# 免疫耐受在牛乳过敏中的研究进展

李　欣[1,2]，　程剑锋[1,2]，　文学方[3]，　马　鑫[1,2]，　陈红兵[1,4]

（1. 食品科学与技术国家重点实验室，南昌大学，江西 南昌 330047；2. 南昌大学 食品学院，江西 南昌 330047；
3. 江西省科学院 应用化学研究所，江西 南昌 330096；4. 南昌大学 中德联合研究院，江西 南昌 330047）

**摘要：**食物过敏是机体对过敏原产生的一种不良免疫反应，而免疫耐受是指机体对摄入的食物抗原不产生此类免疫应答。近年来，牛乳过敏的发生率越来越高，大部分牛乳过敏的儿童3岁之后出现了免疫耐受。基于此，介绍了牛乳过敏及引发免疫耐受的相关免疫细胞包括树突状细胞、调节性B细胞、调节性T细胞在免疫耐受中的作用及3种诱导免疫耐受的方法。

**关键词：**牛乳过敏；免疫细胞；免疫耐受

**中图分类号：**TS 206.1　　**文章编号：**1673-1689(2021)05-0001-11　　DOI：10.3969/j.issn. 1673-1689.2021.05.001

## Research Advances in Immune Tolerance in Cow´s Milk Allergy

*LI Xin*[1,2]，　*CHENG Jianfeng*[1,2]，　*WEN Xuefang*[3]，　*MA Xin*[1,2]，　*CHEN Hongbing*[1,4]

（1. State Key Laboratory of Food Science and Technology, Nanchang University, Nanchang 330047, China; 2. School of Food Engineering, Nanchang University, Nanchang 330047, China; 3. Institute of Applied Chemistry, Jiangxi Academy of Sciences, Nanchang 330096, China; 4. Nanchang University Sino-German Joint Research Institute, Nanchang University, Nanchang 330047, China）

**Abstract:** Food allergy is an adverse immune response that specific to food allergens, while immune tolerance is defined as the absence of such an immunological reaction to the ingested food antigens. The prevalence of cow's milk is increasing in recent years and most children allergic to cow's milk develop immune tolerance after three years old as reported. Based on these facts, the review introduces milk allergy and the related immune cells that trigger immune tolerance including dendritic cells, regulatory B cells and regulatory T cells, and their roles in immune tolerance. Three methods for inducing immune tolerance are also summarized.

**Keywords:** milk allergy, immune cells, immune tolerance

发达国家中约5%~15%的婴儿可能会发生牛乳过敏，但根据严格的诊断标准，婴儿期确诊的牛乳过敏发病率只有2%~3%[1-2]。牛乳过敏是儿童早期最常见的食物蛋白过敏症，据统计，出生后第一年发病率约为2%至3%，而花生、大豆、鸡蛋小麦的过敏率分别为0.8%、0.8%、0.6%和0.2%[3]。牛乳过敏的概率在出生后第一年达到峰值，并且随年龄增长慢慢消退[4-8]。在过去几十年中，儿童期哮喘和鼻结

**收稿日期：**2019-12-31

**基金项目：**国家“十三五”重点研发计划项目(2018YFC1604205)。

**作者简介：**李　欣(1980—)，女，博士，教授，博士研究生导师，主要从事食物过敏研究。E-mail：zhizilixin@ncu.edu.cn

膜炎等过敏性疾病发病率增加[9],总体而言,牛乳的过敏率与其他食物的过敏率都呈增长的趋势[10-11]。

大多数患有牛乳过敏的婴儿会在出生后一个月内、食用牛乳配方奶粉后一周内出现。大多数患者同时有两种症状:其中50%~70%有皮肤症状,50%~60%有胃肠道症状,20%~30%有呼吸道症状。在纯母乳喂养的牛乳过敏患儿中,严重特应性湿疹是主要症状[12-13]。

## 1 牛乳过敏的机理

牛乳过敏是由一种或多种乳蛋白引起的有害机体健康的免疫学反应[14]。牛乳过敏反应可包括3种免疫学机制:一是乳蛋白特异性IgE介导的过敏反应;二是非IgE介导的过敏反应(细胞毒性超敏反应和迟发性超敏反应);三是IgE与非IgE介导的混合型过敏反应,其中牛乳过敏反应主要以乳蛋白特异性IgE介导的过敏反应为主[14-15]。

IgE介导的牛乳过敏的发展分两个阶段发生。首先是"致敏":免疫系统首次接触乳蛋白并产生针对乳蛋白的IgE抗体,这些抗体附着在肥大细胞和嗜碱性粒细胞表面,使机体处于致敏状态。之后是"激发";细胞相关的IgE结合乳蛋白上的过敏原表位,并引发强力炎症介质快速释放,导致过敏症状发生[14]。

非IgE介导的牛乳过敏反应主要包括以下3种类型:由IgG或IgM介导,补体、吞噬细胞和自然杀伤细胞引起细胞溶解和组织损伤的II型超敏反应;由IgG介导,补体和血小板、嗜碱性粒细胞、中性粒细胞引起充血水肿、血管炎性反应和组织损伤的III型超敏反应;由T细胞介导,单核/巨噬细胞和淋巴引起的炎症和组织损伤的IV型超敏反应[16-18]。IgE和非IgE介导的反应并不相互排斥,对牛乳的反应可能涉及免疫机制的混合[19]。

