开发细胞培养和生产工艺、优化抗体纯化及制剂技术都是抑制性受体抗体药物研发努力的方向。相信随着研究的不断深入,T细胞抑制性受体的基因表达调控机制、生化活性、生理特性、免疫调节功能等将会更加清楚,T细胞抑制性受体空间结构的解析也会促进药物的研发。基础研究的深入、药物研发的推动、临床试验的检验,将会共同加速人类治疗免疫疾病、肿瘤、重大传染病等的步伐。

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