芳香烃受体调控调节性T细胞的研究进展

马 娓 黄文娟 余 静 严 军* 梁华平*

(第三军医大学大坪医院野战外科研究所第一研究室, 创伤、烧伤与复合伤国家重点实验室, 重庆 400042)

摘要 T淋巴细胞在适应性免疫中发挥细胞免疫功能。调节性T细胞(regulatory T cell, Treg)是重要的T淋巴细胞亚群, 可有效维持免疫耐受和机体内环境稳定。深入挖掘能够影响Treg生物学特征的关键因子有助于干预Treg相关免疫性疾病和炎症反应的进程, 对于控制炎症发展、改善疾病预后具有潜在的临床应用价值。新近发现, 芳香烃受体(aryl hydrocarbon receptor, AhR)与机体免疫性疾病和炎症反应密切相关, 而且活化的AhR可以影响Treg的生物学特征。该文就AhR对Treg的分布、增殖、分化、凋亡、分泌的影响以及相关调控机制作一综述。

关键词 芳香烃受体; 调节性T细胞; 调控

Progress of the Role-Aryl Hydrocarbon Receptor on Regulatory T cell

Ma Wei, Huang Wenjuan, Yu Jing, Yan Jun*, Liang Huaping*

(*State Key Laboratory of Trauma, Burns and Combined Injury, Department 1, Institute of Surgery Research, Daping Hospital, Third Military Medical University, Chongqing 400042, China*)

Abstract T lymphocytes provide immune cellular function in adaptive immunity. As an important subset of T lymphocytes, regulatory T cell (Treg) can maintain immune tolerance and homeostasis effectively. Identifying the key factors that may affect the biological characteristics of Treg will help us interference with the development of Treg-related immune diseases and inflammation, and will have a potential value for clinical application in controlling inflammation and improving the prognosis of these diseases. The latest study found that the role of aryl hydrocarbon receptor (AhR) was closely concerned with these immune diseases and inflammatory response. Furthermore, activated AhR may influence the biological characteristics of Treg. This review summarized the role of AhR on Treg in the aspects of proliferation, differentiation, apoptosis and secretion, and discussed its related regulatory mechanisms.

Keywords aryl hydrocarbon receptor; regulatory T cell; regulation

调节性T细胞(regulatory T cell, Treg)是T淋巴细胞(又称T细胞)的重要亚群之一, 在机体适应性免疫功能的调控中发挥了重要作用。Treg的缺失会导致严重的多发性自身免疫性疾病, 显著缩短患者寿命[1]。而且, 在自身免疫性疾病和炎症性疾病(例如系统性红斑狼疮、多发性硬化症、动脉粥样硬化、类风湿关节炎等)的患者和动物模型中, 均伴有Treg数目减少和功能减弱的现象[2-3]。研究发现, 自身免疫性疾病和过敏性疾病发病率的增加与低分子量的化学物质有关, 其中某些化合物可以通过芳香烃受体(aryl hydrocarbon receptor, AhR)参与药物代谢, 调节生理功能。作为配体依赖性激活的转录因子, AhR与机

收稿日期: 2016-07-07 接受日期: 2016-10-28

国家自然科学基金(批准号: 81471863)和重庆市基础科学与前沿技术研究专项(批准号: cstc2016jcyjA0048)资助的课题

*通讯作者。Tel: 023-68757413, E-mail: 13883092250@163.com; Tel: 023-68757411, E-mail: 13638356728@163.com

Received: July 7, 2016 Accepted: October 28, 2016

This work was supported by the National Natural Science Foundation of China (Grant No.81471863) and the Basic Science and Advanced Technology Research Project of Chongqing (Grant No.cstc2016jcyjA0048)

*Corresponding authors. Tel: +86-23-68757413, E-mail: 13883092250@163.com; Tel: +86-23-68757411, E-mail: 13638356728@163.com

网络出版时间: 2016-12-29 15:23:58 URL: http://www.cnki.net/kcms/detail/31.2035.Q.20161229.1523.004.html

体免疫性疾病和炎症性疾病密切相关。研究表明, AhR可通过配体依赖的方式影响Treg的生物学特征, 进而干预机体的适应性免疫功能[4-5]。本文就AhR对Treg的分布、增殖、分化、凋亡和分泌的影响以及相关调控机制进行综述。

1　Treg和AhR简介

1.1　Treg

T细胞亚群的研究可追溯到20世纪70年代, 当时即已发现部分T细胞可发挥免疫抑制功能[6]。但最早对Treg进行描述和命名在1995年, 当时Sakaguchi等[7]发现, 成年小鼠中近10%的外周白细胞分化抗原簇4$^+$(cluster of differentiation 4$^+$, CD4$^+$)T细胞表达白细胞介素-2(interleukin-2, IL-2)受体α链CD25, 去除这群细胞后则会引起小鼠自发产生多种自身免疫性疾病, 而回输该细胞则阻止疾病的发生。随后, 这群细胞被命名为CD4$^+$CD25$^+$Treg[8]。之后, 又将叉状头转录因子家族成员3(forkhead box P3, Foxp3)作为其稳定的生物标志物[9-10]。