IgE介导的反应常见于婴儿期,非IgE介导的反应在成人中占主导地位。据报道,非IgE介导的牛乳过敏(与IgE介导的牛乳过敏相比)在儿童时期产生耐受的概率较高[20-22]。这表明非IgE介导的牛乳过敏群体在成年阶段出现概率比较高。

## 2 免疫耐受及相关的免疫细胞

食物免疫耐受是指机体免疫系统接触某种食物抗原后对该抗原的特异性免疫无应答,从而对该抗原不产生特异性免疫效应细胞及特异性抗体[23-24]。若食物过敏原采用特殊方式摄入,诱导免疫系统耐受,则治疗和预防免疫系统失调的过敏和其他非过敏性疾病(如自身免疫和器官移植)具有可行性[25]。免疫耐受主要受3种细胞调节:树突状细胞(DC)、调节性B(Breg)细胞、调节性T(Treg)细胞。

### 2.1 树突状细胞

在肠系膜淋巴结(MLN)中,来自固有层的迁移$CD103^+$ DC可通过多种机制促进肠道归巢Treg细胞的发育,进而产生耐受。$CD103^+$ DC产生转化生长因子-β(TGF-β)和视黄酸(来自维生素A),驱动Treg细胞分化[26]。$CD103^+$ DC的整合素分子avb8上调能刺激产生TGF-β,且能诱导小鼠在对肠抗原产生耐受的过程中产生Treg细胞[27-28]。另外,$CD103^+$ DC可以表达吲哚胺2,3-双加氧酶,这是一种参与色氨酸分解代谢的酶。若抑制吲哚胺2,3-双加氧酶,会导致$CD4^+$ $Foxp3^+$ T调节细胞转化减少和T细胞增殖,有利于诱导Th1和Th17转化[29],抑制耐受性产生。DC上的CD11b通过抑制幼稚T细胞向Th17细胞分化而促进口服耐受[30]。没有炎症信号,用抗原刺激脾$CD11c^+$ DC活化也会导致$CD4^+$ $CD25^+$ Treg细胞扩增,并诱导对确定抗原的耐受性[31]。

肠相关淋巴组织的DC产生视黄酸,与IL-6或IL-5协同作用,诱导IgA分泌;缺乏维生素A和视黄酸的小鼠,其小肠中缺乏IgA分泌细胞[32]。这些研究表明,来自DC和MLN间质细胞的视黄酸对诱导B细胞和T细胞中的耐受性反应非常重要。

### 2.2 调节性B细胞

通常认为:浆细胞通过产生抗原特异性抗体作用于免疫应答,且有助于诱导$CD4^+$ T细胞活化[33]。Breg细胞通过产生抑制细胞因子(IL-10、TGF-β和IL-35)抑制效应T细胞,从而在调节免疫应答中发挥作用[34]。

Breg细胞主要通过IL-10调节过敏性炎症和耐受的免疫反应[35]。产生IL-10的$CD5^+$ Breg细胞在肠系膜淋巴结中发挥作用,特别是在牛乳过敏原激发的小鼠模型中调节IgE介导的过敏反应[36]。$CD9^+$ B细胞通过IL-10抑制Th2和Th17的炎症,使气道炎症减弱、肺功能正常化,从而使哮喘模型小鼠的肺组织恢复良好的免疫平衡[37]。IL-4下调和IL-10上调会导致$IgG_4$水平增加和IgE水平降低,其中IL-10可促进重链免疫球蛋白同种型转换为$IgG_4$,IL-4则诱

导重链免疫球蛋白转换为 IgE[38]。通过检测 IL-10 过表达的 B 细胞,可发现 B 细胞诱导耐受的基本机制:B 细胞可抑制树突细胞成熟、T 效应细胞增殖和 IgE 产生,从而抑制过敏反应发生。此外,过表达 IL-10 的 B 细胞会产生抗炎 IL-1 受体拮抗剂和血管内皮生长因子,抑制促炎细胞因子产生[39]。

TGF-β 是一种多效细胞因子,有促进伤口愈合、组织重塑及免疫调节等功能。更重要的是,它参与幼稚 $CD4^+$ T 细胞转变为 Treg 细胞的过程[40]。IL-35 通过诱导 Treg 细胞增殖并抑制 TH17 反应在免疫抑制中起作用[41]。

此外,1 型 Breg(Br1)细胞转换为浆细胞时产生 $IgG_4$,$IgG_4$ 是一种非炎症性免疫球蛋白同种型,可阻止 IgE 介导的肥大细胞和嗜碱性粒细胞脱颗粒[42]。过敏原特异性 $IgG_4$ 可能参与促进免疫耐受。Santos 等[43]研究表明:与花生过敏患者相比,产生耐受的患者花生特异性 $IgG_4$ 与花生特异性 IgE 的比例更高。

### 2.3 调节性 T 细胞

Treg 细胞在抑制 Th2 介导的炎症和维持免疫耐受中必不可少[44]。$CD4^+$ Treg 细胞分为两类:天然型 Treg(nTreg)细胞和诱导型 Treg(iTreg)细胞。在胸腺中 T 细胞成熟的正常过程中,$CD4^+$ Treg 细胞分化成 $CD4^+$ $CD25^+$ nTreg 细胞;在特定刺激条件下,$CD4^+$ T 细胞被激活产生 $CD4^+$ iTreg 细胞。iTreg 有三种不同的亚组,(1) 诱导性 $Foxp3^+$ Treg 细胞;(2)1 型 Treg(Tr1)细胞;(3)Th3 细胞[45]。

