

## Trp-IDO1,2/TDO2-Kyn 代谢通路介导类风湿关节炎的研究进展

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**摘要:** 类风湿关节炎 (rheumatoid arthritis, RA) 是以自身反应性 T 细胞和 B 细胞过度活化, 自身抗体大量产生为特征, 多关节受累为主要表现的自身免疫病。在遗传和环境等因素影响下, 固有免疫和适应性免疫功能紊乱是其发病的根本原因。近年来, “免疫代谢学”快速发展, 在不同能量代谢途径及相关分子调控免疫细胞分化与功能等方面取得重要进展。多项研究表明, Trp-IDO1,2/TDO2-Kyn 代谢通路介导了 RA 等自身免疫病的病理机制和发生发展。本文综述了此代谢通路中色氨酸 (tryptophan, Trp) 和犬尿氨酸 (kynurenine, Kyn) 等代谢物以及限速酶吲哚胺-2,3-双加氧酶 1 (indoleamine 2,3-dioxygenase 1, IDO1)、吲哚胺-2,3-双加氧酶 2 (indoleamine 2,3-dioxygenase 2, IDO2) 和色氨酸-2,3-双加氧酶 2 (tryptophan-2,3-dioxygenase 2, TDO2) 介导 RA 炎症免疫反应和滑膜炎的作用和研究进展, 为阐明 RA 新的病理机制和发现新的药物靶点提供重要依据。

**关键词:** 类风湿关节炎; 免疫代谢; 色氨酸; 犬尿氨酸; 吲哚胺-2,3-双加氧酶 1; 吲哚胺-2,3-双加氧酶 2; 色氨酸-2,3-双加氧酶 2

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## Progress in research of Trp-IDO1,2/TDO2-Kyn metabolic pathway in the pathogenesis of rheumatoid arthritis

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**Abstract:** Rheumatoid arthritis (RA) is an autoimmune disease characterized by excessive activation of autoreactive T cells and B cells, abundant production of autoantibodies and multiple joint involvement. Under the influence of heredity and environment, the disorder of innate immunity and adaptive immunity is the fundamental cause of the disease. In recent years, with rapid development of immunometabolism, milestone has been made in regulating the differentiation and function of immune cells through different energy metabolism pathways and related molecules. Many studies have shown that Trp-IDO1,2/TDO2-Kyn metabolic pathway mediates the pathogenesis and development of autoimmune diseases such as RA. This review summarizes the role of tryptophan (Trp), kynurenine (Kyn) and other metabolites in this metabolic pathway, as well as the role of rate-limiting enzymes indoleamine 2,3-dioxygenase 1 (IDO1), indoleamine 2,3-dioxygenase 2 (IDO2) and tryptophan-2,3-dioxygenase 2 (TDO2) in mediating RA inflammatory immune response and synovitis inflammation. This provides an important basis for elucidating the new pathological mechanism of RA and discovering new drug targets.

**Key words:** rheumatoid arthritis; immunometabolism; tryptophan; kynurenine; indoleamine 2,3-dioxygenase 1; indoleamine 2,3-dioxygenase 2; tryptophan-2,3-dioxygenase 2

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代谢和免疫之间复杂而密切的相互作用是机体稳态调节的核心机制。免疫应答通常伴随免疫细胞在短时间内大量增殖激活,活化的免疫细胞有赖于改变其能量代谢方式,进行代谢重编程,进而分化、扩增和发挥功能。自2011年《Nat Rev Immunol》杂志第一次出现“immunometabolism”的概念以后<sup>[1]</sup>，“免疫代谢学”快速发展,在不同能量代谢途径及相关分子调控免疫细胞分化与功能等方面取得重要进展<sup>[1-4]</sup>。免疫细胞选择的代谢状态是与其生物学功能以及外界环境相适应的,免疫细胞在受到外界刺激后能够迅速进行代谢重组以适应新的功能状态和外界环境,这也是免疫代谢参与维持机体免疫稳态以及正常免疫反应的重要机制。而代谢方式的改变将直接导致免疫细胞功能的变化和机体免疫稳态的失衡,进而诱发各种疾病,这在肿瘤研究中比较多见,但在自身免疫病中研究较少。新近研究表明,免疫细胞能量代谢异常导致机体免疫稳态失衡,可能介导了自身免疫病的病理机制和发生发展<sup>[5,6]</sup>,包括类风湿关节炎(rheumatoid arthritis, RA)<sup>[7]</sup>、系统性红斑狼疮<sup>[8]</sup>和干燥综合征<sup>[9]</sup>等,但其机制不清楚。