Treg是T细胞亚群的主要成员，参与协调各类辅助性T细胞(helper T cell, Th)亚群如Th1、Th2、Th9、Th17、Th22和滤泡辅助性T细胞(follicular helper T cell, Tfh)等在机体适应性免疫中的作用, 是维持机体内环境稳定和Treg-Th17平衡的关键因素[11-12]。Treg的两种类型即自然型Treg(natural Treg, nTreg)和诱导型Treg(induced Treg, iTreg), 在细胞免疫过程中会发生比例和作用的变化, 例如转化生长因子-β(transforming growth factor-β, TGF-β)可以使CD4$^+$CD62L$^-$Foxp3$^-$细胞诱导为iTreg。这种改变将直接影响机体免疫功能甚至疾病发展进程。

Treg具有免疫抑制性和免疫无反应性两大特征。前者即抑制CD4$^+$和CD8$^+$T细胞的活化和繁殖, 阻碍抗原递呈细胞(antigen presenting cell, APC)的抗原递呈作用, 并直接介导靶细胞的死亡; 后者即表现为在体外对于抗原特异性、同种异体或者多克隆的刺激不应答[13-14], 但这种低反应性可以通过T细胞受体和高浓度IL-2体外刺激产生逆转[15]。此外, Treg可以通过多种途径发挥免疫功能[16]: (1)释放白细胞介素-10(interleukin-10, IL-10)、白细胞介素-35(interleukin-35, IL-35)和TGF-β等免疫抑制性细胞因子; (2)合成并释放大量的环磷酸腺苷(cyclic adenosine monophosphate, cAMP), 从而对其他细胞的代谢进行影响; (3)通过颗粒酶和穿孔素杀伤其他细胞; (4)通过细胞毒性T淋巴细胞相关抗原-4(cytotoxic T lymphocyte-associated antigen-4, CTLA-4)影响树突状细胞的功能, 从而影响其他T细胞的激活。

基于机体免疫平衡对各类免疫性疾病预后的重要性以及Treg在其中发挥的关键作用, 人们一直尝试采用包括特定Treg在内的外源性细胞免疫治疗的手段来纠正各类疾病带来的免疫失衡, 并取得了一定疗效[17-18]。但是, 由于这些细胞进入体内后受机体微环境影响的因素和作用机制仍不清楚, 尤其是针对特定的外源性Treg而言, 其获取数量有限, 细胞功能不稳定, 从而难以保证稳定的治疗效果。因此, 寻找和挖掘能够有效调控Treg功能的关键因子的意义日益凸显。

1.2　AhR

AhR属于碱性螺旋–环–螺旋(basic helix-loop-helix, b-HLH)转录因子家族中的bHLH-PAS(period-aryl hydrocarbon receptor nuclear translocator-single minded, Pre-Arnt-Sim)亚家族成员, 由805个氨基酸构成, N-端区域高度保守, C-端区域保守性低, 易活化, 需依赖配体激活[19]。正常情况下, 无活性的AhR存在于细胞质中, 并与热休克蛋白90(90 kDa heat shock protein, HSP90)二聚体、乙型肝炎病毒X相关蛋白2(hepatitis B virus X-associated protein 2, XAP2)和辅助蛋白P23等多种蛋白质结合成为受体复合物, 再与配体(多为多环芳香烃类和卤代芳香烃类物质)结合形成配体–受体复合物。配体–受体复合物的构象进一步发生改变并入核。在核内, 游离的AhR受酪氨酸激酶作用而发生磷酸化以致活化, 进而与AhR核转位蛋白(arylhydrocarbon receptor nucleartranslocator, ARNT)相结合, 形成异二聚体转录因子, 再与靶基因启动子区域二恶英效应元件相结合, 从而启动靶基因如细胞色素P450家族成员1A1(cytochrome P-450 1A1, CYP1A1)的转录, 并引起一系列下游基因的表达和代谢酶的活化[20]。AhR的配体分为外源性和内源性两类, 前者如2,3,7,8-四氯二苯二恶英(2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD)、姜黄素、白藜芦醇、吲哚-3-甲醇以及槲皮素等, 后者如色氨酸光化产物6-甲酰基吲哚并(3,2-b)咔唑[6-formylindolo(3,2-b)carbazole, FICZ]和2-(1′H吲哚-3′-基羰基)噻唑-4-羧酸甲酯[2-(1′H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methylester,

ITE][17,21-23]。但也有学者认为, FICZ仍属于化学合成产物, 只是结构上与内源性配体吲哚(3,2-b)咔唑[indolo(3,2-b)carbazole, ICZ]相似[24]。AhR与不同的配体结合会产生不同的结果, 导致后续生物学功能的改变[24]。