Treg 细胞能通过几种抑制机制控制食物过敏反应的致敏和效应阶段。Treg 细胞可分泌抑制性细胞因子,如产生 IL-10 和 TGF-β、抑制 IL-2 产生、下调抗原呈递细胞(APC)[46]。Treg 细胞还通过对肥大细胞、嗜碱性粒细胞和嗜酸性粒细胞的作用来抑制过敏性炎症,在 OX40-OX40 配体的相互作用下通过细胞-细胞接触抑制 FceRI 依赖性肥大细胞脱颗粒[47]。DC 细胞是 Treg 细胞介导的免疫耐受的靶标。DC 细胞分泌 CTLA-4(细胞毒性 T 淋巴细胞相关蛋白)和 LFA-1(淋巴细胞功能相关分子),Treg 细胞(除了 $CD4^+$幼稚 T 细胞)优先聚集在这些 DC 周围并且下调 DC 上的 CD80/86 的表达。Treg 细胞可抑制 DC 成熟和幼稚 T 细胞活化[48]。

$CD4^+$ $CD25^{hi}CD127^{lo/-}$ nTreg 细胞在健康个体中通过 IL-10 诱导产生耐受性 DC,而在哮喘患者中,nTreg 细胞诱导产生耐受性 DC 的效率低得多,这导致哮喘严重程度增加[49]。在哮喘的实验模型中,缺乏 nTreg 细胞导致 DC 介导的气道炎症增强[50]。

Foxp3 敲除小鼠发生了与过敏性炎症相关的多器官炎症反应[51-52]。过继转移 Treg 细胞能抑制小鼠食物过敏模型中的过敏反应,并能控制 Th2 免疫反应[53-54]。与健康对照相比,IgE 介导的食物过敏儿童的 Foxp3 表达显著降低[55-56]。

与 $Foxp3^+$ iTreg 不同,Tr1 和 Th3 细胞不表达主调节因子的转录因子 Foxp3。Tr1 细胞的特点是:共表达 CD49b 和 LAG-3 表面标志物,并分泌高水平的 IL-10[57]。而 Th3 细胞不表达 Foxp3 或 CD25,但在其表面表达潜伏激活肽(LAP),且 LAP 能产生抑制性细胞因子 TGF-β。在小鼠中用卵白蛋白诱导 Th3 细胞进行表皮免疫治疗,通过抑制 TGF-β 的产生进而抑制肥大细胞活化,以此预防过敏反应[58]。在牛乳过敏的口服耐受模型中,低聚果糖可诱导 Th3 细胞抑制过敏反应[59]。此外,Th3 细胞能促进 iTreg 细胞发育[60]。

TGF-β 不仅由 Th3 细胞产生,也由 $Foxp3^+$ Treg 产生,且表达表面分子 GARP。Treg 细胞表达表面分子 GARP 对诱导口服耐受至关重要[61]。IL-6,IL-21 和 IL-35 可抑制 GARP 在 $Foxp3^+$ Treg 细胞上的表达,从而抑制 LAP 和 TGF-β。阻断 IL-6 途径可促进小鼠口服耐受[62]。过量 IL-4 也会抑制过敏原特异性 Treg 细胞的诱导,并在小鼠模型中引起肠道炎症[63]。

## 3 诱导免疫耐受在食物过敏中的应用

### 3.1 口服耐受

口服耐受(OIT)指:通过口服途径预先施用抗原,达到特异性抑制细胞和体液免疫应答的目的[64]。口服耐受在胃肠道中发挥作用。为维持口服耐受性,肠相关淋巴组织继续区分自身与非自身抗原,并识别可导致组织炎症或肠道疾病的病原体。当肠相关淋巴组织不能发挥功能时,该过程失效,导致口服耐受性丧失和不必要的过敏反应[65]。影响口服耐受诱导的因素包括:抗原剂量、抗原来源、宿主遗传信息、宿主正常菌群和宿主年龄[66]。

给予单次高剂量抗原或重复较低剂量后,小鼠可诱导口服耐受[67]。这两种形式的耐受性,分别称为高剂量耐受和低剂量耐受。高剂量的口服抗原可诱导淋巴细胞无能[68]或缺失[69]。高剂量耐受由淋巴细胞的无反应性介导,可通过 $CD8^+$ T 细胞受体连接发

生,或通过 T 细胞上的共刺激受体(CD28)和 APC 上的受体(CD80 和 CD86)相互作用发生,而不存在由可溶性细胞因子(如 IL-2)提供的共刺激信号[70]。低剂量耐受由调节性 T 细胞介导。除上述抑制性 $CD8^+$ T 细胞外,不同类型的调节性 $CD4^+$ T 细胞在抗原的口服耐受性方面发挥了重要作用[71-73]。

口服耐受性也可由携带 NK1.1 标记的肝相关淋巴细胞($NK1.1^+$ T 细胞)介导。通过肠上皮细胞后,抗原可能被吸收到毛细血管中,进入门静脉,并且在肝脏中免疫细胞可能对这些抗原产生耐受性,此现象称门静脉耐受。通过在大鼠中进行门腔分流证明了发生这种机制的可能性,它是一种绕过肝脏抗原加工的过程,此过程不会对可溶性蛋白质抗原产生耐受性[74]。通过结肠炎的实验模型可知:$NK1.1^+$ T 细胞为耐受介质。$NK1.1^+$ T 细胞的消耗加剧了这些动物的结肠炎症[75]。