### 1 免疫代谢紊乱与类风湿关节炎

RA以受累关节的慢性滑膜炎为基本病变,其病理机制与T、B细胞和成纤维样滑膜细胞(fibroblast-like synoviocyte, FLS)等各种细胞以及白细胞介素(interleukin, IL) 1和肿瘤坏死因子 $\alpha$ (tumor necrosis factor  $\alpha$ , TNF- $\alpha$ )等炎性细胞因子共同作用有关,产生针对自身抗原(关节软骨II型胶原)的自身抗体,最终导致滑膜炎和骨、软骨破坏<sup>[10]</sup>。RA发病机制中免疫稳态的失衡一直是研究者广泛关注的热点;而免疫细胞代谢紊乱导致的免疫功能失调,可能是RA新的病理机制。研究表明,RA患者炎性关节滑膜组织糖酵解活性增强<sup>[11]</sup>。PET-CT影像学检查证实,RA患者肿胀大关节2-氟-2-脱氧-D-葡萄糖摄取增加,提示关节炎部位细胞糖代谢异常<sup>[12]</sup>,且代谢改变与炎症程度密切相关<sup>[13]</sup>。代谢谱检测结果显示,RA患者滑膜组织FLS糖代谢明显异常<sup>[14-16]</sup>。在TNF- $\alpha$ 体外刺激下,通过糖酵解和线粒体呼吸促进FLS的葡萄糖代谢;葡萄糖缺失或糖酵解抑制剂则降低RA-FLS的增殖、分泌、迁移和侵袭<sup>[17]</sup>。Fearon等<sup>[18]</sup>发现,低氧微环境下,滑膜组织血管翳的形成限制浸润免疫细胞对氧的利用,也可以诱导免疫细胞糖代谢和线粒体代谢的改变。而在RA早期,在慢性刺激和炎性微环境下,RA患者CD4<sup>+</sup>T细胞的糖酵解限速酶6-磷酸果糖-2-激酶/果糖-2,6-二磷酸酶(6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3, PFKFB3)表达降低,代谢方式由糖酵解转变为以戊糖磷酸途径(pentose phosphate pathway, PPP)为

主,NADPH产生增加<sup>[19]</sup>,升高的NADPH中和活性氧(reactive oxygen species, ROS),促进T细胞活化和滑膜炎。与正常组相比,RA患者T细胞葡萄糖-6-磷酸脱氢酶(glucose-6-phosphate dehydrogenase deficiency, G6PD) mRNA和蛋白水平以及酶活性明显升高,葡萄糖-6-磷酸进入PPP循环,产生大量NADPH,谷胱甘肽产生减少。研究显示,G6PD/PFKFB3比值与RA患者临床疾病活动度(DAS28)密切相关<sup>[20]</sup>。以上研究结果提示,RA炎性关节滑膜中,FLS和免疫细胞代谢改变共同决定了滑膜低氧状态和线粒体功能障碍,转变为糖酵解代谢为主,一些中间代谢物作为信号分子促进细胞-细胞之间相互作用,促进炎症免疫反应,最终诱导滑膜炎和组织损伤。

