芳香烃受体调控树突状细胞的研究进展

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摘要 树突状细胞(dendritic cell, DC)作为体内功能最强的抗原递呈细胞(antigen presenting cell, APC), 是连接先天性和适应性免疫系统的桥梁, 在启动和放大免疫应答信号中发挥着重要作用。研究表明, 芳香烃受体(aryl hydrocarbon receptor, AhR)可通过DC调控机体的免疫功能, 参与各种伤病导致的机体免疫功能紊乱的防治。该文就近年来AhR对DC的调控及其机制作一综述, 为进一步研究免疫调理关键分子提供文献依据和新思路。

关键词 芳香烃受体; 树突状细胞; 调控

Progress of the Role-Aryl Hydrocarbon Receptor on Dendritic Cell

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Abstract As the strongest antigen presenting cell (APC) *in vivo*, dendritic cell (DC) is a bridge between innate and adaptive immunity. Furthermore, it plays an important role in triggering and amplifying the signals of immune response. Recent studies showed that aryl hydrocarbon receptor (AhR) can regulate the immune functions via DC, and may be a potential key molecule of immune modulation to participate in the prevention and cure of immune dysfunction caused by various injuries and diseases. This review summarized the role and regulatory mechanism of AhR on DC according to the related reports for the past few years, so as to provide the literature evidence and new idea to investigate the key molecule for immunomodulation.

Keywords aryl hydrocarbon receptor; dendritic cell; regulation

创伤、疾病、感染和应激都可能导致机体免疫功能紊乱, 严重时还可引发各种并发症, 威胁人类健康。在机体免疫失衡的过程中, 各类免疫细胞发挥了重要作用, 尤其是树突状细胞(dendritic cell, DC)。作为目前发现的功能最强的抗原递呈细胞(antigen presenting cell, APC), DC是启动和放大先天性及适应性免疫应答信号中重要的始动者, 也是机体免疫应答的重要细胞之一[1]。新近研究发现, 芳香烃受体(aryl hydrocarbon receptor, AhR)能通过影响DC功能进而调节机体免疫应答[2], 可能作为防治免疫性疾病的关键分子参与机体的免疫调理。因此, 本文就近年来AhR调控DC的研究进展进行综述。

1 DC和AhR概述

1.1 DC

DC是美国学者Steinman于1973年发现的, 因其

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成熟细胞具有许多树突状突起而得名, 广泛分布于机体各重要器官(例如: 皮肤、心脏、肺、肠和脾)[3], 与免疫激活和免疫耐受密切相关, 在免疫诱导中具有独特的地位[4-5]。

广义上, DC来源于共同树突状细胞前体(common dendritic cell precursor, CDP), CDP进一步分化为浆细胞样DC(plasmacytoid dendritic cells, pDC)和常规/经典DC(classical dendritic cells or conventional dendritic cells, cDC)[5-7]。一般而言, DC类型可以细分为pDC、cDC、朗罕氏细胞(langerhans cell, LC)和单核细胞来源的DC(monocyte-derived DCs, mo-DC)等, 其中pDC又称E2-2依赖型DC, 系驻留DC; cDC包括3型ATF样碱性亮氨酸拉链转录因子(basic leucine zipper transcription factor ATF-like 3, BATF3)依赖型DC[又称cDC1, 为驻留外周$CD8^+$ DC和迁移的$CD103^+$ $langerin^+$ DC]和干扰素调节因子(interferon-regulatory factor 4, IRF4)依赖型DC(又称cDC2, 为驻留$CD8^-$ $CD11b^+$ DC和迁移的$CD11b^+$ DC)[8-9]。DC在不同种属中的表面生物标志物和亚群略有不同。研究表明, 小鼠DC表达高水平的MHC II类分子和CD11c[8], 而人DC则高度表达HLA-DR[10]。Guilliams等[8]研究证明, 除与小鼠相同的DC亚群外, 人体皮肤和阴道黏膜还存在$CD1a^+$ DC和$CD14^+$ DC等亚群。

正常情况下, 机体DC处于非成熟状态, 尽管具有极强的内吞和加工处理抗原的能力, 但表达辅助因子和黏附分子的水平低, 激发混合淋巴细胞反应(mixed lymphocyte reaction, MLR)的能力也很弱。如果接受抗原或受到某些分子刺激, 则DC可成熟并活化, 并将抗原通过MHC分子递呈给T细胞受体, 从而激活初始T细胞(naïve T cell, Th0)向不同T细胞亚群分化(例如, IL-12刺激Th0分化为Th1, IL-4刺激Th0分化为Th2), 进而调节T细胞免疫应答, 并维持自身抗原免疫耐受[10-13]。研究已经证实, DC亚群的分化可增加体内适应性免疫的功能[5]。虽然DC在启动机体免疫功能的重要作用已经得到广泛共识, 但单独应用DC临床治疗免疫性疾病的效果仍不理想。因此, 深入探寻能够有效调控DC功能的关键因子始终是调理机体免疫失衡的重要策略。