尽管已证明了 OIT 对脱敏的临床疗效,但通过荟萃分析发现:进行全面的疗效评估缺乏充分数据,仍存在安全性问题,需进一步评估[76-80]。一般以口为主的症状,其副作用属轻度至中度,采用 OIT 治疗可行性较强[81-85]。而对较严重的过敏反应,如全身性荨麻疹/血管性水肿、喘息/呼吸窘迫、喉头水肿、反复呕吐,则效果不好。Skripak 等[84]对牛乳过敏患者进行 OIT 治疗时,发现 45.4%OIT 人员的症状与剂量有关,而只有 11.2%安慰剂人员的症状与剂量有关,且大多是轻度和口咽的症状。

### 3.2 舌下免疫疗法

舌下免疫疗法(SLIT)是将食物过敏原提取物留在口腔中 2~3 min,然后吐出或吞咽。此法的原理是:过敏原与口腔黏膜中致突变的朗格汉斯细胞相互作用,从而诱导产生耐受[86-87]。此过程中,过敏原被类似朗格汉斯细胞的树突状细胞捕获在口腔黏膜内,随后树突状细胞成熟并迁移至近端引流淋巴结[88-89]。这些淋巴结形成了专门的微环境,通过产生封闭性 IgG 抗体(小鼠中的 IgG2b)并诱导具有抑制功能的 T 淋巴细胞,有利于诱导黏膜耐受性[90-91]。最终,由于过敏原特异性活化的效应 T 细胞在体内进行循环并且产生的记忆细胞存活时间足够长,在脱敏过程中局部(即舌下)施用过敏原会导致全身和黏膜保护性免疫应答。与 OIT 相比,SLIT 通常能获得更好的治疗效果,且治疗过程中需要的过敏原剂量更低,但脱敏的临床效果较差[92]。

SLIT 方案有两个阶段:建立阶段(在 4 至 6 周内逐渐增加剂量)和维持阶段(在几年内每周一次,最多 3 次给药),后者起决定性作用。用此方案开展治疗,给药后几天内会发生:促炎症细胞减少、IgG 抗体上调和 IL-10 的产生[93]。几个月内会产生对 Th1 和 Th2 反应及适应性免疫的可检测影响[93]。通常情况下,免疫治疗后不久即可发现免疫学变化,但 SLIT 治疗至少 1 年后才对症状有效,在 2 年后才观察到最大益处[94]。但是,几种 SLIT 的急诊和超急诊方案已经证明:它可以在几周甚至几天内使皮肤反应性下降,并获得易于检测的临床获益[93,95-96]。SLIT 诱导的免疫调节作用的持续时间少有报道,但几项独立研究表明:患有鼻结膜炎的儿童对草花粉或屋尘螨的 SLIT 可预防哮喘及新的过敏反应[94,97-98]。Rienzo 等对 SLIT 进行了长达 10 年的随访,推测此法基于免疫记忆机制[97]。

大量临床经验证实:成人和幼儿对 SLIT 的耐受性都很好[99-101]。副作用通常发生在局部,包括口腔瘙痒、肿胀和刺激,且通常在给药后数分钟内发生,推测可能是 IgE 介导的反应。因 SLIT 期间炎症标记物(如类胰蛋白酶)不会局部增加,舌下接收过敏原刺激后,口腔中发生的 IgE 介导反应通常受到限制[102]。另外,在人体中进行的变应原实验已证实:舌下黏膜的反应性至少比鼻黏膜或皮肤低 10 倍[103],可能是因为口腔黏膜中促炎症细胞(如肥大细胞)较少。

尽管 SLIT 功效与过敏原剂量明显相关,但高剂量方案未显著提高全身或局部不良事件的发生频率[104]。在体外,高剂量的过敏原在诱导肥大细胞释放促炎症介质中的作用不如低剂量[105]。对于治疗哮喘和过敏性鼻炎,SLIT 可改善临床症状并具有良好的安全性[99,106-107]。

### 3.3 表皮免疫疗法

表皮免疫疗法(EPIT)用含过敏原的贴片激活皮肤朗格汉斯细胞,随后朗格汉斯细胞迁移至淋巴结并下调效应细胞反应[86,108-109]。动物实验表明:EPIT 诱导 Th2 型应答下调,以重新平衡 Th2/Th1[110]。EPIT 可显著提高所有过敏原的特异性 IgG2a 水平,从而降低 IgE/IgG2a[111]。

这种表皮脱敏过程需要完整的皮肤屏障,为使 EPIT 有效,皮肤上层必须具有完整性,这突显了最外层的皮肤免疫系统的重要性。角质形成细胞构成结构屏障,并参与皮肤免疫应答:角质形成细胞能

产生和分泌多种免疫试剂,且反应迅速[112]。刺激后的表皮中 TNF-α (肿瘤坏死因子-α)、IL-1α、IL-1β和 GM-CSF(粒细胞-巨噬细胞集落刺激因子)水平升高,共同促进朗格汉斯细胞分化并激活成表皮内树突状细胞[112]。角质形成细胞可产生趋化因子,是全身性免疫细胞的主要募集信号[113]。在表皮层水平上,丝聚蛋白是人皮肤角质层中表皮分化复合物的关键成分。特应性湿疹患者中已显示出丝聚蛋白功能丧失的突变[114-116],并与过敏风险增加相关[117-121]。因此,旨在恢复屏障功能的疗法不仅在特应性湿疹治疗中发挥作用,也在预防过敏性疾病的进一步发展中发挥作用[121]。