有趣的是,临床治疗RA常用药物的作用机制与调控细胞代谢密切相关<sup>[21]</sup>。早在20世纪中期,糖皮质激素以代谢为靶点在治疗RA等自身免疫病上取得了革命性的进展。糖皮质激素与其受体结合,调控一系列参与代谢过程的基因转录,抑制糖酵解,发挥抗炎免疫调控作用。大部分改善病情抗风湿药(disease-modifying antirheumatic drugs, DMARDs)包括甲氨蝶呤(methotrexate, MTX)、霉酚酸酯和来氟米特,主要靶向嘌呤和嘧啶核苷酸代谢,在抑制FLS和免疫细胞功能及活化中发挥重要作用。新近研究发现,柳氮磺胺吡啶可能通过抑制胱氨酸/谷氨酸反向转运体,发挥抗炎作用<sup>[22]</sup>。新的DMARDs药物阿普斯特同样靶向嘌呤代谢,增加环磷酸腺苷(cyclic adenosine monophosphate, cAMP)水平和cAMP依赖的蛋白激酶A活性<sup>[23]</sup>。FLS和单核细胞PI3K/AKT/mTOR信号通路活化,促进葡萄糖转运到细胞表面进行葡萄糖摄取和糖酵解<sup>[24]</sup>。雷帕霉素通过作用于雷帕霉素靶蛋白复合体1(mammalian target rapamycin complex 1, mTORC1),激活AMP依赖的蛋白激酶,抑制FLS侵袭和免疫细胞功能活性,发挥治疗自身免疫病的作用<sup>[25]</sup>。这些药物在发挥治疗作用的同时,也会引起胃肠道不良反应和骨髓抑制等不良反应。现有靶向生物制剂如TNF- $\alpha$ 拮抗剂等,虽有较好的治疗效果,但在治疗自身免疫病的同时,会抑制免疫系统和细胞正常的生理功能,导致严重感染和诱发肿瘤的危险。而通过调控代谢途径恢复免疫细胞功能,只针对激活的代谢活跃免疫细胞,不会影响基本免疫功能。因此,深入探讨免疫细胞代谢调控机制,纠正细胞异常代谢恢复其正常的免疫状态,将为临床有效治疗RA提供重要理论依据。

### 2 色氨酸-犬尿酸代谢通路紊乱参与了RA的病理机制和发生发展

色氨酸(tryptophan, Trp)是哺乳动物体内的必需

氨基酸之一,参与合成蛋白质、脂类和核酸等生物大分子,对维持细胞活化和增殖具有重要作用。其分解途径有两个:5-羟色胺途径和犬尿氨酸(kunurenine, Kyn)途径。少部分Trp通过色氨酸羟化酶生成5-羟色胺,约95% Trp经过犬尿氨酸通路(kunurenine pathway, KP)代谢,在限速酶吲哚胺-2,3-双加氧酶1(indoleamine 2,3-dioxygenase 1, IDO1)、吲哚胺-2,3-双加氧酶2(indoleamine 2,3-dioxygenase 2, IDO2)、色氨酸-2,3-双加氧酶2(tryptophan-2,3-dioxygenase 2, TDO2)的酶促作用下生成重要中间代谢物Kyn, Kyn经多级酶促反应生成3-羟邻氨基苯甲酸(3-hydroxyanthranilic acid, 3-HAA)、犬尿喹啉酸(kynurenic acid, KYNA)、邻氨基苯甲酸(anthranilic acid, AA)、喹啉酸(quinolinic acid, QA)和尼克酰胺腺嘌呤二核苷酸(NAD<sup>+</sup>)等活性分子。