1.2 AhR

AhR是配体依赖性激活的转录因子, 由805个氨基酸构成, 属于碱性螺旋–环–螺旋转录因子家族成员[14-15]。AhR蛋白的功能结构由3部分组成: bHLH结构域、PAS(Per-ARNT-Sim)结构域和一个富含Q-结构域, 其中bHLH位于AhR蛋白的N末端区域, 参与芳香烃反应元件(aryl hydrocarbon response elements, AHRE)和AhR核转运蛋白(AhR nuclear translocator, ARNT)的结合, PAS结构域是ARNT结合和配体结合所必需的, 蛋白C末端区域富含Q-结构域, 主要影响该蛋白的转录激活[16]。

研究表明, 在缺乏配体的情况下, AhR是作为胞质蛋白复合物四聚体[包括2个热休克蛋白90(heat shock protein 90, HSP90)、辅助蛋白p23和乙型肝炎病毒X相关蛋白(hepatitis B virus X-asspcoated protein 2, XAP2)]的组成部分[17-19], 与配体如2,3,7,8-四氯二苯二噁英(2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD)、色氨酸光化产物6-甲酰基吲哚并(3,2-b)咔唑[6-formylindolo(3,2-b) carbazole, FICZ]、犬尿氨酸(kynurenine, KYN)、吲哚-3-甲醇(indole-3-carbinol, I3C)等结合后, AhR复合物被激活移位到细胞核, 并与ARNT结合在AHRE上启动靶基因转录[20-21], 激活下游靶基因如细胞色素P450家族成员1A1(cytochrome P450 1A1, CYP1A1)、CYP1A2、CYP1B1、谷胱甘肽S-转移酶-α、UDP葡萄糖醛酸转移酶、醛脱氢酶和NAD(P)H醌还原酶-1等的表达[22]。

传统的AhR研究多集中在二噁英的毒理学效应、药物和杀虫剂代谢、胚胎发育和肿瘤发生等生物学领域。近年来的研究发现, AhR不但在伤病介导的免疫功能紊乱中能够影响巨噬细胞的活性, 而且在T细胞、单核细胞和DC的功能调控中作用显著[23-26]。

2 AhR对DC生物学功能的影响

2.1 成熟及分化

研究表明, AhR能够活化DC, 而AhR缺失则会延缓LC的成熟[26-27]; TCDD能够通过AhR促进骨髓来源树突状细胞(bone marrow derived dendritic cell, BMDC)的成熟, 该过程与RelB、吲哚胺2,3-双加氧酶(indoleamine 2,3-dioxygenase, IDO)、趋化因子受体6(chemokine receptor 6, CCR6)和白细胞介素-22(interleukin-22, IL-22)有关, 并伴有CD80、CD86、RelB和MHC II的表达水平增加, 但对CD83及CD40的表达无影响[25,28-29]; 而在脾脏和肠系膜淋巴结(mesenteric lymph nodes, MLN)的DC中, TCDD激活AhR对CD8α、CD40、CD54、CD80、CD86和MHC II

的表达没有明显的影响[30]。另外, AhR激活还可促进粒细胞巨噬细胞集落刺激因子(granulocyte macrophage-colony stimulating factor, GM-CSF)诱导的小鼠骨髓细胞分化为CD11c$^+$ DC[31]。

AhR可调节DC的免疫原性, 改变DC的生物学功能, 从而影响机体的免疫耐受。研究表明, 一种低分子量复合物转录因子VAF347激活AhR后, 可抑制人BMDC分泌CD86、HLA-DR和IL-6[32], 原因可能是VAF347在CDP阶段阻止了单核细胞和LC的分化, 而祖细胞扩增及粒细胞生成未受到影响[26]。AhR在髓系亚群分化过程中受到高度调控, LC表达高水平AhR, 其次是单核细胞, 而嗜中性粒细胞缺乏AhR表达[26]。