与其他免疫疗法技术相反,EPIT 不需注射或口服过敏原,这是其安全性的基础。对 18 名牛乳过敏的儿童(年龄 0.8~7.7 岁)进行了为期 3 个月的双盲安慰剂对照试验[122]。治疗内容包括背部 3 遍 48 小时贴剂(脱脂奶粉作为活性物质),每周 3 次,几乎没有发生严重的全身性不良症状。这项试验表明 EPIT 是安全的,EPIT 具有前两种方法无法比拟的优势。但是在花生过敏原的 EPIT 治疗期间却出现了持续副作用:局部红斑/湿疹,并持续数天可见,从而造成中途退出率接近 20%[81-83,123-124]。因此表皮免疫疗法仍需要进一步完善。

## 4 展 望

食物过敏的根本解决方法是使机体产生免疫耐受,而非避食过敏原。目前对于免疫耐受的机制研究还不完善,且过敏个体差异性大,需进一步完善免疫耐受的机制,结合诱导剂诱导个体产生免疫耐受。将诱导免疫耐受的机制引入到低致敏的奶粉研发中,既可保证奶粉的食用安全性,又可使牛乳过敏人群从中获得较全面的营养素,这应是未来开发相关低致敏产品目标。

## 参考文献:

[1] FOX A,BROWN T,WALSH J,et al. An update to the milk allergy in primary care guideline [J]. **Clinical and Translational Allergy**,2019,9(1):1-7.

[2] MOUSAN G,KAMAT D. Cow's milk protein allergy[J]. **Clinical Pediatrics**,2016,55(11):1054-1063.

[3] HOST A,HALKEN S. Cow's Milk allergy:where have we come from and where are we going?[J]. **Endocrine,Metabolic & Immune Disorders-Drug Targets**,2014,14(1):2-8.

[4] LAU S,NICKEL R,NIGGEMANN B,et al. The development of childhood asthma:lessons from the German Multicentre Allergy Study(MAS)[J]. **Paediatric Respiratory Reviews**,2002,3(3):265-272.

[5] ILLI S,VON MUTIUS E,LAU S,et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma[J]. **Journal of Allergy and Clinical Immunology**,2004,113(5):925-931.

[6] TAUSSIG L M,WRIGHT A L,HOLBERG C J,et al. Tucson children's respiratory study:1980 to present [J]. **Journal of Allergy and Clinical Immunology**,2003,111(4):661-675.

[7] WICKMAN M. Experience with quantitative IgE antibody analysis in relation to allergic disease within the BAMSE birth cohort - towards an improved diagnostic process[J]. **Allergy**,2004,59(Suppl. 78):30-31.

[8] KURUKULAARATCHY R J,MATTHEWS S,ARSHAD S H. Defining childhood atopic phenotypes to investigate the association of atopic sensitization with allergic disease [J]. **Allergy:European Journal of Allergy and Clinical Immunology**,2005,60(10):1280-1286.

[9] HALKEN S. Prevention of allergic disease in childhood:clinical and epidemiological aspects of primary and secondary allergy prevention[J]. **Pediatric Allergy and Immunology**,2004,15(Suppl. 16):4-5.

[10] GUPTA R,SHEIKH A,STRACHAN D P,et al. Time trends in allergic disorders in the UK[J]. **Thorax**,2007,62(1):91-96.

[11] HU Y,CHEN J,LI H. Comparison of food allergy prevalence among Chinese infants in Chongqing,2009 versus 1999 [J]. **Pediatrics International**,2010,52(5):820-824.

[12] SAMPSON H A,ANDERSON J A. Summary and recommendations:classification of gastrointestinal manifestations due to

immunologic reactions to foods in infants and young children [J]. **Journal of Pediatric Gastroenterology and Nutrition**, 2000, 30(Suppl. 1): 87-94.

[13] HOST A. Cow's milk protein allergy and intolerance in infancy Some clinical, epidemiological and immunological aspects[J]. **Pediatric Allergy and Immunology**, 1994, 5(Suppl. 5): 1-36.

[14] CRITTENDEN R G, BENNETT L E. Cow's milk allergy: a complex disorder [J]. **Journal of the American College of Nutrition**, 2005, 24(Suppl. 6): S582-S591.

[15] WALSH J, MEYER R, SHAH N, et al. Differentiating milk allergy (IgE and non-IgE mediated) from lactose intolerance: understanding the underlying mechanisms and presentations[J]. **British Journal of General Practice**, 2016, 66(649): 609-611.

[16] SKRIPAK J M, MATSUI E C, MUDD K, et al. The natural history of IgE-mediated cow's milk allergy [J]. **Journal of Allergy and Clinical Immunology**, 2007, 120(5): 1172-1177.

[17] WALKER-SMITH J. Cow's milk allergy: a new understanding from immunology [J]. **Annals of Allergy, Asthma & Immunology**, 2010, 90(Suppl. 3): 81-83.

[18] WILSON T, TEMPLE N J. Beverage Impacts on Health and Nutrition[M]. Switzerland: Springer, 2016: 131-150.

[19] LOZANO-OJALVO D, LEZMI G, CORTES-PEREZ N, et al. Non-IgE mediated food allergy [J]. **Drug Discovery Today: Disease Models**, 2015, 17/18: 45-53.