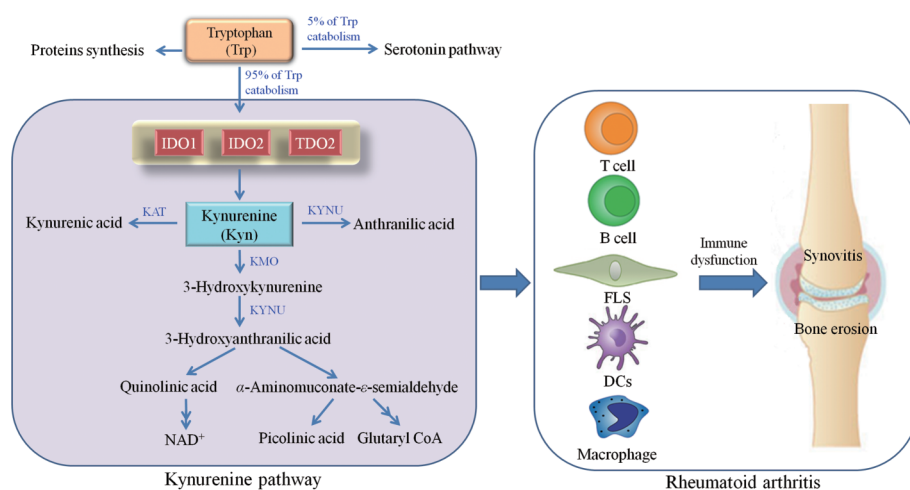
**2.1 KP代谢物与炎症免疫反应** KP是Trp代谢的主要途径,产生多种具有生物活性的中间代谢物,参与多个病理生理过程,与神经精神性疾病、自身免疫病、心血管疾病和肿瘤等疾病的发生发展密切相关<sup>[26-28]</sup>。KP代谢物在免疫系统的免疫调控方面发挥重要作用<sup>[26,29]</sup>。在局部组织微环境中,Trp耗竭可导致细胞周期阻滞、抑制细胞增殖、促进细胞凋亡<sup>[30-33]</sup>。Munn等<sup>[34]</sup>认为,Trp是T细胞增殖、分化的必需氨基酸,Trp减少将导致T细胞进入细胞周期但停滞于G<sub>0</sub>期,从而抑制T细胞增殖,即“Trp饥饿”造成了T细胞的增殖抑制甚至凋亡。研究表明,Kyn在IDO介导的免疫功能的调节、IDO依赖的胸腺细胞凋亡以及抗原特异性CD4<sup>+</sup>T细胞分化中有着重要作用<sup>[32]</sup>。Bauer等<sup>[35]</sup>发现,Kyn能抑制同种异型基因T细胞的增殖,同时伴随着诱导T细胞凋亡的现象。进一步研究发现,低浓度Kyn可诱导T细胞的凋亡,且与caspase-8的活化及线粒体释放的细胞色素C有关<sup>[33]</sup>。Kyn与芳香烃受体(aryl hydrocarbon receptor, AHR)结合负向调节树突状细胞(dendritic cells, DCs)的免疫原性,促使初始T细胞向调节性T细胞分化,阻止其向Th17细胞分化<sup>[36-38]</sup>。同时,Kyn可直接作用于RA-FLS上的AHR,诱导FLS异常活化,参与关节滑膜炎和关节破坏<sup>[39]</sup>。3-HAA促进DCs产生转化生长因子- $\beta$ ,进而诱导Treg的分化<sup>[40]</sup>。3-HAA衍生物曲尼司特抑制信号传导及转录激活因子1(signal transducers and activators of transcription 1, STAT1)磷酸化,下调CXC趋化因子配体(CXC chemokine ligand, CXCL)9和CXCL10的表达,抑制CD4<sup>+</sup>T细胞的增殖和分泌<sup>[41]</sup>。另外,低浓度Trp和KP代谢物的累积协同作用,共同参与机体的免疫调节作用,如低浓度Trp和KP代谢物混合物包括Kyn、AA、3-HAA和QA剂量依赖性抑制Th17功能<sup>[42]</sup>,促进Treg

