



SOD3免疫调节作用的研究进展

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摘要 超氧化物歧化酶3(superoxide dismutase 3, SOD3)是一种作用于细胞外的抗氧化酶,其主要功能是催化超氧化物转化为过氧化氢和氧。最近有研究表明, SOD3还参与多种疾病的免疫调节过程。在宿主体内,宿主来源的SOD3直接参与调控氧化应激、免疫细胞的成熟、增殖和分化及炎症反应等免疫调节过程。此外,病原体也可以高表达SOD3逃避宿主免疫防御,并通过抑制宿主的细胞反应以完成入侵过程。SOD3表达水平也与多种免疫相关疾病进展密切相关。因此, SOD3有望成为免疫治疗的关键靶点。本文对SOD3免疫调节作用的研究进展进行了综述。

关键词 超氧化物歧化酶3, 免疫调节, 免疫功能障碍, 寄生虫疾病

活性氧(reactive oxygen species, ROS)主要包括超氧化物阴离子自由基($O_2^{\cdot-}$)、过氧化氢(H_2O_2)、羟基自由基($\cdot OH$)和单态氧(1O_2)等,是宿主先天免疫系统抵御微生物入侵的第一道防线。研究表明,在嗜中性粒细胞等先天免疫细胞的呼吸爆发和免疫细胞趋化等防御病原体入侵过程中都会产生ROS从而发挥抗病原功能^[1]。但ROS也存在双向作用,适量的ROS有助于宿主通过免疫信号的氧化还原调节和诱导炎性小体激活等方式对细菌、寄生虫等病原体(尤其是胞内寄生的病原)发挥直接杀伤作用^[2]。但过量ROS的产生和积累导致的氧化应激,对细胞中蛋白质、脂质和核酸等重要细胞结构造成损伤。此外,过量的ROS诱发动脉粥样硬化、糖尿病和白癜风等多种疾病^[3-5]。

超氧化物歧化酶(superoxide dismutase, SOD)是一类催化超氧化物歧化过氧化氢和氧分子的酶。SOD有三种异构体,包括主要分布于细胞质内的SOD1(Cu, Zn-SOD)、分布于线粒体内的SOD2(Mn-SOD)和定位于细胞外的SOD3(EC-SOD)^[6]。在SOD家族中, SOD3是唯一一种介导组织细胞外基质中 $O_2^{\cdot-}$ 歧化为 H_2O_2 和 O_2 的酶^[7],在其氨基酸序列中含有一段N端信号肽,介导该分子的细胞外分泌。SOD3的活性结构域结合铜或锌离子,在其C-末端还含有一个肝素结合区^[8]。SOD3与带负电荷的细胞外基质元素(如硫酸肝素)和内皮细胞结合,对调节SOD3在细胞外基质中的分布很重要^[9]。这种分布特点及抗氧化特性使SOD3在保护细胞外基质蛋白免受氧化应激损伤方面发挥着关键作用,同时

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也有利于延缓组织慢性炎症的进展^[10,11]。

SOD3除了具有抗氧化活性,它在免疫调节方面也扮演着非常重要的角色。在类风湿性关节炎等免疫性疾病中,低表达量的SOD3就有可能导致严重的疾病,这表明了SOD3与类风湿性关节炎的发生有一定的关系。除自身免疫性疾病外,研究表明,SOD3还对多种炎症性疾病,如过敏性哮喘、银屑病、炎症性肠病等具有保护作用^[11,12]。SOD3在免疫细胞的成熟、增殖、分化等过程也发挥了调节作用,例如,SOD3可以调节树突状细胞(dendritic cells, DCs)成熟、B细胞增殖、T细胞激活和增殖、辅助型T细胞2(Th₂)和辅助型T细胞17(Th₁₇)分化^[11,13,14]。SOD3还通过增加IκBα的表达、下调细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)磷酸化等抑制核因子κB(nuclear factor-κB, NF-κB)、蛋白酪氨酸激酶(Janus kinase, JAK)-信号传导转录激活因子(signal transducer and activator of transcription, STAT)、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)等炎症信号通路以实现其抗炎作用^[15,16]。SOD3除参与宿主的免疫外,还可以由病原体分泌参与免疫逃逸过程,抑制宿主的免疫应答。

SOD3的这些免疫调节功能使其有望成为多种免疫疾病的治疗靶点,并且其治疗效果已在多种疾病模型中得到证实,如过敏性皮炎、银屑病、过敏性气道炎、炎症性肠病(包括溃疡性结肠炎和克罗恩病)等^[12]。本文将从SOD3与疾病的关系、对病原体免疫逃逸的影响、调节免疫细胞亚群、抗炎作用及其治疗潜力、临床应用价值等多个方面对SOD3的免疫调节功能进行全面综述,并对SOD3的进一步研究进行展望。

1 SOD3缺失与疾病发生的关系

1.1 SOD3缺失与自身免疫疾病进展密切相关

银屑病是一种CD4⁺ T细胞相关的慢性皮肤炎症性疾病。Lee等人^[17]通过比较白介素(interleukin, IL)-23诱导皮肤炎症的野生型(wild-type, WT)和SOD3缺失(SOD3^{-/-})小鼠的免疫细胞,发现SOD3^{-/-}小鼠皮肤中单核细胞的浸润增多、CD4⁺ T细胞激活且Th₁₇细胞分化增加,加重了IL-23诱导的皮肤炎症。提示缺乏SOD3会诱发更严重的IL-23介导的银屑病样皮肤炎症(表1)。

类风湿性关节炎是以侵蚀性关节炎为主要症状的

自身免疫病。在胶原诱导的关节炎小鼠模型中,SOD3^{-/-}小鼠比WT小鼠的临床疾病活动性和关节及骨损伤程度更为严重,这种严重程度差异伴随着细胞因子产生的变化。其中,SOD3^{-/-}小鼠关节中肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)、白介素1β(IL-1β)和干扰素-γ(interferon-γ, IFN-γ)的mRNA水平明显增加,而抗炎细胞因子IL-1Ra的mRNA水平降低^[18]。由此说明,类风湿性关节炎的发生与SOD3的变化具有很大的相关性(表1)。