AhR对不同类型DC的分化调控作用各不相同。Liu等[27]发现, AhR可能选择性抑制pDC的分化但对cDC的分化无影响。研究表明, AhR沉默可减少mo-DC分化, 同时增加单核细胞来源的巨噬细胞(monocyte-derived macrophages, mo-Mac)分化: FICZ激活AhR后, 可促进mo-DC同时阻止mo-Mac的分化; 而SR1(stemregenin-1)抑制AhR后, 则促进mo-Mac同时阻止mo-DC的分化[33]。因此, 有观点认为, AhR可能是mo-DC与mo-Mac分化的分子开关, 其中IRF4和V-MAF肌肉腱膜纤维肉瘤癌基因同源体B(v-maf musculoaponeurotic fibrosarcoma oncogene homolog B, MAFB)可能是关键的调节剂[33]。研究还表明, AhR活化后可导致MLN中CD11c$^+$ DC数量减少, 同时不影响CD11b$^+$ DC的数量; 却可使脾脏中CD11c$^+$ CD103$^+$ DC的数量增加, 同时不影响CD11c$^+$ CD103$^-$ DC和CD11b$^+$ DC的数量[30]。

2.2 增殖、凋亡与分泌

研究表明, AhR沉默后可导致人肝癌细胞系HepG2和人乳腺癌细胞系MCF-7细胞周期停滞, 并且细胞在G_0/G_1期中的百分比增加; 而从AhR缺失小鼠获得的原代肝细胞和胚胎成纤维细胞则表现出较低的细胞增殖速率, 同时凋亡水平增加[34], 表明AhR能够影响细胞的增殖和凋亡; Singh等[35]研究也发现, TCDD与DC中的AhR结合后, 可以诱导与之共培养或抗原递呈后的Th0发生凋亡。但目前尚缺乏AhR直接调控各类DC增殖和凋亡的证据。

Vogel等[31]发现, TCDD激活AhR后可导致BMDC的分泌功能发生改变: 对脂多糖(lipopolysaccharide, LPS)刺激的BMDC, AhR活化可使其分泌IL-6、IL-10、IL-22和IL-23的水平升高, 同时可抑制特异性趋化因子DC-CK1的增高; 而对未受LPS刺激的BMDC, AhR活化提高CXCL2(C-X-C motif chemokine 2)、CXCL3和IL-22的表达, 降低IL-10的表达, 不影响IL-6、IL-12和肿瘤坏死因子α(tumor necrosis factor α, TNFα)的表达。另外, 研究还发现, TCDD处理未受LPS刺激的BMDC后, 还可以导致补体C3a受体1(C3aR1)和清道夫受体A1(scavenger receptor A1, SRA1)的表达增加[31]。

2.3 抗原递呈和T/B细胞分化

DC是启动适应性应答免疫最重要的APC。DC活化后还能通过共刺激分子、共抑制分子和MHC分子的共同作用完成特异性抗原的识别和传递, 诱导淋巴细胞(包括T细胞和B细胞)的分化, 引发细胞免疫和体液免疫[13]。Chng等[36]通过流式细胞分析发现, AhR缺失能够导致小肠固有层(lamina propria, LP)中CD103$^+$ CD11b$^-$ DC、CD103$^+$ CD11b$^+$ DC和CD103$^-$ F4/80$^+$巨噬细胞细胞表面标志物的表达不稳定, 进而影响后续对T、B细胞的抗原递呈过程[8]。研究表明, AhR活化后可导致胶质瘤细胞CD103表达增加[37]; 而Bruhs等[38]发现, AhR依赖型激动剂4-n-壬基苯酚(4-n-nonylphenol, NP)可调控小鼠DC使其不发生致敏, 还可诱导调节性T细胞(regulatory T cell, Treg)的分化。这些结论都提示, AhR可能影响DC的抗原递呈, 但调控细节仍缺乏详实的证据支撑。

研究表明, AhR缺失的DC引发的抗原递呈可能改变T细胞的行为, 使其倾向于向Th2分化, 并发生强烈的炎症反应[39]。Jurado-Manzano等[21]发现, FICZ激活mo-DC中的AhR后, 可促进DC的分化和成熟, 并诱导Th0分化成功能性CD4$^+$ CD25$^+$ Foxp3$^+$ Treg细胞, 从而反馈抑制Th0的分化, 引起免疫耐受。Wei等[40]在研究过敏性鼻炎(allergic rhinitis, AR)病例时发现, AhR可促进DC和CD4$^+$ T细胞中IL-10分泌的增加, 并减少CD4$^+$ T细胞中IL-17的表达, 通过AhR的内源性配体2-(1′H-吲哚-3′-羰基)-噻唑-4-羧酸甲酯[2-(1′H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methylester, ITE]治疗后可抑制Th17对AR的应答。de Araújo等[41]的研究证明, IDO-AhR轴可通过对pDC的影响来调节Treg-Th17的平衡。除此之外, 还有研究发现, ITE活化的AhR可诱导DC产生视黄酸(retinoic acid, RA), 进而干扰Th17细胞的发育并促进Foxp3$^+$ Treg的分化[42-45]。