[20] SAVAGE J, SICHERER S, WOOD R. The natural history of food allergy [J]. **Journal of Allergy and Clinical Immunology: In Practice**, 2016, 4(2): 196-203.

[21] HOST A, HALKEN S, HP J, et al. Clinical course of cow ' s milk protein allergy/intolerance and atopic diseases in childhood[J]. 2002, 13(Suppl. 15): 23-28.

[22] VANTO T, HELPPILÄ S, JUNTUNEN-BACKMAN K, et al. Prediction of the development of tolerance to milk in children with cow's milk hypersensitivity[J]. **Journal of Pediatrics**, 2004, 144(2): 218-222.

[23] 朱俐光, 李中跃. 儿童食物免疫耐受形成影响因素研究进展[J]. 中国当代儿科杂志, 2019, 21(6): 613-618.

[24] 李七渝, 张绍祥. 免疫耐受机制研究进展[J]. 免疫学杂志, 2012, 18(3): 98-101.

[25] AKDIS C A, AKDIS M. Mechanisms of immune tolerance to allergens: role of IL-10 and Tregs[J]. **Journal of Clinical Investigation**, 2014, 124(11): 4678-4680.

[26] COOMBES J L, SIDDIQUI K R R, ARANCIBIA-CARCAMO C V, et al. A functionally specialized population of mucosal $CD103^+$ DCs induces $Foxp3^+$ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism [J]. **The Journal of Experimental Medicine**, 2007, 204(8): 1757-1764.

[27] WORTHINGTON J J, CZAJKOWSKA B I, MELTON A C, et al. Intestinal dendritic cells specialize to activate transforming growth factor-β and induce $Foxp3^+$ regulatory T cells via integrin αvβ8[J]. **Gastroenterology**, 2011, 141(5): 1802-1812.

[28] PAIDASSI H, ACHARYA M, ZHANG A, et al. Preferential expression of integrin αvβ8 promotes generation of regulatory T cells by mouse $CD103^+$ dendritic cells[J]. **Gastroenterology**, 2011, 141(5): 1813-1820.

[29] MATTEOLI G, MAZZINI E, ILIEV I D, et al. Gut $CD103^+$ dendritic cells express indoleamine 2, 3-dioxygenase which influences T regulatory/T effector cell balance and oral tolerance induction[J]. **Gut**, 2010, 59(5): 595-604.

[30] EHIRCHIOU D, XIONG Y, XU G, et al. CD11b facilitates the development of peripheral tolerance by suppressing Th17 differentiation[J]. **Journal of Experimental Medicine**, 2007, 204(7): 1519-1524.

[31] YAMAZAKI S, DUDZIAK D, HEIDKAMP G F, et al. $CD8^+$ $CD205^+$ splenic dendritic cells are specialized to induce $Foxp3^+$ regulatory T cells[J]. **The Journal of Immunology**, 2008, 181(10): 6923-6933.

[32] MORA J R, IWATA M, EKSTEEN B, et al. Generation of gut-homing IgA-secreting B cells by intestinal dendritic cells [J]. **Science**, 2006, 314(5802): 1157-1160.

[33] NOH G, LEE J H. Regulatory B cells and allergic diseases[J]. **Allergy, Asthma and Immunology Research**, 2011, 3(3): 168-177.

[34] ROSSER E C, MAURI C. Regulatory B cells: origin, phenotype, and function[J]. **Immunity**, 2015, 42(4): 607-612.

[35] VAN-DE-VEEN W, STANIC B, WIRZ O F, et al. Role of regulatory B cells in immune tolerance to allergens and beyond[J].

**Journal of Allergy and Clinical Immunology**，2016，138(3)：654-665.

[36] KIM A R，KIM H S，KIM D K，et al. Mesenteric IL-10-producing $CD5^+$ regulatory B cells suppress cow's milk casein-induced allergic responses in mice[J]. **Scientific Reports**，2016，6(1)：19685.

[37] BRAZA F，CHESNE J，DURAND M，et al. A regulatory $CD9^+$ B-cell subset inhibits HDM-induced allergic airway inflammation[J]. **Allergy**，2015，70(11)：1421-1431.

[38] RACHID R，UMETSU D T. Immunological mechanisms for desensitization and tolerance in food allergy [J]. **Seminars in Immunopathology**，2012，34(5)：689-702.

[39] STANIC B，VAN DE VEEN W，WIRZ O F，et al. IL-10-overexpressing B cells regulate innate and adaptive immune responses[J]. **Journal of Allergy and Clinical Immunology**，2015，135(3)：771-780.

[40] PALOMARES O，MARTIN-FONTECHA M，LAUENER R，et al. Regulatory T cells and immune regulation of allergic diseases：roles of IL-10 and TGF-β[J]. **Genes and Immunity**，2014，15(8)：511-520.

[41] AKDIS M，BURGLER S，CRAMERI R，et al. Interleukins，from 1 to 37，and interferon-γ：receptors，functions，and roles in diseases[J]. **Journal of Allergy and Clinical Immunology**，2011，127(3)：701-21

[42] VAN-DE-VEEN W，STANIC B，YAMAN G，et al. $IgG_4$ production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses[J]. **Journal of Allergy and Clinical Immunology**，2013，131(4)：1204-1212.