1.2 SOD3缺失与炎症疾病进展密切相关

过敏性哮喘是由肥大细胞、嗜酸性粒细胞和T淋巴细胞参与的慢性呼吸道炎症^[19],其特征是支气管收缩、炎症和气道重塑^[20]。在卵白蛋白诱导的过敏性哮喘模型中,与对照组相比,SOD3^{-/-}的小鼠哮喘症状(支气管收缩、炎症和气道重塑)更为严重,其肺部炎症程度高于WT小鼠,表现为肺部淋巴细胞浸润数量增多。同时,较野生型小鼠相比,SOD3^{-/-}小鼠血清中免疫球蛋白(immunoglobulin, Ig)E、炎症细胞因子(包括IL-4、IL-5和IL-13)水平显著增加^[21]。这说明在过敏性哮喘模型中,SOD3是一种关键的免疫调节因子。

过敏性结膜炎是一种以Th₂介导的免疫反应和IgE介导的超敏反应为特征的炎症性眼病。在实验性过敏性结膜炎模型中,SOD3^{-/-}小鼠的Th₂型细胞因子反应加剧,眼结膜中卵白蛋白特异性IgE和嗜酸性粒细胞增多,而T_{reg}型细胞因子IL-10减少^[22]。这表明SOD3在预防Th₂驱动的过敏性结膜炎炎症反应中有重要作用。

炎症性肠病,包括溃疡性结肠炎和克罗恩病,是一种复杂的多因素疾病,影响胃肠道功能,并伴有慢性或过度炎症。给水溶性葡聚糖硫酸钠诱导的结肠炎模型小鼠注射SOD3,发现疾病表征(体重减轻、腹泻、便血、出血和皮毛粗糙度)在10天后显著降低、肠系膜淋巴结缩小。组织学检查发现,结肠上皮损伤、黏膜下水肿和淋巴细胞浸润得到改善^[15]。此外,痤疮是毛囊皮脂腺单位的一种慢性炎性皮肤病,主要与皮脂分泌过多、毛囊皮脂腺导管堵塞、细菌(主要是痤疮丙酸杆菌)感染和炎症反应等因素密切相关。给感染痤疮丙酸杆菌的小鼠注射SOD3,1天后观察到小鼠耳后皮肤厚度、红斑减少,炎症细胞浸润度降低^[23],这表明SOD3能够显著性抑制痤疮的发展。

SOD3还能减弱肺部炎症,缓解肺气肿、慢性阻塞

表 1 SOD3与自身免疫性疾病、炎性疾病和癌症的相关性

Table 1 Correlation of SOD3 with autoimmune, inflammatory diseases, and cancer

类别	名称	临床表现变化	SOD3变化 ^{a)}	参考文献
自身免疫病	银屑病	表皮、真皮厚度+	SOD3敲除	[17]
	类风湿性关节炎	软骨损伤、骨损伤、局部炎症、血管翳+	SOD3敲除	[18]
炎性疾病	过敏性哮喘	哮喘、气道阻塞+	SOD3敲除	[19~21]
	过敏性结膜炎	结膜充血、分泌物、流泪、眼球结膜及眼睑水肿+	SOD3敲除	[22]
	炎症性肠病(溃疡性结肠炎和克罗恩病)	体重减轻、腹泻、便血、出血和皮毛粗糙度-	SOD3↑	[15]
	痤疮丙酸杆菌引起的皮肤炎症	耳后皮肤厚度、红斑-	SOD3↑	[23]
	COPD/肺气肿	肺总阻力、动脉氧饱和度、运动能力(心肺功能和骨骼肌功能)↑	SOD3↑	[24,25]
癌症	肺癌	肺腺癌或肺鳞癌患者生存率、化疗敏感性↓	SOD3↑	[29]
	前列腺癌	细胞增殖、迁移、入侵↓	SOD3↑	[36]
	胰腺癌	侵袭性、生长速度、腹膜转移↓	SOD3↑	[35]
	头颈部鳞状细胞癌	生存率↓ 分化程度、侵袭性↑	SOD3↓	[30]
	乳腺癌	复发、临床阶段↑	SOD3↓	[32~34]

a) ↑: 表达升高; ↓: 表达降低; +: 症状加剧; -: 症状减轻

性肺疾病。香烟烟雾暴露和给药弹性蛋白酶导致肺部气腔增大、肺炎和肺功能下降。在SOD3过表达小鼠和注射SOD3拟态化合物后,小鼠肺顺应性降低,肺总阻力增加,动脉氧饱和度增加,支气管肺泡灌洗液总量、中性粒细胞和巨噬细胞数量都减少。此外,促炎介质(如粒细胞-巨噬细胞集落刺激因子、IFN- γ 、IL-13、IL-17、IL-1 β 、IL-6、角蛋白细胞衍生趋化因子、单核细胞趋化蛋白-1、巨噬细胞炎症蛋白-2和TNF- α)的释放减少,肺部氧化应激水平降低^[24,25]。

此外,基因突变导致的SOD3表达或功能的遗传变化与多种疾病密切相关。研究表明,SOD3序列多态性与成人肺功能下降和对慢性阻塞性肺病的易感性有关^[26]。SOD3编码序列中第213密码子第一位的胞嘧啶(C)转换成鸟嘌呤(G),所编码的氨基酸由精氨酸变成甘氨酸(R213G),是SOD3的肝素结合域中常见的人类基因变体。SOD3_{R213G}突变体与细胞外基质的结合减弱和组织分布水平下降^[27]。对丹麦普通人群进行横截面和前瞻性研究发现,SOD3_{R213G}杂合子人群中慢性阻塞性肺疾病的进展相对缓慢^[28]。

这些研究结果表明,SOD3的缺乏或功能变化均会导致免疫功能障碍,诱发多种免疫相关疾病(表1)。

1.3 SOD3与肿瘤免疫微环境的关系

Zhang等人^[29]通过Kaplan-Meier生存分析评估了肺癌患者SOD3表达的预后价值,发现低生存率与肺腺癌患者或肺鳞癌患者的高SOD3表达显著相关。SOD3基因的低表达患者可能使肿瘤对化疗药物的敏感性增加,有更好的预后结果。

头颈部鳞状细胞癌患者的生存率下降、肿瘤分化程度及侵袭性都与SOD3表达减少有关。与良性组织相比,良性原位癌和侵袭性组织中的SOD3蛋白表达显著降低。此外,与低分化肿瘤相比,中度分化肿瘤中的SOD3进一步减少。SOD3表达的改变可能发生在肿瘤发育的早期,是识别存活率下降、淋巴结入侵和肿瘤分化不良患者的潜在生物标志物^[30]。