近来发现, AhR不但在脂多糖(lipopolysaccharide, LPS)诱导的炎症基因表达以及炎性巨噬细胞的活性调节中发挥了重要作用, 而且参与了感染过程中对包括Treg在内的Th细胞亚群的调节, 并在其分化过程中作用显著[25-27]。

2 AhR对Treg生物学特征的影响

2.1 分布及数量

Treg在不同种属中的分布和功能各不相同。小鼠外周血中$CD25^+$Treg约占$CD4^+CD8^-$T细胞的5%~10%[28]; 而人外周血中约10%的$CD4^+$T细胞表达CD25抗原[29], 但真正具有免疫抑制活性的却不及2%[13]。

研究表明, AhR的活化可以改变Treg的分布情况[30]。AhR激活后通过升高Treg的百分比以抑制包括变应性致敏在内的免疫应答。Schulz等[30]用TCDD治疗C3H/HeOuJ小鼠8 d后, 分离小鼠胸腺、脾脏和肠系膜淋巴结, 发现TCDD的干预可以降低各组织中$CD4^-CD8^+$、$CD4^-CD8^-$、$CD4^+CD8^+$和$CD4^+CD8^-$等前体T细胞的数量, 减少脾脏中Th1、Th2和细胞毒性T细胞, 增加脾脏中Treg($CD4^+CD25^+Foxp3^+$)数量, 但胸腺中Treg($CD4^+CD25^+Foxp3^+$)数量未见减少。同时, TCDD还可抑制周围淋巴结中Treg($CD4^+CD25^+Foxp3^+$)、Th1和Th2的数量。

AhR与不同配体结合并活化后能够引起Treg数量的变化[31]。TCDD是AhR的高亲和力配体, 它与AhR结合后可以通过$CD4^+CD25^+$Treg数量的变化影响移植物抗宿主反应(host versus graft reaction, HVGR), 并且抑制同种特异性细胞毒性T细胞的产生。同时, TCDD还可通过扩增Treg($Foxp3^+$)的数量来抑制实验性自身免疫性脑炎(experimental autoimmune encephalitis, EAE)的病理进程[32]。Kerkvliet等[32]发现, 采用TCDD可以有效缓解非肥胖型糖尿病(non-obese diabetes, NOD)小鼠自身免疫性1型糖尿病的病情, 并且可以通过增加胰淋巴结中$CD4^+CD25^+Foxp3^+$细胞的数量来有效地减轻胰岛炎症。用TCDD治疗NOD小鼠15周后停药, 在随后的8周里, 小鼠机体AhR活化降低, Treg数量减少, 小鼠糖尿病的病情发展更为严重。这表明, TCDD诱导的AhR活化能够导致体内Treg数量的上升。

然而, 这种活化的AhR对Treg数量的正向影响并非绝对。Ehrlich等[31]研究发现, 当给小鼠口服另一种AhR高亲和力配体10氯-7H-苯并咪唑[2,1-α]苯并(脱)异喹啉-7-酮(10-chloro-7H-benzimidazo[2,1-α]benzo(de)iso-quinolin-7-one, 10-CL-BBQ)时, 能够有效防止胰岛内淋巴细胞浸润, 而使用AhR缺陷的NOD小鼠时则无该现象。进一步研究表明, AhR激活后是通过Treg的耗竭以阻止胰岛炎症的发病进程[31]。这表明, AhR的活化也能够导致Treg数量的下降, 不过AhR途径能够对Treg不足进行代偿。可见, 尽管TCDD和10-CL-BBQ与AhR结合并引发AhR活化后对Treg数量的影响不同, 但最后达到的免疫效果是类似的。

2.2 增殖与分化

AhR有助于Treg达到最佳增殖状态。研究发现, 犬尿氨酸(kynurenine, Kyn)可以通过AhR依赖的方式诱导Treg的增殖[33]。Mezrich等[33]分离野生型和*AhR*敲除小鼠的初始$CD4^+$T细胞(Th0)后, 通过TGF-β刺激定向诱导分化, 采用qPCR检测目的细胞中$Foxp3^+$的表达水平, 结果发现, 野生型小鼠*Foxp3*$^+$的mRNA水平是*AhR*敲除小鼠的40倍。流式细胞检测结果也显示, 野生型小鼠Treg的增殖百分比明显超过*AhR*敲除小鼠。

研究表明, AhR参与了对Treg分化的调节, 而这种调节是通过AhR激动剂(部分属于AhR配体)完成的[34]。Quintana等[26]发现, TCDD与AhR结合后可诱导小鼠Th0向Treg分化, 并缓解EAE的病情。无独有偶, Apetoh等[35]也发现, 转录因子c-Maf与AhR相互作用可促进IL-27介导的Treg的分化, 并增强IL-21基因启动子活性而促进转录, 同时改善EAE的病情。除此之外, Funatake等[36]采用脾脏移植动物模型, 也证实TCDD可以提高机体外周血中Treg的分化水平。其他研究显示, 作为哚胺2,3-二氧化酶(indoleamine 2,3-dioxygenase, IDO)降解色氨酸的第一产物, 内源性激动剂犬尿氨酸与AhR结合并导致AhR活化后, 可促进T细胞向Treg分化, 并增强Treg的活性, 同时Treg可再作用于树突状细胞(dendritic cell, DC), 然后通过DC促进其他Th0向Treg分化, 形成一个正反馈的过程[33,37]。 此外, ITE也可以参与诱导体内Treg的分化[22]。