[43] SANTOS A F，JAMES L K，BAHNSON H T，et al. $IgG_4$ inhibits peanut-induced basophil and mast cell activation in peanut-tolerant children sensitized to peanut major allergens [J]. J**ournal of Allergy and Clinical Immunology**，2015，135(5)：1249-1256.

[44] AKDIS M. Immune tolerance in allergy[J]. **Current Opinion in Immunology**，2009，21(6)：700-707.

[45] TODA A. Development and function of naturally occurring $CD4^+$ $CD25^+$ regulatory T cells [J]. **Journal of Leukocyte Biology**，2006，80(3)：458-470.

[46] NGUYEN K D，VANICHSARN C，NADEAU K C. Impaired IL-10-dependent induction of tolerogenic dendritic cells by $CD4^+$ $CD25hiCD127^{lo/-}$ natural regulatory T cells in human allergic asthma [J]. **American Journal of Respiratory and Critical Care Medicine**，2009，180(9)：823-833.

[47] LEWKOWICH I P，HERMAN N S，SCHLEIFER K W，et al. $CD4^+$ $CD25^+$ T cells protect against experimentally induced asthma and alter pulmonary dendritic cell phenotype and function[J]. **Journal of Experimental Medicine**，2005，202(11)：1549-1561.

[48] MONDOULET L，DIOSZEGHY V，BUSATO F，et al. Gata3 hypermethylation and Foxp3 hypomethylation are associated with sustained protection and bystander effect following epicutaneous immunotherapy in peanut-sensitized mice [J]. **Allergy**，2019，74(1)：152-164.

[49] LIN W，TRUONG N，GROSSMAN W J，et al. Allergic dysregulation and hyperimmunoglobulinemia e in Foxp3 mutant mice[J]. **Journal of Allergy and Clinical Immunology**，2005，116(5)：1106-1115 .

[50] SMALDINI P L，DELGADO M L O，FOSSATI C A，et al. Orally-induced intestinal $CD4^+$ $CD25^+$ $FoxP3^+$ treg controlled undesired responses towards oral antigens and effectively dampened food allergic reactions [J]. **PLoS ONE**，2015，10(10)：e0141116.

[51] YAMASHITA H，TAKAHASHI K，TANAKA H，et al. Overcoming food allergy through acquired tolerance conferred by transfer of Tregs in a murine model[J]. **Allergy**，2012，67(2)：201-209.

[52] KROGULSKA A，POLAKOWSKA E，WASOWSKA-KROLIKOWSKA K，et al. Decreased FOXP3 mRNA expression in children with atopic asthma and IgE-mediated food allergy[J]. **Annals of Allergy，Asthma and Immunology**，2015，115(5)：415-421.

[53] KROGULSKA A，BOROWIEC M，POLAKOWSKA E，et al. FOXP3，IL-10，and TGF-β genes expression in children with IgE-dependent food allergy[J]. **Journal of Clinical Immunology**，2011，31(2)：205-215.

[54] GAGLIANI N，MAGNANI C F，HUBER S，et al. Coexpression of CD49b and LAG-3 identifies human and mouse T regulatory type 1 cells[J]. **Nature Medicine**，2013，19(6)：739-746.

[55] TORDESILLAS L，MONDOULET L，BLAZQUEZ A B，et al. Epicutaneous immunotherapy induces gastrointestinal $LAP^+$

regulatory T cells and prevents food-induced anaphylaxis[J]. **Journal of Allergy and Clinical Immunology**, 2017, 139(1): 189-201.

[56] VONK M M, DIKS M A P, WAGENAAR L, et al. Improved efficacy of oral immunotherapy using non-digestible oligosaccharides in a murine cow's milk allergy model: a potential role for Foxp3$^+$ regulatory T cells [J]. **Frontiers in Immunology**, 2017, 8: 1230.

[57] CARRIER Y, YUAN J, KUCHROO V K, et al. Th3 cells in peripheral tolerance. I. Induction of Foxp3-positive regulatory T cells by Th3 cells derived from TGF-β T cell-transgenic mice[J]. **The Journal of Immunology**, 2014, 178(1): 179-185.

[58] EDWARDS J P, HAND T W, MORAIS D F D, et al. The GARP/Latent TGF-β1 complex on Treg cells modulates the induction of peripherally derived Treg cells during oral tolerance[J]. **European Journal of Immunology**, 2016, 46(6): 1480-1489.

[59] KUHN C, REZENDE R M, M'HAMDI H, et al. IL-6 inhibits upregulation of membrane-bound TGF- beta 1 on CD4$^+$ T cells and blocking IL-6 enhances oral tolerance[J]. **The Journal of Immunology**, 2017, 198(3): 1202-1209.

[60] NAKAJIMA-ADACHI H, SHIBAHARA K, FUJIMURA Y, et al. Critical role of intestinal interleukin-4 modulating regulatory T cells for desensitization, tolerance, and inflammation of food allergy[J]. **PLoS ONE**, 2017, 12(2): e0172795.

[61] NOVAL RIVAS M, CHATILA T A. Regulatory T cells in allergic diseases [J]. **Journal of Allergy and Clinical Immunology**, 2016, 138(3): 639-652.

[62] RING S, SCHAFER S C, MAHNKE K, et al. CD4$^+$CD25$^+$ regulatory T cells suppress contact hypersensitivity reactions by blocking influx of effector T cells into inflamed tissue[J]. **European Journal of Immunology**, 2010, 36(11): 2981-2992.