SOD3蛋白表达减少在乳腺癌中表现为肿瘤复发和患者预后不佳,局部复发对于接受过乳房保护术的乳腺癌患者来说仍是重大问题^[31]。科学家在利用乳腺癌的乳房保存手术模型研究驱动局部复发机制的研究中发现,与原发恶性肿瘤相比,SOD3基因在复发性肿瘤中表达更低^[32]。与对照组相比,复发性肿瘤的增长速度明显加快,这表明SOD3的下调是导致肿瘤具备侵袭性的因素之一^[33]。此外,SOD3的表达与乳腺癌发展

呈负相关性^[34]。研究表明, SOD3在胰腺导管腺癌细胞系中的过度表达导致肿瘤入侵性降低。胰腺癌异种移植组织过度表达SOD3, 癌细胞生长缓慢, 腹膜转移减少^[35]。人前列腺癌PC-3细胞中的SOD3过度表达抑制了癌细胞的增殖、迁移和入侵, 免疫组织化学显示, SOD3在前列腺癌组织中的表达减少^[36]。总之, SOD3的表达与肿瘤的发生、发展有明显相关性, 但其作用机理还有待深入研究(表1)。

2 SOD3与寄生虫及真菌的免疫逃逸关系

SOD3与多种寄生虫的生长发育、迁移和寄生过程相关, 并在宿主的抗寄生虫免疫及寄生虫对宿主的免疫逃逸中发挥着重要作用。宿主感染寄生虫后会产生细胞和体液免疫反应, 以阻止寄生虫入侵并减轻其迁移造成的损害。这种反应的特点是粒细胞增殖、巨噬细胞和淋巴细胞迁移到寄生虫入侵和繁殖的部位。Th₁等免疫细胞应答产生IFN- γ , 活化巨噬细胞等^[37]。巨噬细胞在对病原体的免疫防御中起着核心作用^[38], 高度活化的巨噬细胞产生足够的ROS才能将寄生虫有效杀伤。ROS在病原体入侵后宿主的先天免疫反应早期发挥着至关重要的作用^[2], 主要表现在通过氧化还原反应调节免疫信号的传导及诱导炎症小体激活等。为避免ROS对宿主组织或细胞的损伤, SOD3分子作为一种抗氧化剂, 维持ROS在体内的动态平衡。但过量表达, 反而会有助于病原体抵抗宿主基于ROS的免疫杀伤作用(图1)。另一方面, 有些病原还能够分泌SOD3拮抗宿主ROS的作用。例如, 肝片吸虫(*Fasciola hepatica*)通过分泌虫源性SOD3(FhSOD3)调节宿主免疫应答和免疫逃逸。FhSOD3在囊蚴中呈现高表达, 在其排泄-分泌产物发现有大量的FhSOD3蛋白质。推测FhSOD3很可能保护寄生虫免受宿主先天免疫系统产生的ROS, 有利于其在体内的寄生^[39]。此外, 类圆线虫(*Strongyloidea*)雌虫的排泄-分泌蛋白组中也发现大量的虫源性SOD3, 表明SOD3可能有益于其在宿主内寄生^[40]。

弓形虫卵囊成熟后从肠上皮细胞脱出进入大肠腔, 随粪便排出体外。排出体外的卵囊经2~3天发育成熟, 并具有感染性^[41]。弓形虫SOD3蛋白是与弓形虫卵囊阶段发育相关的基因。它在弓形虫卵囊阶段中表达量增加, 猜测其可能参与猫肠中配子发育和卵囊形成^[42]。然而, 具体功能及机制仍有待进一步探究。

除寄生虫外, 真菌分泌的SOD3也有类似的拮抗宿主ROS的作用。荚膜组织胞浆菌(*Histoplasma*)是双向真菌, 在自然界以菌丝形态存在, 在人体组织中又以酵母菌形态出现。酵母型组织胞浆菌需要对抗宿主细胞的ROS等防御分子。组织胞浆酵母(非菌丝)会分泌SOD3, 其中一部分结合在酵母表面, 并通过N-末端和C-末端信号将其引导到细胞外环境, 这些信号促进其分泌和与酵母细胞表面的关联。这种定位使SOD3保护酵母免受外源性超氧化物的影响^[43]。SOD3能分解宿主巨噬细胞或多形核白细胞产生的细胞外超氧化物。因此, SOD3的活性是组织胞浆菌对抗吞噬细胞的必要条件, 也是呼吸道感染和播散感染模型中产生毒力的必要条件。如果没有自身分泌的SOD3, 组织胞浆酵母的感染的能力就会减弱, 并被宿主适应性免疫应答反应清除^[44]。

这些研究结果表明, 一些病原体来源的SOD3在病原体发育不同时期的表达量不同, 发挥拮抗宿主ROS的作用以实现免疫逃逸。

3 SOD3参与免疫调节的分子机制

在树突状细胞成熟期间, 主要组织相容复合体(major histocompatibility complex, MHC)II及其共刺激分子CD80和CD86在细胞表面表达, 它们通过向T细胞呈递抗原, 在适应性免疫中发挥关键作用。研究发现, 分离骨髓中未成熟树突状细胞并与SOD3共培养5天后, 用流式细胞术检测骨髓源树突状细胞发现, SOD3通过抑制MHC II, CD80和CD86的表达来抑制DC成熟^[21], 从而间接抑制T细胞的激活和增殖。

初始T细胞(naïve T cell)在共刺激信号以及细胞因子共同作用下活化增殖, 表达表面激活标志物^[45], 进而分化为效应T细胞, 分泌细胞因子, 完成对抗原的清除和对免疫应答的调节。体外实验发现, 用抗CD3/CD28模拟T细胞活化双信号, 并与SOD3共培养, 与对照组相比, SOD3组的CD25⁺ T减少了40.4%, CD69⁺ T减少了39.5%。说明SOD3通过下调CD4⁺ T细胞中表面激活标志物的表达水平抑制了CD4⁺ T细胞激活, 并通过BrdU(5-bromodeoxyuridine)细胞增殖检测实验证明了SOD3抑制T细胞增殖。此外, 在SOD3实验组中发现, IL-2, IL-4, IL-5, IL-6, IL-10, IL-10, IL-13, IFN- γ 和TNF- α 等T细胞产生的因子表达水平降低^[13]。SOD3还可以