然而, 也有一些激动剂与AhR结合后的作用与

上述结果相反[4,26]。例如, 用FICZ处理EAE小鼠后发现, 小鼠Treg的分化被抑制而Th17的分化得到增强, 主要表现为$CD4^+IL17^+$和$CD4^+IFN\text{-}\gamma^+$T细胞比例增大, IL-17和IFN-γ分泌水平增高, EAE病情加重。

2.3　分泌

Treg可分泌多种细胞因子, 如TGF-β、IL-10和IL-35等, 发挥免疫抑制作用, 同时Treg的分化也依赖于细胞因子的刺激[38]。虽然小鼠中近10%的外周$CD4^+$T细胞表达IL-2受体α链CD25, 但并不能分泌IL-2[39]。

Cai等[40]研究发现, 小鼠腹腔注射TCDD后, 血清中IL-10升高, IFN-γ和IL-17降低, 推测AhR的活化可能诱导Treg的分化, 而IL-10则是由Treg分泌产生。Apetoh等[35]分别对小鼠Th0转入绿色荧光蛋白(green fluorescent protein, GFP)标记的AhR过表达病毒载体及其对照GFP病毒载体, 然后检测GFP^+细胞中IL-10的表达量。结果发现, 当Th0细胞过表达AhR时, IL-10的分泌水平显著升高, 说明AhR可以通过Treg的分化以影响其分泌IL-10。此外, AhR与转录因子c-Maf相互作用也可以促进小鼠和人类Treg的IL-10分泌功能, 从而抑制炎性反应。

2.4　凋亡

目前关于AhR如何引起或导致Treg凋亡的相关研究较少。Veiga-Parga等[41-42]研究显示, TCDD活化AhR之后能够有效减弱基质性角膜炎的损害, 它能引起$Foxp3^-CD4^+$T细胞的凋亡和数量减少, 但是对$Foxp3^+CD4^+$T细胞没有影响, 因此增加了效应T细胞中Treg的比率。Pot[43]的研究结果也显示, 与其他传统的T细胞相比, Treg更能够抵抗TCDD诱导的凋亡。研究还发现, 核因子-κB(nuclear factor-kappaB, NF-κB)参与许多凋亡相关基因的表达, 可促进某些凋亡基因的表达上调。若AhR在某种条件下激活NF-κB通路, 则有可能启动肝脏或胃内Treg的凋亡程序[44-45]。除此之外, 激素的使用也会引起Treg($CD4^+CD25^+$)凋亡, 如地塞米松等在大剂量长期使用过程中会引起细胞内AhR耐受, 从而通过Fas及Fas配体(Fas/Fas ligand, Fas/Fas L)信号来介导Treg凋亡[46]。

3　AhR调控Treg功能的信号通路

AhR活化后, 可通过多条信号通路影响Th0的分化和Treg-Th17平衡, 从而参与对机体适应性免疫功能的调控, 但不同类型的配体与AhR结合后导致的效应各不相同(图1)。

3.1　IDO/AhR通路

IDO和AhR在T细胞的分化过程中相互作用, IDO表达的重要信号通路由AhR激活, 而TCDD激活AhR促进Treg分化的关键因子是IDO[47-48]。最近有研究显示, 哮喘小鼠的IDO和Foxp3表达降低, Treg数量减少, 且IDO蛋白质水平与Treg占$CD4^+$细胞的百