的分化和功能<sup>[43]</sup>。

**2.2 KP代谢紊乱与RA** 早在20世纪50年代末,有学者提出可以根据关节滑液中Trp含量来区分炎症性关节病和非炎症性关节病。紧接着,多项临床试验显示,RA患者体内KP代谢异常,Trp水平降低,Kyn、3-HAA和黄尿酸等增加<sup>[44-47]</sup>。因此研究者们认为低Trp饮食可以影响Trp代谢,进而改善关节炎症状<sup>[48]</sup>。进一步研究发现,血清中Trp改变与疾病进程密切相关,随着RA疾病的进展而减少<sup>[49]</sup>。RA患者关节滑液中Kyn降低,且与C反应蛋白呈正相关,为寻找诊断和治疗RA生物标记物提供重要理论依据<sup>[50]</sup>。动物实验同样表明,胶原性关节炎(collagen-induced arthritis, CIA)小鼠和佐剂性关节炎(adjuvant-induced arthritis, AA)大鼠尿液中Trp和Kyn含量异常变化,Kyn/Trp比值升高<sup>[51-53]</sup>。Inglis等<sup>[54,55]</sup>研究表明,3-HAA衍生物曲尼司特抑制CIA小鼠和AA大鼠的炎症表现,改善病理学变化,抑制T、B细胞增殖、减少淋巴结Th1细胞比例和 $\gamma$ -干扰素(interferon- $\gamma$ , IFN- $\gamma$ )产生、升高血清IL-10水平。Parada-Turska等<sup>[56]</sup>发现,RA患者关节滑液中检测到KYNA,体外实验进一步发现KYNA可以抑制RA-FLS的增殖,促进非甾体抗炎药的抗增殖活性。以上研究结果表明,KP代谢异常在RA病理机制中发挥重要作用(图1)。

### 3 KP代谢酶介导了RA异常免疫反应和关节滑膜炎

**3.1 IDO1、IDO2和TDO2与RA** IDO1、IDO2和TDO2均是KP代谢通路催化Trp产生Kyn的重要限速酶,它们都参与KP代谢,但它们的底物特异性不同,且具有组织细胞特异性表达。IDO1是最先发现的IDO亚型,IDO1和IDO2的氨基酸同源性为43%,与TDO2同源性较低。IDO1广泛分布于人和动物的组织和细胞(巨噬细胞和DCs等)中,主要介导免疫调节和免疫耐受,参与自身免疫病、免疫排斥和肿瘤等疾病的病理机制<sup>[26,31,37]</sup>。但IDO1在RA中的作用主要表现为两种不同的结果。一方面,IDO1的抗炎作用。RA患者Treg细胞表达细胞毒性T淋巴细胞相关抗原4(cytotoxic T lymphocyte antigen 4, CTLA-4)发挥免疫抑制作用,主要与其升高IDO1功能和活性有关<sup>[57]</sup>。IDO1基因敲除小鼠,经II型胶原诱导为CIA,表现为关节炎症状加重,炎症后期关节滑膜Th1和Th17细胞浸润增多<sup>[53]</sup>。IDO1抑制剂1-MT体内给药后,促进Th1细胞的极化,加重CIA小鼠关节炎临床表现<sup>[58]</sup>。IDO1基因过表达经关节腔或尾静脉给药,显著降低CIA大鼠关节肿胀和病理学评分,与其诱导CD4<sup>+</sup>T细胞凋亡,降低关节滑液IL-17水平和增加Kyn水平有关<sup>[59,60]</sup>。Seo等<sup>[61]</sup>发



**Figure 1** Kynurenine pathway (KP) metabolic dysfunction in the abnormal immune response and joint synovitis of rheumatoid arthritis (RA). IDO1: Indoleamine 2,3-dioxygenase 1; IDO2: Indoleamine 2,3-dioxygenase 2; TDO2: Tryptophan-2,3-dioxygenase 2; KAT: Kynurenine amino transferase; KYNU: Kynureninase; KMO: Kynurenine 3-monooxygenase; FLS: Fibroblast-like synoviocyte; DC: Dendritic cell; NAD<sup>+</sup>: Nicotinamide adenine dinucleotide