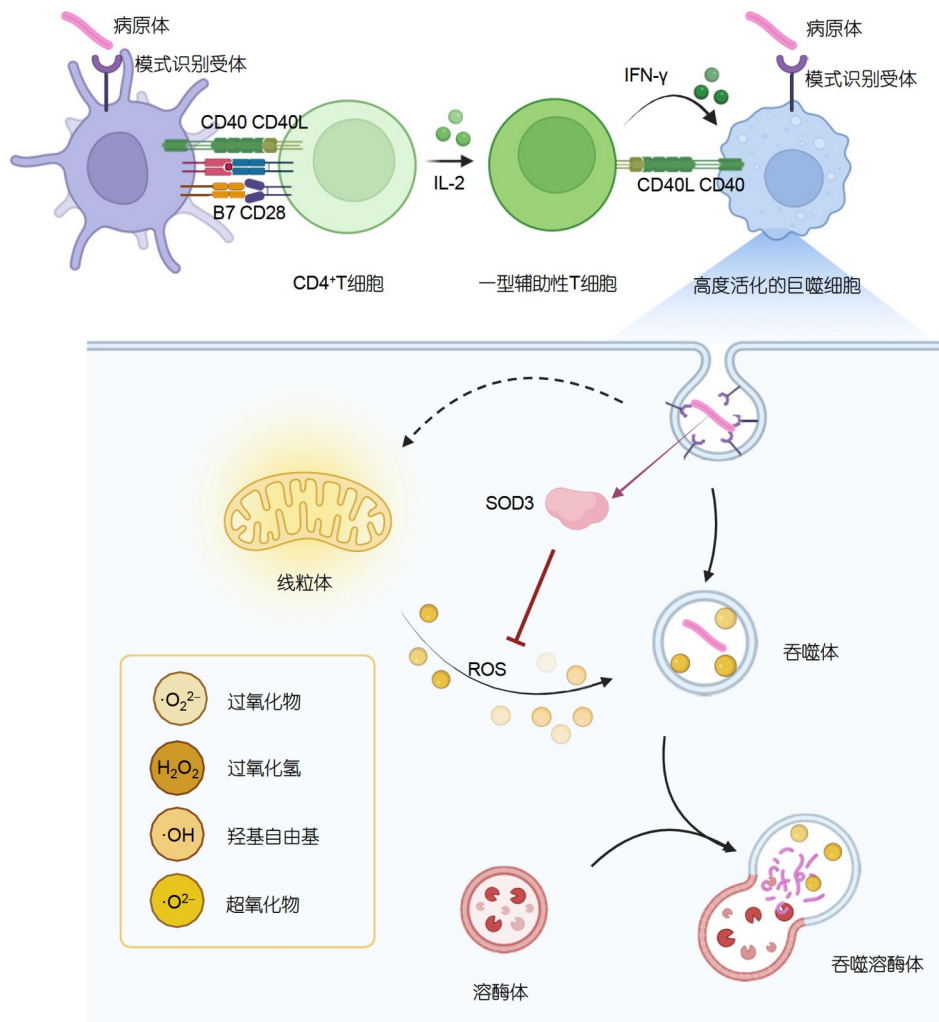


图 1 SOD3 促进入侵病原体的免疫清除。树突状细胞识别病原体并将抗原肽提呈给 $CD4^+$ T 细胞, 诱导 T 细胞活化及分化。Th₁ 细胞释放 IFN- γ 辅助巨噬细胞活化, 产生大量 ROS, 杀伤病原体。当吞噬细胞表面模式识别受体与病原体表面配体结合时, 启动细胞吞噬过程。病原体首先被吞噬细胞质膜包围, 形成吞噬体。吞噬体与细胞内一个或多个溶酶体融合产生吞噬溶酶体并释放 ROS 等物质, 杀死病原体^[2,37,38]

Figure 1 SOD3 facilitates immune clearance of invading pathogens. DCs recognize pathogens and present antigens to activate $CD4^+$ T cells. Subsequently, Th₁ cells release IFN- γ to facilitate macrophage activation which results in an increased production of ROS to eliminate pathogens. When the pattern recognition receptor on phagocytes' surface binds to the pathogen surface ligand, phagocytosis is initiated. The pathogen engulfed to the plasma membrane of phagocyte, leading to the formation of a phagosome enclosing the pathogen. The phagosome fuses with one or more intracellular lysosomes, generating phagolysosomes that produce ROS and other components, ultimately resulting in pathogen clearance^[2,37,38]

促进 Th₁ 细胞分化, 但抑制 Th₂ 和 Th₁₇ 分化^[17], 从而达到双向免疫调节的作用。

病原体及其抗原成分进入机体后可诱导抗原特异性 B 细胞活化、增殖并最终分化为浆细胞, 产生特异性抗体进入体液以完成体液免疫应答。其中 IgE 介导多种过敏性疾病^[46]。SOD3 在 LPS/IL-4 和抗 CD40/IL-4 条件下显著抑制了 B 细胞中 IgE 的产生、B 细胞的增殖及趋化因子配体 CCL22 和 CCL17 的产生, 并通过抑制转

录水平上的种系基因表达从而抑制 B 细胞中的 IgE 同类转换^[47]。这些证据表明, SOD3 直接参与了对免疫细胞的调节(图 2)。

炎症是过度的免疫反应结果之一, 是机体对各种损伤因子的刺激所发生的保护性应答反应, 需要多种免疫细胞及免疫分子的参与。炎症的过程主要分为四个阶段: 第一阶段为病原(包括细菌、病毒、寄生虫等)、异物、过敏反应原等致炎因子对机体的组织和