此外, DC可直接调控B细胞的生长、分化以及免疫球蛋白的产生, 从而在自身免疫性疾病中发挥作用[46-47]。AhR是调控B细胞发育和功能的关键分子, 活化的AHR可以使造血干细胞依次分化为前体B细胞、成熟B细胞和抗体分泌的浆细胞[16,48]。AhR可通过BTB与CNC同源基因2(BTB and CNC homology 2, *Bach2*)调节B淋巴细胞诱导成熟蛋白-1(B lymphocyte induced maturation protein-1, Blimp-1), 在体内抑制B细胞分化成浆母细胞和分泌抗体的浆细胞, 提示AhR可能成为调控B细胞反应的新型分子靶标[49]。

3 AhR调控DC的分子机制

3.1 IDO1/TDO2-KYN-AhR信号通路

有研究显示, 将AhR缺失的BMDC与Th0共培养, 然后加入LPS/CpG刺激并添加合成的L-Kyn后, Th0分化形成的Treg-Th17平衡右移[2,50], γ干扰素(γ-interferon)和LPS处理DC后也会引起Treg增殖, 同时诱导IDO1表达[51]。因此, AhR的激活可介导DC促进Treg的分化和增殖[45,48,52-53], 其机制可能与KYN和RA的作用有关[54]。Cheong等[55]发现, 色氨酸可通过IDO1/色氨酸2,3-双加氧酶2(tryptophan 2,3-dioxygenase 2, TDO2)催化产生KYN, 进而激活AhR, 然后促使调节性树突状细胞(regulatory DC, rDC)产生并释放IL-10, 进一步引起Treg的分化, 最终抑制肿瘤微环境(tumor microenvironment, TME)的适应性免疫。可见, 靶向调节IDO1/TDO2-KYN-AhR信号通路可能为肿瘤免疫疗法提供了新的思路。

3.2 IL-2和STAT信号通路

研究表明, NP和ITE[38,45]激活AhR后可驱动DC分泌IL-2, 并诱导Foxp3的表达[38,56-58]; 而FICZ或ITE活化AhR导致DC显著抑制Th0向Th1和Th17的分化[28]。上述结果提示, AhR活化后介导DC分泌IL-2可能是细胞后续发生免疫抑制的关键事件, IL-2可能是诱导Treg分化的关键分子[38]。Quintana等[45]使用转化生长因子-β1(transforming growth factor-β1,TGF-β1)和IL-2激活AhR后, 发现小鼠体内$CD4^+$ T细胞中STAT1(signal transducer and activator of transcription 1)磷酸化水平增加, 而STAT5的磷酸化水平没有变化; 而在Th0分化为Treg和Th17的过程中, STAT3发生了磷酸化。

3.3 TLR和NF-κB信号通路

DC功能受核因子-κB(nuclear factor-kappaB, NF-κB)信号途径的高度调控[59], 阻断NF-κB通路会影响DC和淋巴细胞的发育, 并与人类的免疫缺陷和自身免疫相关[60], 而Toll样受体(Toll-like receptor, TLR)与NF-κB信号途径的交互作用已得到确认[61]。Kado等[62]发现, TCDD、FICZ和I3C等激活AhR后, 可引起TLR诱导的Mo-DC中细胞因子和DC特异性表面标志物的表达, 其中涉及NF-κB家族成员RelB[63-64]和免疫调节因子CDX2的表达, 最终使TLR介导的Mo-DC中IL-1β的表达水平升高, 同时降低了IL-12A和CYP1A1的表达水平。此外, AhR的活化还可以通过对TLR和NF-κB信号通路的调控, 促进Th17的极化[65]。

3.4 MEK-ERK信号通路

作为有丝分裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号传递网络的重要组成部分, MAPK激酶–细胞外调节激酶(MAPK kinase-extracellular regulated protein kinases, MEK-ERK, MAPKK-ERK)信号途径可通过级联磷酸化途径高效地进行信号传递。研究表明, MEK-ERK信号通路的活化能够减少共刺激分子(如CD49、CD83和CD86等)、MHC-II的表达以及IL-12p40和IL-12p70的产生, 增加促炎因子的分泌, 弱化DC对T细胞的刺激能力, 而抑制该信号途径的效果正好相反[66-68], 提示MEK-ERK信号通路能够负向调控DC成熟。另外, Aguilera-Montilla等[65]利用MEK抑制剂U0126处理未成熟的mo-DC后发现, 抑制MEK后可导致AhR转录活性增强, 并且改变原有AhR介导未成熟mo-DC的关键效应分子的表达, 提示AhR对部分DC的调控可能依赖于MEK-ERK信号通路。