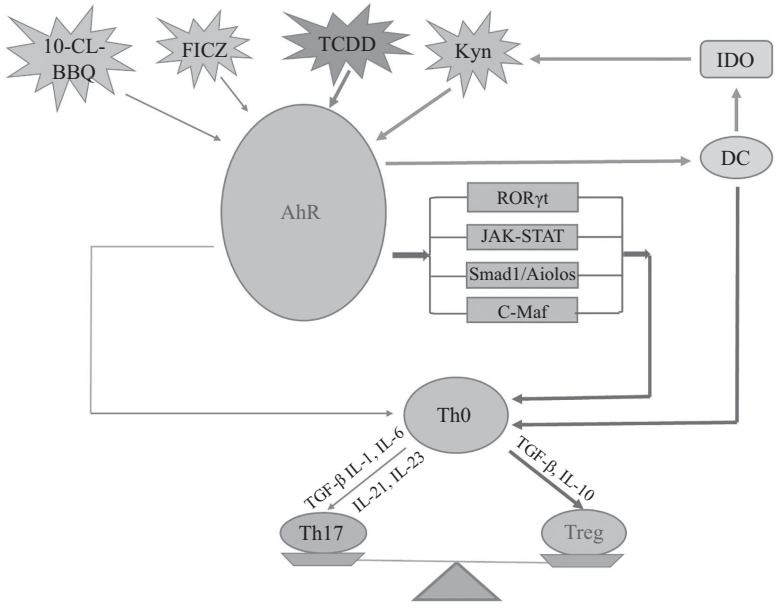

图1　AhR调控Treg的分子机制示意图

Fig.1　The molecular mechanism of AhR on Treg

分率呈正相关, 表明IDO与Treg相互调节, 打破免疫耐受, 进而诱导哮喘发生[49-50]。

3.2 JAK-STAT通路

一些新的研究表明, JAK-STAT(Janus kinase-signal transducer and activator of transcription)信号通路在Treg的各种功能中都发挥着重要作用。如Chaudhry等[31]认为, Treg内的STAT3活化可使Treg通过增加抑制性细胞分子和趋化因子受体的表达来抑制Th17炎性反应, 而Treg内STAT3的缺失可导致结肠炎的发生。Quintana等[51]发现, 活化的AhR可以通过调节STAT1来促进iTreg的分化。在体外Treg/Th17生长分化环境中, STAT3的缺失严重削弱了Th17的分化, 使Treg-Th17平衡左移, 而AhR能够与其配体结合后激活通过包括STAT3、NF-κB等在内的信号途径促使细胞向Th17分化[52-53]。

3.3 RORγt通路

相关研究表明, 维甲酸相关孤核受体γt(retinoid-related orphan nuclear receptor γt, RORγt)是Th17细胞分化中主要转录因子。AhR可通过诱导RORγt/C2表达进而启动RORγt/C2信号转导通路, 从而促进Treg的分化。RORγt缺陷型小鼠能够减少Treg的组织浸润并缓解自身免疫性疾病[54]。当T细胞同时表达RORγt和Foxp3时, 用IL-6和IL-21处理可降低或消除Foxp3对RORγt的抑制作用, 使其向Th17分化[55]。有学者对早孕蜕膜中AhR和RORγt关系进行研究, 同时涉及到Treg在其中的作用。结果显示, 正常早孕蜕膜中的AhR与RORγt mRNA水平之间呈正相关, 自然流产组中AhR与RORγt mRNA水平之间也呈正相关[56]。

3.4 Foxp3通路

Foxp3是Treg的调节功能密切相关的特异性转录因子, 高表达的Foxp3转基因小鼠其Treg数量增加。Foxp3不是传统意义上与IL-2、IL-4和INF-γ基因启动子直接相互作用的转录抑制因子, 而是通过阻断多种细胞因子表达所必需的转录活化因子NFAT、NF-κB的活化, 而达到抑制相应细胞因子表达的作用[57]。最近一些研究发现, 在任何条件下, AhR的缺失与否并不能很明显地影响Foxp3的表达[58]。此外, 犬尿氨酸可通过AhR依赖的方式使$Foxp3^+$Treg增殖, 即犬尿氨酸与AhR结合后导致Th0分化为$CD25^+Foxp3^+$T细胞[59]。

3.5 Smad通路

AhR通过转录因子Smad1和Aiolos, 促进$Foxp3^+$Treg分化, Smad1调节+2079到+2198区域的Foxp3增强子, Aiolos与Foxp3形成复合物体后沉默IL-2的表达, 从而增强Foxp3的表达来发挥免疫调节作用[60]。

4 结论与展望

AhR与机体适应性免疫功能密切相关。在一定程度上, AhR参与机体免疫功能的调节是通过影响Treg的生物学特征而实现的。核内活化的AhR可以影响Treg在体内的数量和分布, 促进其增殖、分化和分泌功能, 其调控机制涉及到多条信号通路。因此, AhR可能作为有效调控Treg功能的关键因子应用于各类免疫性疾病的治疗。现有研究证实, 利用AhR干预Treg能够明显缓解结肠炎[43]、关节炎[61]、EAE[23,26,32,62]、HVGR[58]和肿瘤[22]等疾病。

尽管AhR与Treg的关系研究已经取得了一定进展, 但仍有许多问题尚待进一步商榷和探讨: AhR对Treg的数量、分化的影响还存在不同观点[4,22,26,31,32]; 关于AhR、Treg介导的免疫应答机制仍不清晰; 部分结论上的分歧仍然存在, 例如, 从Rohlman[62]和Veldhoen[63]的研究中发现, 不同培养基的使用可能是导致“AhR是否为IL-22表达所必需”结论产生差异的原因等。这些问题的解决将为自身免疫性疾病或炎性疾病的临床治疗提供新的线索及思路。

参考文献 (References)

1 SakaguchiS, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. Cell 2008; 133(5): 775-87.

2 Buckner JH. Mechanisms of impaired regulation by $cd4^+cd25^+foxp3^+$ regulatory T cells in human autoimmune diseases. Nat Rev Immunol 2010; 10: 849-59.