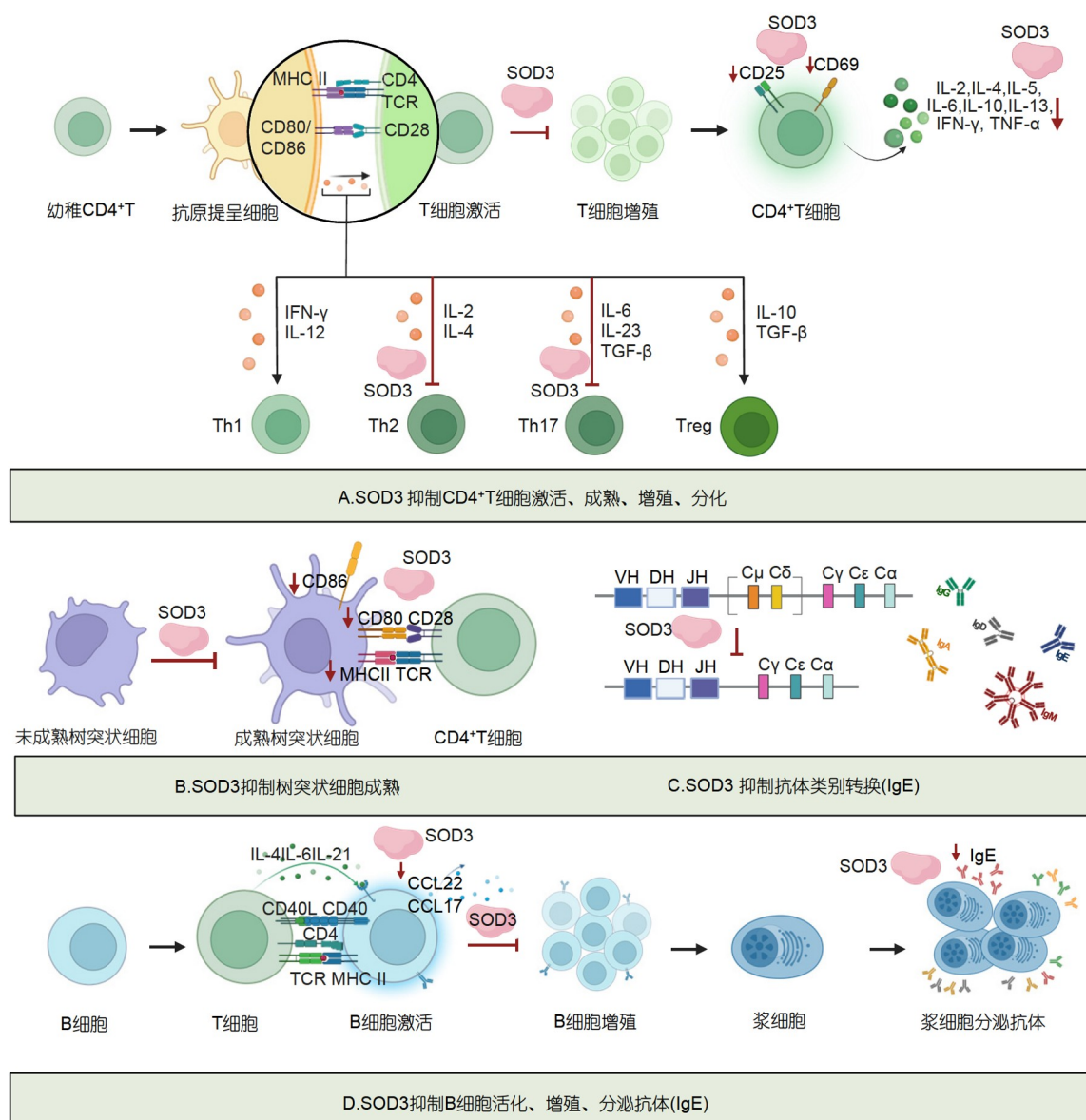


图2 SOD3对免疫细胞的调节作用。A: SOD3下调CD4⁺T细胞中表面激活标志物的表达水平并降低IL-2, IL-4, IL-6等细胞因子表达水平,从而抑制T细胞激活、增殖分化过程;B: SOD3通过抑制MHC II, CD80和CD86的表达来抑制DC成熟,从而间接抑制T细胞的激活和增殖;C: 在抗原激活后,受刺激的B细胞经历类开关重组(CSR)过程,其中免疫球蛋白重链恒定区 μ (C μ)外显子被删除,并由几组CH外显子(如C γ , C α 和C ϵ)之一取代,以改变抗体的类型,从而产生特异性抗体。SOD3减少了IgE同型类开关重组基因的表达,限制IgE类别转换;D: SOD3抑制B细胞增殖、趋化因子和抗体(IgE)分泌^[13,17,21,45-47]

Figure 2 Regulatory effect of SOD3 on immune cells. Note: A: SOD3 downregulates the expression of surface activation markers on CD4⁺T cells and reduces the expression of cytokines such as IL-2, IL-4 and IL-6, thereby inhibiting T cell activation and proliferation; B: SOD3 inhibits DCs maturation by suppressing the expression of MHC II, CD80 and CD86, thereby indirectly inhibiting T-cell activation and proliferation; C: after antigen activation, stimulated B cells undergo class switch recombination (CSR), in which the constant region μ (C μ) exon of immunoglobulin heavy chains is deleted and replaced by one of several CH exons (eg., C γ , C α and C ϵ) to change the type of antibody produced, resulting in the generation of specific antibodies. SOD3 reduces the expression of IgE isotype switch recombination genes, thereby limiting IgE class switching; D: SOD3 inhibits B cell proliferation, chemokine secretion and antibody (IgE) secretion^[13,17,21,45-47]

细胞造成损伤;第二阶段是在损伤周围组织中的单核免疫细胞(单核细胞、巨噬细胞和淋巴细胞)识别损伤

因子及组织坏死物,产生促炎介质(ROS、TNF、IL-1、花生四烯酸代谢产物、血管活性胺等)^[48,49],第三

阶段中, 炎症介质激活宿主的血管反应及白细胞反应^[50]. 血管反应使血流动力学改变、内皮细胞损伤导致血管通透性增加^[51], 血浆蛋白(抗体、补体、纤维素等)和白细胞渗出到血管外. 白细胞反应使白细胞渗出血管, 并在趋化因子(细菌产物如有N-甲酰甲硫氨酸末端的多肽、单核细胞趋化蛋白-1(monocyte chemoattractant protein-1, MCP-1), 补体如C5a、细胞白三烯、细胞因子特别是IL-8等)的作用下聚集到炎症部位^[52]. 白细胞聚集后, 通过多种受体来识别感染的微生物和坏死组织, 然后被激活, 通过免疫细胞的吞噬作用(主要为中性粒细胞和吞噬细胞)和免疫作用(主要是单核细胞、淋巴细胞、浆细胞)稀释、中和、杀伤及清除致炎物质^[53]. 第四阶段主要是炎症反应消退. 实质细胞和间质细胞增生, 修复受损伤的组织.

在炎症反应过程中, SOD3抑制了炎症反应局部的炎症细胞(单核/巨噬细胞、白细胞)的迁移和浸润, 诱导中性粒细胞凋亡^[54,55], 降低巨噬细胞中促炎细胞因子TNF- α 和MIP-2的分泌. 此外, SOD3还可减少黏附分子VCAM-1和ICAM-1在体内的表达^[56,57](图3).