现, 抗 4-1BB (CD137) 单克隆抗体抑制抗原特异的 CD11c<sup>+</sup>CD8<sup>+</sup> 细胞克隆扩增, 产生大量 IFN- $\gamma$ , 诱导 DCs 表达 IDO1, 抑制 CD4<sup>+</sup> T 细胞功能, 从而发挥改善小鼠 CIA 关节炎的作用。另有报道, IDO1 也具有促炎作用, RA 患者血中 IDO1 活性 (Kyn/Trp 比值) 升高, 且与疾病的严重程度密切相关<sup>[62]</sup>。在 K/BxN 小鼠自发性关节炎模型中, 炎症前期给予 IDO1 抑制剂 1-MT 可降低 B 细胞产生抗体和细胞因子水平, 抑制 K/BxN 小鼠关节炎<sup>[63,64]</sup>。MTX 和 1-MT 联合给药治疗 K/BxN 关节炎小鼠, 比 MTX 单独给药能更好地抑制关节炎, 其机制与阻断叶酸代谢密切相关<sup>[65]</sup>。

IDO2 与 IDO1 作用于相似的酶底物, 但其酶解效率明显低于 IDO1, 生物学功能不明确, 研究较少。近年来研究发现, IDO2 与肿瘤和机体免疫相关。IDO2 在胰腺癌、结肠癌、胃癌、肾癌等都有过度表达<sup>[66,67]</sup>, 但其促进肿瘤发生的作用机制尚不清楚。IDO2 基因敲除的 KRN 关节炎小鼠, CD4<sup>+</sup> T 细胞活化抑制和自身抗体产生减少, 关节炎状明显减轻<sup>[68]</sup>。进一步研究表明, IDO2 可以直接作用于 B 细胞, 或者通过 B-T 细胞之间的相互作用, 介导自身免疫性关节炎的病理机制<sup>[69]</sup>。Merlo 等<sup>[70]</sup>研究发现, IDO2 特异单克隆抗体降低自身反应性 T、B 细胞反应, 抑制自身免疫性关节炎表现。也有相反的研究, IDO2 在人外周血 DCs 表达, 且能诱导 Treg 表达, 提示 IDO2 在机体稳态中可能起免疫抑制作用<sup>[71]</sup>。

TDO2 主要表达于肝脏, 调节系统 Trp 水平和肝脏 Kyn 水平。最初关于 TDO2 的研究是 TDO2 抑制剂在抗抑郁症中的作用<sup>[72]</sup>。直到 2011 年, Opitz 等<sup>[38]</sup>首次

报道 TDO2 (而不是 IDO1 和 IDO2) 在神经胶质瘤高表达, 并且 TDO2 表达高的部位, CD8<sup>+</sup> 细胞浸润非常少; 动物实验显示, 高表达 TDO2 的神经胶质瘤小鼠 T 细胞释放 IFN- $\gamma$  明显减少。紧接着, 2012 年 Pilotte 等<sup>[73]</sup> 研究结果显示 TDO2 在肝癌、乳腺癌、直肠癌和肺癌等多种肿瘤中均有高表达, 肿瘤细胞利用 TDO2 介导的 T 细胞免疫调节作用抑制抗肿瘤免疫反应, 促进肿瘤生长。有趣的是, 在正常具有免疫活性小鼠中, 小分子 TDO2 抑制剂 LM10 促进高表达 TDO2 肥大细胞瘤小鼠的免疫排斥反应, 抑制肿瘤生长; LM10 对高表达 TDO2 的免疫缺陷小鼠没有任何作用, 提示 TDO2 发挥作用与机体免疫系统密切相关。但 TDO2 在 RA 等自身免疫病中的作用, 未见文献报道, 有待于进一步研究探讨。