3 Lahoute C, Herbin O, Mallat Z, TedguiA. Adaptive immunity in atherosclerosis: Mechanisms and future therapeutic targets. Nat Rev Cardiol 2011; 8: 348-58.

4 Singh NP, Singh UP, Singh B, Price RL, Nagarkatti, M, Nagarkatti PS. Activation of aryl hydrocarbon receptor (AhR) leads to reciprocal epigenetic regulation of FoxP3 and IL-17 expression and amelioration of experimental colitis. PLoS One 2011; 6(8): e23522.

5 Vogel CF, Goth SR, Dong B, Pessah IN, Matsumura F. Aryl hydrocarbon receptor signaling mediates expression of indoleamine 2,3-dioxygenase. BiochemBiophys Res Commun 2008; 375(3): 331-5.

6 Jonuleit H, Schmitt E. The regulatory T cell family: Distinct subsets and their interrelations. J Immunol 2003; 171(12): 6323-7.

7 Rueda CM, Jackson CM, Chougnet CA. Regulatory T-cell-mediated suppression of conventional T-cells and dendritic cells by different cAMP intracellular pathways. Front Immunol 2016;

7: 216.
8 Mercadante ER, Lorenz UM. Breaking free of control: How conventional T cells overcome regulatory T cell suppression. Front Immunol 2016; 7: 193.
9 Li X, Zheng Y. Regulatory T cell identity: Formation and maintenance. Trends Immunol 2015; 36(6): 344-53.
10 SakaguchiS. Naturally arising Foxp3-experessing $CD4^+$ $CD25^+$ regulatory T-cells in immunological tolerance to self and non-self. Nat Immunol 2005; 699(4): 345-52.
11 Luo X, Tarbell KV, Yang H, Pothoven K, Bailey SL, Ding R, *et al*. Dendritic cells with TGF-beta1 differentiate naïve $CD4^+$ $CD25^-$ T cells into islet-protective $Foxp3^+$ regulatory T cells. Proc Natl Acad Sci USA 2007; 104(8): 2821-6.
12 Horwitz DA, Zheng SG, Gray JD. Natural and TGF-β-induced $Foxp3^+$ $CD4^+$ $CD25^+$ regulatory T cells are not mirror images of each other. Trends in Immunol 2008; 29(9): 429-35.
13 Baecher-Allan C, Brown JA, Freeman GJ, Hafler DA. $CD4^+$ $CD25^+$ high regulatory cells in human peripheral blood. J Immunol 2001; 167(3): 1245-53.
14 Ng WF, Duggan PJ, Ponchel F, Matarese G, Lombardi G, Edwards AD, *et al*. Human $CD4^+CD25^+$ cells: A naturally occurring population of regulatory T cells. Blood 2001; 98(9): 2736-44.
15 Setoguchi R, Hori S, Takahashi T, Sakaguchi S. Homeostatic maintenanceof natural $Foxp3^+$ $CD25^+$ $CD4^+$ regulatory T cells by interleukin (IL)-2 and induction of autoimmune disease by IL-2 neutralization. J Exp Med 2005; 201(5): 723-35.
16 Tang Q, Bluestone JA. The $foxp3^+$ regulatory T cell: A jack of all trades, master of regulation. Nat Immunol 2008; 9: 239-44.
17 Heuer JG, Zhang T, Zhao J, Ding C, Cramer M, Justen KL, *et al*. Adoptive transfer of *in vitro*-stimulated $CD4^+CD25^+$ regulatory T cells increases bacterial clearance and improves survival in polymicrobial sepsis. J Immunol 2005; 174(11): 7141-6.
18 Kühlhorn F, Rath M, Schmoeckel K, Cziupka K, Nguyen HH, Hildebrandt P, *et al*. $Foxp3^+$ regulatory T cells are required for recovery from severe sepsis. PLoS One 2013; 8(5): e65109.
19 Stevens EA, Mezrich JD, Bradfield CA. The aryl hydrocarbon receptor: A perspective on potential roles in the immune system. Immunology 2009; 127: 299-311.
20 RannugA, FritscheE. The aryl hydrocarbon receptor and light. Biol Chem 2006; 387(9): 1149-57.
21 Hao N, Whitelaw ML. The emerging roles of AhR in physiology and immunity. Biochem Pharmacol 2013; 86(5): 561-70.
22 Korn T. How T cells take developmental decisions by using the aryl hydrocarbon receptor to sense the environment. Proc Natl Acad Sci USA 2010; 107(48): 20597-8.
23 Nugent LF, Shi G, Vistica BP, Ogbeifun O, Hinshaw SJH, Gery I. ITE, a novel endogenous nontoxic aryl hydrocarbon receptor ligand, efficiently suppresses EAU and T-cell-mediated immunity. Invest Ophthalmol Vis Sci 2013; 54: 7463-9.