炎性细胞因子TNF- α 、IL-1 α 、IL-6、巨噬细胞炎性蛋白2(macrophage inflammatory proteins-2, MIP-2)和MCP-1以及细胞黏附分子-1(intercellular cell adhesion molecule-1, ICAM-1)和血管细胞黏附分子-1(vascular cell adhesion molecule-1, VCAM-1)等炎症相关因子基因的启动子中含有NF- κ B结合位点, NF- κ B通过调节细胞因子的表达, 在对炎症信号的反应中起着核心作用^[14]. 应激活化蛋白激酶(c-Jun N-terminal kinase, JNK)和AP-1也可以控制内皮趋化因子和黏附分子表达.

SOD3使I κ B α 表达增加, 促进NF- κ B的细胞质定位, 使其无法结合DNA, NF- κ B活性下降50%. 这会导致炎症细胞因子(TNF- α , IL-1 α , IL-6)和趋化因子(MIP-2和MCP-1)的表达减少^[16]. SOD3还抑制TLR4聚集到细胞膜脂筏, 从而导致下游NF- κ B的激活受到抑制, 继而使炎症细胞因子(TNF- α 、IFN- γ 、转化生长因子(transforming growth factor, TGF)- β 、IL-1 β)和II类转活化剂(CITA)表达减少, 以实现抗炎作用^[58].

此外, SOD3还通过下调转录因子的磷酸化, 抑制p-JNK和p-ERK1/2的激活(尤其是ERK的磷酸化), 导致TNF- α 介导的MAPK信号通路的激活受到抑制, IL-1 β 、IL-6、IL-8和TNF- α 表达减少^[15]. SOD3还能抑制B细胞

中IL-4介导的JAK1, JAK3和STAT6信号的激活. 同样, 有报道发现, SOD3通过下调LPS或抗CD40抗体介导的p38, JNK和NF- κ B激活^[47](图4).

以上研究表明, SOD3通过调节信号通路减少炎症细胞因子和趋化因子的表达, 并抑制炎症细胞的浸润等机制实现其抗炎作用.

4 SOD3的治疗潜力

4.1 SOD3在免疫相关疾病中的治疗潜力

如前所述, SOD3通过各种机制抑制炎症, 包括调节免疫细胞功能(T细胞、巨噬细胞、自然杀伤细胞、树突状细胞)、减少炎症介质以及调节细胞信号的级联反应(TLRs, NF- κ B, MAPKs和JAK-STAT)等. 因此, 我们推测, 可以通过调节SOD3的作用达到对一些感染、肿瘤和自身性免疫疾病治疗的目的.

间充质干细胞(mesenchymal stem cells, MSCs)是一种具有强大免疫调节能力的成体干细胞, MSCs作为细胞治疗产品, 被广泛应用于自身免疫性疾病的辅助治疗^[59-61]. SOD3过度表达的间充质干细胞(SOD3-MSCs)能限制Th₂和Th₁₇分化, 使中性粒细胞、巨噬细胞和树突状细胞数量减少, 并通过抑制TLR7, NF- κ B, MAPK和JAK-STAT信号的激活来抑制炎症细胞因子(IL-1 β , IL-6, IL-17, IL-22, IL-23, TNF- α , IFN- γ)和趋化因子(CXCL-1, CCL-17, CCL-20)的表达.

SOD3和SOD3-MSCs的治疗作用在多种免疫相关疾病的动物模型中已得到证实. 对卵白蛋白诱导的过敏性哮喘小鼠腹腔注射SOD3, 发现治疗组气道中的嗜酸性粒细胞、中性粒细胞、巨噬细胞和淋巴细胞显著减少, 血清中IgE下降. 组织学检查发现, 上皮细胞增生、纤维化、黏液化增生和平滑肌质量增加得到缓解, 气道重塑被抑制^[21]. SOD3-MSCs还显著抑制小鼠的咪喹莫特诱导的类牛皮癣炎症, 使小鼠背部皮肤红斑、增厚度明显减少、单核细胞浸润程度下降, 并抑制信号通路(TLR-7, NF- κ B, p38)以及腺苷受体激活^[62]. SOD3和SOD3-MSCs还能上调紧密连接和黏连蛋白的表达水平以降低肠道上皮细胞通透性, 抑制MAPKs激活, 保护肠道上皮屏障, 在炎症性肠病(包括溃疡性结肠炎和克罗恩病)表现出良好的治疗效果^[15]. 此外, SOD3还对痤疮丙酸杆菌引起的皮肤炎症、尘螨引起的过敏性皮肤炎症等也有抑制作用^[23,63,64]. 这说