4 结论与展望

AhR全面参与了先天性和适应性免疫的调节, 而DC是AhR发挥免疫调节作用的重要靶细胞之一。AhR通过与内、外源性配体的作用, 直接影响DC的成熟、分化、增殖、凋亡等生物学功能, 并通过对其分泌和抗原递呈功能的调控, 干预机体的免疫平衡, 其机制涉及多条信号通路(图1)。研究表明, ITE激活的AhR影响了DC的活化和功能从而引起ITE抑制实验性自身免疫性葡萄膜视网膜炎(experimental autoimmune uveoretinitis, EAU)的发展[69]; FICZ和ITE激活AHR通过影响白塞病(Behçet's disease)人来源的DC的成熟和功能, 抑制Th1和Th17的应答[28], 提示AhR活化影响DC分化、成熟及功能, 从而调节免

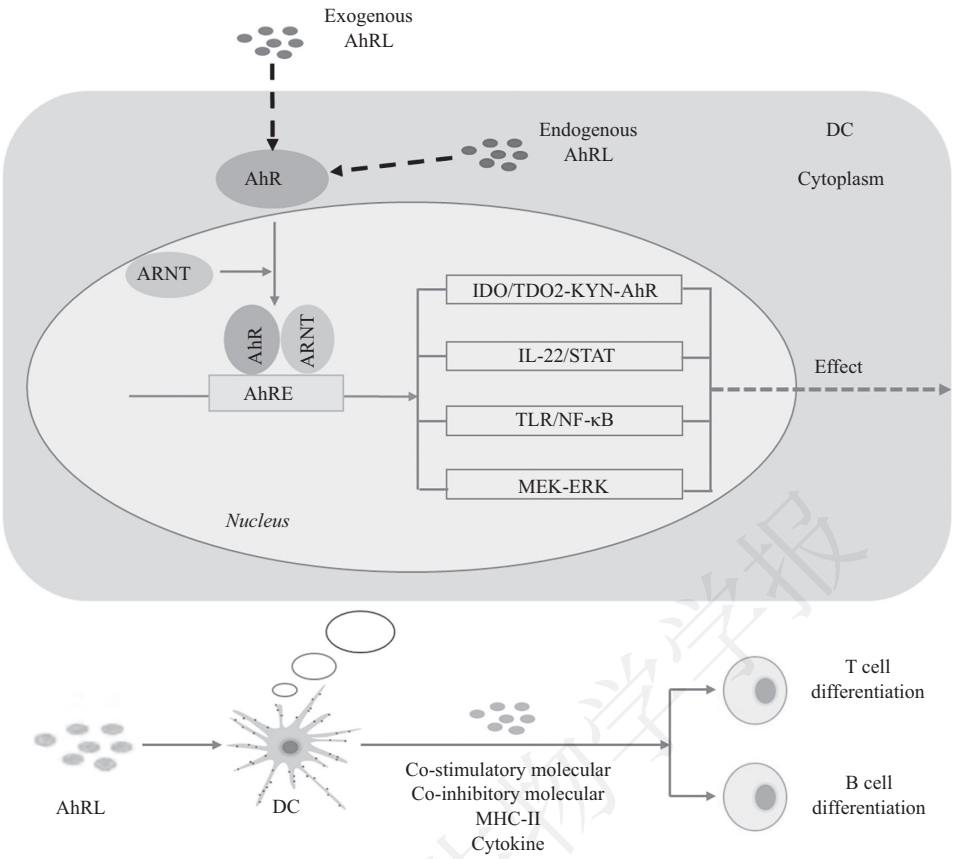

图1 AhR调控DC示意图

Fig.1 The regulatory role of AhR on DC

疫相关疾病的进程。因此, AhR可能成为调控DC功能的关键分子, 参与创伤、疾病、感染、应激等因素导致的机体免疫功能紊乱的防治。

但是, 目前对AhR对DC调控的研究还存在许多问题: AhR对各类DC乃至包括DC在内的各类免疫细胞功能的影响是否存在交互作用和反馈机制？涉及的诸多信号途径有无主次之分？能否筛选出以AhR为靶点、针对部分免疫系统疾病的中西医药物并开展临床研究？这些问题还有待于长期的、深入的研究和探讨。

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