24 Ho PP, Steinman L. The aryl hydrocarbon receptor: A regulator of Th17 and Treg cell development in disease. Cell Res 2008; 18(6): 605-8.
25 Wu D, Li W, Lok P, Matsumura F, Adam Vogel CF. AhR deficiency impairs expression of LPS-induced inflammatory genes in mice. Biochem Biophys Res Commun 2011; 410(2): 358-63.
26 Quintana FJ, Basso AS, Iglesias AH, Korn T, Farez MF, Bettelli E, *et al*. Control of T(reg) and T(H)17 cell differentiation by the aryl hydrocarbon receptor. Nature 2008; 453(7191): 65-71.
27 Nguyen NT, Kimura A, Nakahama T, Chinen I, Masuda K, Nohara K, *et al*. Aryl hydrocarbon receptor negatively regulates dendritic cell immunogenicity via a kynurenine-dependent mechanism. Proc Natl Acad Sci USA 2010; 107(46): 19961-6.
28 Itoh M, Takahashi T, Sakaguchi N, Kuniyasu Y, Shimizu J, Otsuka F, *et al*. Thymus and autoimmunity: Production of $CD25^+CD4^+$ naturally anergic and suppressive T cells as a key function of the thymus in maintaining immunologic self-tolerance. J Immunol 1999; 162(9): 5317-26.
29 Stephens LA, Mottet C, Mason D, Powrie F. Human $CD4^+$ $CD25^+$ thymocytes and peripheral T cells have immune suppressive activity *in vitro*. Eur J Immunol 2001; 31(4): 1247-54.
30 Schulz VJ, Smit JJ, Bol-Schoenmakers M, van Duursen MBM, van den Berg M, Pieters RH. Activation of the aryl hydrocarbon receptor reduces the number of precursor and effector T cells, but preserves thymic $CD4^+CD25^+Foxp3^+$ regulatory T cells. Toxicol Lett 2012; 215(2): 100-9.
31 Chaudhry A, Rudra D, Treuting P, Robert MS, LiangY, Kas A, *et al*. $CD4^+$ regulatory T cells control TH17 responses in a Stat3-dependent manner. Science 2009; 326(5955): 986-91.
32 Kerkvliet NI, Steppan LB, Vorachek W, Oda S, Farrer D, Wong CP, *et al*. Activation of aryl hydrocarbon receptor by TCDD prevents diabetes in NOD mice and increases $Foxp3^+$ T cells in pancreatic lymph nodes. Immunotherapy 2009; 1(4): 539-47.
33 Mezrich JD, Fechner JH, Zhang XJ, Johnson BP, Burlingham WJ, Bradfield CA. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. J Immunol 2010; 185: 3190-8.
34 Mascanfroni ID, Takenaka MC, Yeste A, Patel B, Wu Y, Kenison JE, *et al*. Metabolic control of type 1 regulatory T cell differentiation by AHR and HIF1-α. Nat Med 2015; 21(6): 638-46.
35 Apetoh L, Quintana FJ, Pot C, Joller N, Xiao S, Kumar D, *et al*. The Aryl hydrocarbon Receptor (AhR) interacts with c-Maf to promote the differentiation of IL-27-induced regulatory type 1 (TR1) cells. Nat Immunol 2010; 11(9): 854-61.
36 Funatake CJ, Marshall NB, Steppan LB, Mourich DV, Kerkvliet NI. Cutting edge: Activation of the aryl hydrocarbon receptor by 2,3,7,8-tetrachlorodibenzo-p-dioxin generates a population of $cd4^+$ $cd25^+$ cells with characteristics of regulatory T cells. J Immunol 2005; 175(7): 4184-8.
37 Julliard W, Fechner JH, Mezrich JD. The aryl hydrocarbon receptor meets immunology: Friend or foe? A Little of Both. Front Immunol 2014; 5: 458.
38 Zhang L, Zhang Y, Zhong W, Di C, Lin X, Xia Z. Heme oxygenase-1 ameliorates dextran sulfate sodium-induced acute murine colitis by regulating Th17/Treg cell balance. J Biol Chem 2014; 289(39): 26847-58.
39 Wirnsberger G, Hinterberger M, Klein L. Regulatory T-cell differentiation versus clonal deletion of autoreactivethymocytes. Immunol Cell Biol 2011; 89(1): 45-53.
40 Cai LJ, Yu DW, Gao Y, Yang C, Zhou HM, Chen ZH. Activation of aryl hydrocarbon receptor prolongs survival of fully mismatched cardiac allografts. J Huazhong Univ Sci Technolog Med Sci 2013; 33(2): 199-204.