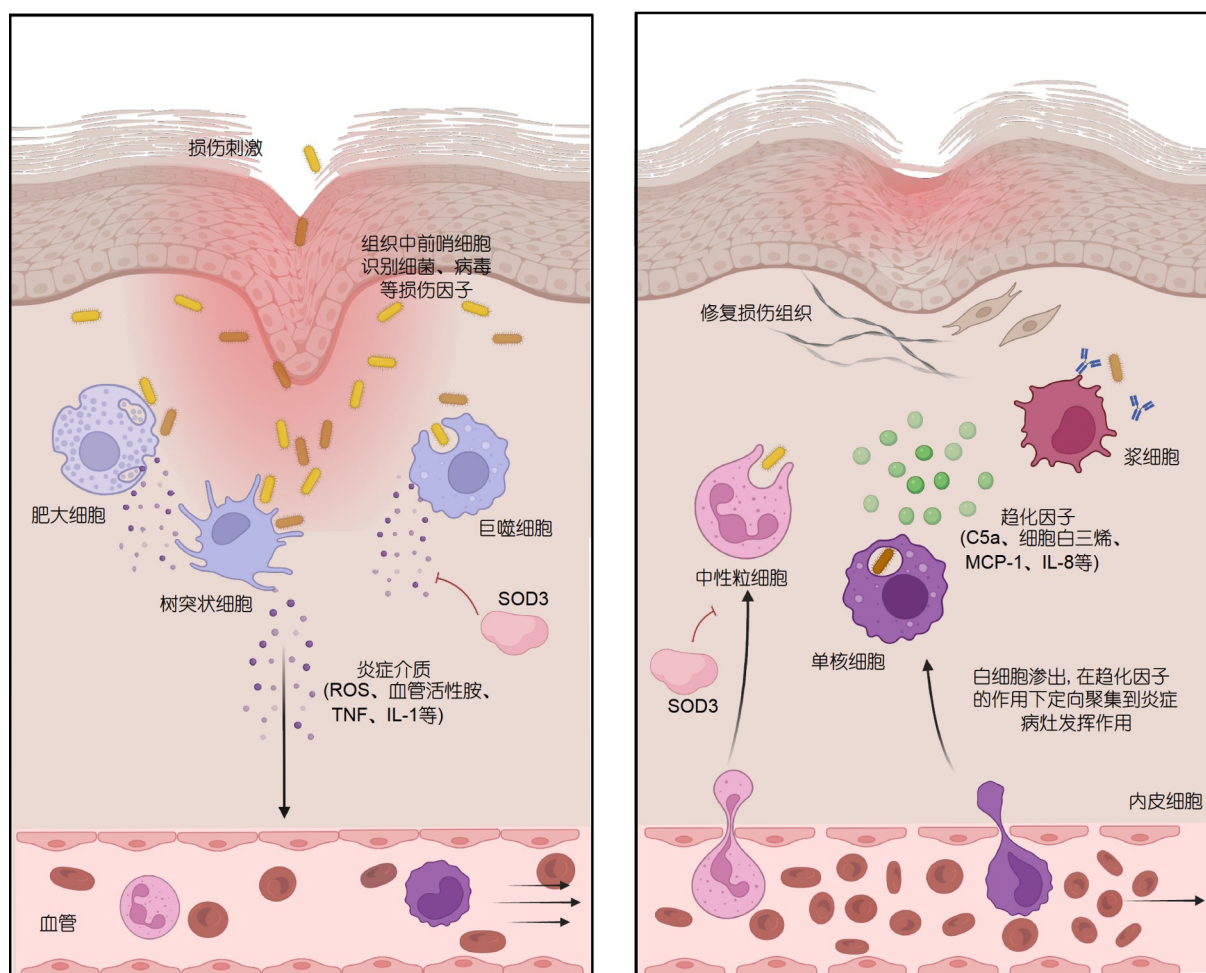


图 3 SOD3抑制炎症反应. 损伤因子对机体造成损伤, 损伤组织周围前哨细胞识别损伤因子、产生炎症介质. 炎症介质激活宿主的血管反应及白细胞反应. 血管扩张, 血流加快, 血管通透性增加导致血浆渗出, 而后血流速度减慢, 白细胞渗出, 在趋化因子作用下聚集到损伤因子所在部位, 清除微生物及坏死组织. SOD3抑制炎症细胞的迁移和浸润, 降低巨噬细胞中促炎因子的分泌^[48-55]

Figure 3 SOD3 inhibits inflammatory responses. Injury factors cause damage to the organism, and sentinel cells around the injured tissue recognise the injury factors and produce inflammatory mediators. These inflammatory mediators activate the host's vascular and leukocyte responses. Vasodilation, accelerated blood flow and increased vascular permeability lead to plasma exudation, followed by a slowing of blood flow and leukocyte exudation which, under the influence of chemokines, aggregates at the site of the injury to remove microorganisms and necrotic tissue. SOD3 inhibits the migration and infiltration of inflammatory cells and reduces the secretion of pro-inflammatory factors in macrophages^[48-55]

明SOD3及SOD3-MSC有望在更多免疫相关疾病中发挥治疗作用.

4.2 SOD3拟态化合物

SOD3是分泌型蛋白质, 在肌肉中的半衰期长达85小时, 在循环系统中长达20小时^[65]. 与之相比, SOD1在循环系统中的半衰期只有7分钟且迅速降解^[66], 因此SOD3更适用于基因治疗. 类风湿性关节炎是一种自身免疫性疾病^[67], SOD3基因转移具有改善

类风湿性关节炎的效果, 使用转基因治疗小鼠的临床症状(关节肿胀、畸形、后爪厚度增加)被显著抑制, 组织学异常(软骨及骨骼的破坏、单核细胞浸润、滑膜细胞异常增殖)也得到显著改善^[68]. SOD3基因治疗降低了TNF- α 、IL-1、TGF- β 、血管细胞黏附着分子-1和细胞间黏附分子-1的表达并减少了免疫细胞的迁移^[69,70]. 此外, 腺病毒介导的SOD3的体外基因转移单独或与金属蛋白酶-1的组织抑制剂(SOD3⁺TIMP-1)或牛痘病毒抗炎蛋白(SOD3⁺35K)的组合在可以减少巨