**3.2 IDO1、IDO2 和 TDO2 在 RA 中的作用与思考**  
IDO1、IDO2 和 TDO2 在 RA 病理机制中的作用, 仍然存在争议, 可能与以下几个方面有关: ① 不同动物模型具有不同的病理机制和发病特点, 三者介导免疫调控的作用也不尽相同; 在疾病的不同阶段, 酶的功能活性可能呈现一个动态的变化。② 炎症微环境下产生大量细胞因子, 如 IFN- $\gamma$  促进 IDO1 的表达, 而 IDO1 对自身免疫反应起反馈性抑制, 可能是一种自我保护机制, 这也能解释大多数自身免疫病自限性和反复发作的特点。③ IDO1、IDO2 和 TDO2 表达和活性具有组织细胞特异性, 在不同病理生理条件下, 酶功能和活性不同; 调控酶的机制非常复杂, 同一上游信号分子可以由不同的中间通路调控酶的产生, 中间信号通路相同而上游信号分子不同对于酶的调控亦不相同。④ 除

了IDO1、IDO2和TDO2同样介导催化Trp产生Kyn,当把其中一个酶活性阻断,另外两个酶可能会代偿性地发挥作用,调控机制复杂。因此,深入研究IDO1、IDO2和TDO2的免疫调控作用,明确其介导的KP代谢通路在RA发病中的分子作用机制,具有重要的理论意义和应用前景。

#### 4 展望

随着对“免疫代谢学”的不断认识和深入研究,探讨代谢途径与免疫反应之间的相互关系,不仅有助于深入阐明免疫应答本质及其调控机制,同时可以通过调控免疫细胞的异常能量代谢影响其功能,进而干预某些免疫病理过程的发生和发展,为RA等自身免疫病的防治提供临床治疗新策略。目前,针对这3个酶的药物主要集中在肿瘤治疗的临床和临床前研究阶段,比如IDO1小分子抑制剂包括epacadostat (INCB024360)、BMS-986205、navoximod (NLG919/GDC-0919)等,临床上多与免疫检查点抑制剂联合应用于肿瘤的治疗;IDO1/TDO2双重抑制剂如HTI-1090/SHR9146,目前处于实体肿瘤治疗的临床研究阶段。TDO2抑制剂较少,经典的TDO2抑制剂680C91体外作用较好,但体内给药效果不好。在680C91基础上通过结构改造合成了LM10,大大提高了其抑制活性、溶解性及生物利用度,临床前研究中显示出良好的抗肿瘤作用,而且长时间给药不会造成肝功能损伤和毒副作用,但离应用于临床仍有距离。虽然多项研究表明,Trp-IDO1,2/TDO2-Kyn代谢通路介导了RA异常免疫反应和滑膜炎,在RA病理机制中发挥重要作用,但IDO1、IDO2和TDO2靶向药物治疗RA等自身免疫病尚处于临床前研究阶段。KP代谢通路涉及3个限速酶,在RA中的机制复杂多变,在不同的动物模型表现不一样的酶活性,在炎症的不同阶段表现不同的生物学效应,在不同的细胞表现不同的功能。未来研究将进一步明确IDO1、IDO2和TDO2在RA不同阶段(早期、中期和缓解期)异常免疫反应和滑膜炎中的调控特点,阐明3个酶分别调控FLS和免疫细胞功能活性的分子病理机制,揭示其介导的KP异常代谢与自身免疫紊乱的关系,为RA等自身免疫病的药物研发提供有效分子靶标,并为探索临床防治新策略提供重要理论依据和实验依据。通过纠正细胞异常代谢,恢复细胞免疫反应和机体稳态,从而达到治疗疾病的目的,这也是将来研发炎症免疫相关疾病的创新药物新方向,即炎症免疫反应软调节药物<sup>[74]</sup>,通过选择性调控细胞异常活性至生理水平,恢复细胞的动态平衡,发挥治疗作用,并尽量减少不良反应。

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