41 Veiga-Parga T, Suryawanshi A, Rouse BT. Controlling viral immuno-inflammatory lesions by modulating aryl hydrocarbon receptor signaling. PLoS Pathogens 2011; 7(12): e1002427.
42 Veiga-Parga T, Sehrawat S, Rouse BT. Role of regulatory T cells during virus infection. Immunol Rev 2013; 255(1): 182-96.
43 Pot C. Aryl hydrocarbon receptor controls regulatory $CD4^+$ T cell function. Swiss Medical Weekly 2012; 142: w13592.
44 Xu R, Tao A, Zhang S, Zhang M. Neutralization of interleukin-17 attenuates high fat diet-induced non-alcoholic fatty liver disease in mice. Acta Biochim Biophys Sin (Shanghai) 2013; 45(9): 726-33.
45 Pasparakis M. Regulation of tissue homeostasis by NF-kappaB signalling: Implications for inflammatory diseases. Nat Rev Immunol 2009; 9(11): 778-88.
46 Akiyama K, Chen C, Wang DD, Xu X, Qu C, Yamaza T, *et al*. Mesenchymal-stem-cell-induced immunoregulation involves FAS-ligand-/FAS-mediated T cell apoptosis. Cell Stem Cell 2012; 10(5): 544-55.
47 Hao K, Zhou Q, Chen W, Jia W, Zheng J, Kang J, *et al*. Possible role of the 'IDO-AhR axis' in maternal-foetal. Cell BiolInt 2013; 37(2): 105-8.
48 Teresa Z, Rossana GI,Francesca F, Marco G, Antonella L, Silvia M, *et al*. Tryptophan feeding of the IDO1-AhR axis in host-microbial symbiosis. Front Immunol 2014; 5: 640.
49 Jaronen M, Quintana FJ. Immunological relevance of the coevolution of IDO1 and AHR. Front Immunol 2014; 5(5): 521.
50 Mellor AL, Munn DH. IDO expression by dendritic cells: Tolerance and tryptophan catabolism. Nat Rev 2004; 4(10): 762-74.
51 Quintana FJ, Weiner HL. Environmental control of Th17 differentiation. Eur J Immunol 2009; 39(3): 655-7.
52 Yang EJ, Lee J, Lee SY. EGCG attenuates autoimmune arthritis by inhibition of STAT3 and HIF-1α with Th17/Treg control. PLoS One 2014; 9(2): e86062.
53 Rosillo MA, Sánchez-Hidalgo M, Sánchez-FidalgoS, Aparicio-Soto M, Villegas I, Alarcón-de-la-Lastra C. Dietary extra-virgin olive oil prevents inflammatory response and cartilage matrix degradation in murine collagen-induced arthritis. Eur J Nutr 2015; 55(1): 1-11.
54 Chen Z, Lin F, Gao Y, Li Z, Zhang J, Xing Y, *et al*. FOXP3 and ROR gammat: Transcriptional regulation of Treg and Th17. Int Immunopharmacol 2011; 11(5): 536-42.
55 Ueno A, Jijon H, Chan R, Ford K, Hirota C, Kaplan GG, *et al*. Increased prevalence of circulating novel IL-17 secreting Foxp3 expressing $CD4^+$ T cells and defective suppressive function of circulating $Foxp3^+$ regulatory cells support plasticity between Th17 and regulatory T cells in inflammatory bowel disease patients. Inflamm Bowel Dis 2013; 19(12): 2522-34.
56 Zhang H, Hu X, Liu X, Zhang R, Fu Q, Xu X. The Treg/Th17 imbalance in toxoplasma gondii-infected pregnant mice. Am J Reprod Immunol 2011; 67(2): 112-21.
57 Punj S, Kopparapu P, Jang HS, Phillips JL, Pennington J, Rohlman D, *et al*. Benzimidazoisoquinolines: A new class of rapidly metabolized aryl hydrocarbon receptor (AhR) ligands that induce AhR-dependent Tregs and prevent murine graft-versus-host disease. PLoS One 2014; 9(2): e88726.
58 Christiaansen AF, Boggiatto PM, Varga SM. Limitations of $Foxp3^+$ Treg depletion following viral infection in DEREG mice. J Immunol Methods 2014; 406(4): 58-65.
59 Mizuno T, Suzuki R, Umeki S, Okuda M. Crossreactivity of antibodies to canine CD25 and Foxp3 and identification of canine $CD4^+CD25^+Foxp3^+$ cells in canine peripheral blood. J Vet Med Sci 2009; 71(12): 1561-8.
60 Pang N, Zhang F, Ma X, Zhu J, Zhao H, Xin Y, *et al*. TGF-β/Smad signaling pathway regulates Th17/Treg balance during echinococcusmultilocularis, infection. Int Immunopharmacol 2014; 20(1): 248-57.
61 Yuan X, Tong B, Dou Y, Wu X, Wei Z, Dai Y. Tetrandrine ameliorates collagen-induced arthritis in mice by restoring the balance between Th17 and Treg cells via the aryl hydrocarbon receptor. Biochem Pharmacol 2016; 101: 87-99.
62 Rohlman D, Pham D, YuZ, Steppan LB, Kerkvliet NI. Aryl hydrocarbon receptor-mediated perturbations in gene expression during early stages of $CD4^+$ T-cell differentiation. Front Immun 2012; 3: 223.
63 Veldhoen M, Hirota K, Westendorf AM, Buer J, Dumoutier L, Renauld JC, *et al*. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. Nature 2008; 453(7191): 106-9.