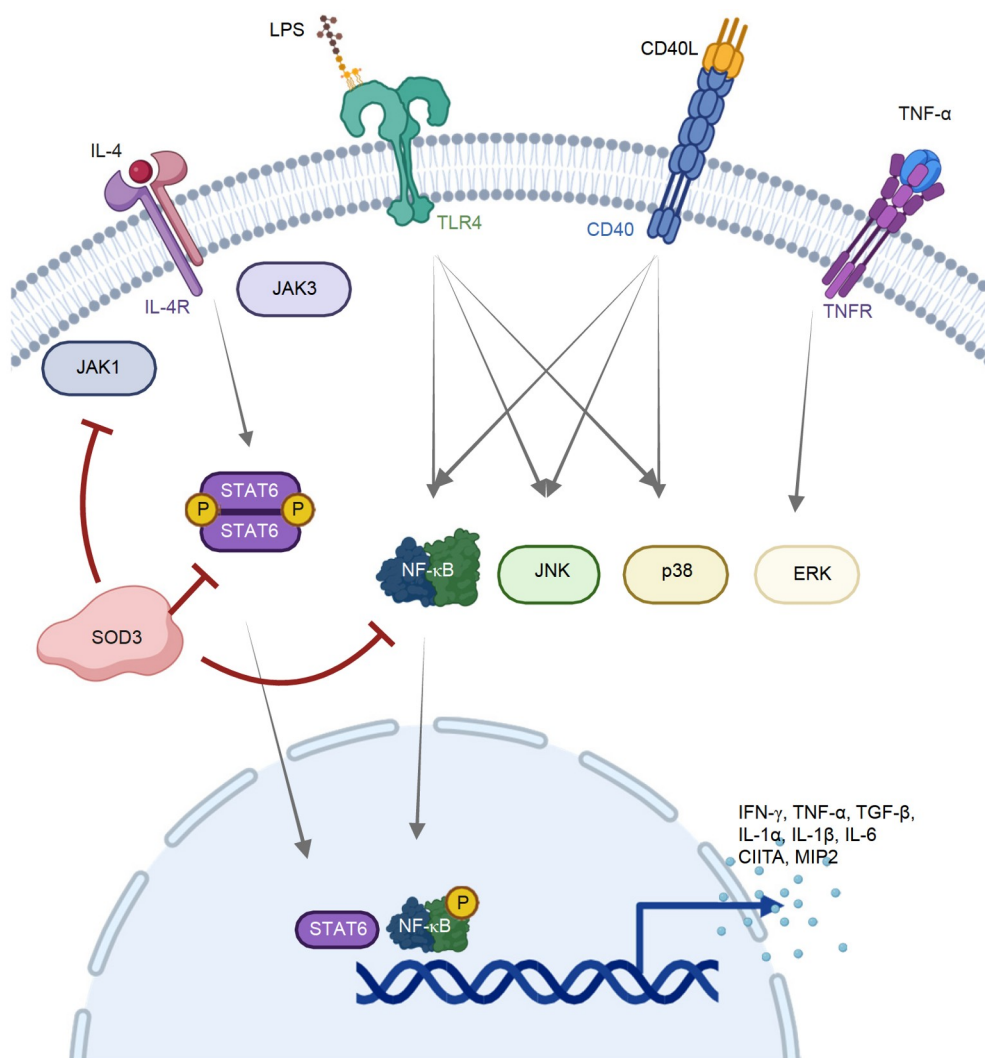


图 4 SOD3抑制炎症信号通路. IL-4, LPS, CD40L, TNF- α 与其对应受体互相结合, 会激活NF- κ B, JNK, p38, ERK等下游信号通路, 启动细胞内信号转导的级联反应从而增加炎性细胞因子和趋化因子的分泌, 引发炎症反应. SOD3通过下调磷酸化等方式抑制这些信号通路以抑制炎症反应^[15,16,47,58]

Figure 4 SOD3 inhibits the inflammatory signaling pathways. IL-4, LPS, CD40L and TNF- α bind to their respective receptors and activate downstream signalling pathways such as NF- κ B, JNK, p38, ERK and others. This initiates intracellular signalling cascades leading to increased the secretion of inflammatory cytokines and chemokines, triggering inflammatory responses. SOD3 inhibits these signalling pathways through mechanisms such as down-regulating phosphorylation to suppress the inflammatory response^[15,16,47,58]

噬细胞积累, 用于防治兔颈静脉移植模型中的静脉移植狭窄^[71].

因存在制造成本高、细胞通透性低等问题, SOD3的临床使用具有局限性. 近年来, 也有研究发现了SOD拟态化合物、纳米材料、抗氧化剂等清除ROS及对于免疫疾病、炎症的潜在治疗用途^[72~74]. 与之相比, SOD3拟态化合物具有低分子量, 在血液中的半衰期更长等优点^[75]. 现有的SOD拟态化合物主要类别有锰-

金属卟啉、锰环聚胺、锰-炔-炔复合物、MnPLED衍生物以及亚硝基化物^[76].

Tempol是亚硝基化物类的SOD3拟态化合物, 在炎症、高血压、糖尿病和内皮功能障碍的动物模型中表现出有益的作用^[77]. Neil等人^[78]的研究表明, 在已建立的多发性硬化症模型中, 口服Tempol限制了中枢神经系统自身免疫性疾病和损害. 锰复合物M40403, 有减轻过敏性哮喘症状及肺部病理变化的功能^[79], 还可以

减少TNF- α 等促炎因子的释放,对胶原蛋白诱导的关节炎有治疗作用^[77]。MnL4也属于锰化合物,在过敏性支气管哮喘模型中已被证明有抗炎作用^[80]。SOD3拟态化合物的作用机理、临床应用及其副作用有待进一步研究。

5 总结与展望

SOD3的功能不仅是作为ROS清除剂,其在控制免疫反应方面的也有着独特作用。SOD3通过多种机制抑制炎症,例如,调节细胞信号级联(TLRs, NF- κ B, MAPKs和JAK-STAT),抑制炎症因子和黏附分子的表达,减少炎性细胞浸润。SOD3还调控免疫细胞(T细胞、巨噬细胞、自然杀伤细胞、树突状细胞)的激活、成熟、增殖、分化、归巢。许多免疫疾病的发病机制与临床表现的严重程度与SOD3的缺乏相关,如银屑病、过敏性哮喘、过敏性结膜炎等。直接注射SOD3蛋白以及使用SOD3-MSC在过敏性皮炎、过敏

性气道炎、银屑病、炎症性肠病(包括溃疡性结肠炎和克罗恩病)等免疫相关疾病中已被证实有明显的治疗效果。SOD3还可以在多种癌症中(肺癌、头颈部鳞状细胞癌、乳腺癌等)评估生存率、肿瘤分化程度及侵袭性,并作为诊断及预后指标。此外,SOD3还能调节寄生虫的生长发育、入侵宿主过程以及细菌、病毒的复制和感染过程。这些研究强调了SOD3在调节免疫调节功能方面的重要性,并佐证了SOD3是潜在的治疗免疫相关疾病的药物。

目前针对各种免疫疾病模型的研究结果都证明了SOD3与疾病的高度相关性。许多关于SOD3的研究仍在继续,以探索其在预防、诊断、治疗各类免疫相关疾病中的潜力。未来应将SOD3对于免疫系统调控的生物学机制和其作为药物治疗的临床结果联系起来,进行临床转化、提高临床疗效。特别是对于SOD3拟态化合物的研究,应增强其活性和稳定性并提供更好更有效的治疗。此外,还需要进一步的研究来阐明SOD3作为药物产生的副作用。

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New insights into the immunoregulatory role of SOD3

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Superoxide dismutase 3 (SOD3) is an antioxidant enzyme that acts outside of cells. Its primary function has been believed to convert superoxide into hydrogen peroxide and oxygen. Recent studies indicated SOD3 also participates in sophisticated immune regulation in diverse diseases. Host-derived SOD3 plays a direct role in modulation of immune processes, including oxidative stress, immune cell maturation, proliferation, differentiation, and inflammation. Pathogens can also express SOD3 to evade host immune defense and facilitate invasion by suppressing host cellular responses. SOD3 expression levels are linked to the progression of immune-related diseases, making it a potential target for immunotherapy. This article thoroughly reviewed the research progress and current knowledge in the immunomodulatory mystery of SOD3.

superoxide dismutase 3, immunomodulation, immune dysfunction, parasitosis

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