[63] ONISHI Y, FEHERVARI Z, YAMAGUCHI T, et al. Foxp3$^+$ natural regulatory T cells preferentially form aggregates on dendritic cells *in vitro* and actively inhibit their maturation [J]. **Proceedings of the National Academy of Sciences of the United States of America**, 2008, 105(29): 10113-10118.

[64] WEINER H L. Oral tolerance: immune mechanisms and the generation of Th3-type TGF-beta-secreting regulatory cells [J]. **Microbes and Infection**, 2001, 3(11): 947-954.

[65] SICHERER S H, SAMPSON H A. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment [J]. **Journal of Allergy and Clinical Immunology**, 2014, 133(2): 291-307.

[66] CHEHADE M, MAYER L. Oral tolerance and its relation to food hypersensitivities [J]. **Journal of Allergy and Clinical Immunology**, 2005, 115(1): 3-12.

[67] FRIEDMAN A, WEINER H L. Induction of anergy or active suppression following oral tolerance is determined by antigen dosage [J]. **Proceedings of the National Academy of Sciences**, 1994, 91(14): 6688-6692.

[68] WHITACRE C C, GIENAPP I E, OROSZ C G, et al. Oral tolerance in experimental autoimmune encephalomyelitis III. Evidence for clonal anergy[J]. **The Journal of immunology**, 1991, 147(7): 2155-2163.

[69] CHEN Y, INOBE J I, MARKS R, et al. Peripheral deletion of antigen-reactive T cells in oral tolerance [J]. **Nature**, 1995, 376 (6536): 177-180.

[70] APPLEMAN L J, BOUSSIOTIS V A. T cell anergy and costimulation[J]. **Immunological Reviews**, 2003, 192: 161-180.

[71] CHEN Y, INOBE J, WEINER H L. Induction of oral tolerance to myelin basic protein in CD8-depleted mice: both CD4$^+$ and CD8$^+$ cells mediate active suppression[J]. **The Journal of immunology**, 1995, 155(2): 910-916.

[72] BARONE K S, JAIN S L, MICHAEL J G. Effect of *in vivo* depletion of CD4$^+$ and CD8$^+$ cells on the induction and maintenance of oral tolerance[J]. **Cellular Immunology**, 1995, 163(1): 19-29.

[73] GARSIDE P, STEEL M, LIEW F Y, et al. CD4$^+$ but not CD8$^+$ T cells are required for the induction of oral tolerance [J]. **International Immunology**, 1995, 7(3): 501-504.

[74] CALLERY M P, KAMEI T, FLYE M W. The effect of portacaval shunt on delayed-hypersensitivity responses following antigen feeding[J]. **Journal of Surgical Research**, 1989, 46(4): 391-394.

[75] TROP S, SAMSONOV D, GOTSMAN I, et al. Liver-associated lymphocytes expressing NK1.1 are essential for oral immune tolerance induction in a murine model[J]. **Hepatology**, 1999, 29(3): 746-755.

[76] NURMATOV U, DEVEREUX G, WORTH A, et al. Effectiveness and safety of orally administered immunotherapy for food

allergies:a systematic review and meta-analysis[J]. **British Journal of Nutrition**,2014,111(1):12-22.

[77] YEUNG J P,KLODA L A,MCDEVITT J,et al. Oral immunotherapy for milk allergy:a systematic review [J]. **Allergy,Asthma & Clinical Immunology**,2012,8(Suppl. 1):A14.

[78] VAZQUEZ-ORTIZ M,ALVARO-LOZANO M,ALSINA L,et al. Safety and predictors of adverse events during oral immunotherapy for milk allergy:severity of reaction at oral challenge,specific IgE and prick test [J]. **Clinical and Experimental Allergy**,2013. 43(1):92-102.

[79] FISHER H R,TOIT G D,LACK G. Specific oral tolerance induction in food allergic children:is oral desensitisation more effective than allergen avoidance[J]. **Archives of Disease in Childhood**,2011,96:259-264.

[80] BROZEK J L,TERRACCIANO L,HSU J,et al. Oral immunotherapy for IgE-mediated cow's milk allergy:a systematic review and meta-analysis[J]. **Clinical and Experimental Allergy**,2012,42(3):363-374.

[81] HOFMANN A M,SCURLOCK A M,JONES S M,et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy[J]. **Journal of Allergy and Clinical Immunology**,2009,124(2):286-291.

[82] BLUMCHEN K,ULBRICHT H,STADEN U,et al. Oral peanut immunotherapy in children with peanut anaphylaxis [J]. **Journal of Allergy and Clinical Immunology**,2010,126(1):83-91.

[83] VARSHNEY P,JONES S M,SCURLOCK A M,et al. A randomized controlled study of peanut oral immunotherapy:clinical desensitization and modulation of the allergic response [J]. **Journal of Allergy and Clinical Immunology**,2011,127(3):654-660.

[84] SKRIPAK J M,NASH S D,ROWLEY H,et al. A randomized,double-blind,placebo-controlled study of milk oral immunotherapy for cow's milk allergy[J]. **Journal of Allergy and Clinical Immunology**,2008,122(6):1154-1160.

[85] BURKS A W,JONES S M,WOOD R A,et al. Oral immunotherapy for treatment of egg allergy in children [J]. **New England Journal of Medicine**,2012,367(3):233-243.

[86] NOWAK-WEGRZYN A,ALBIN S. Oral immunotherapy for food allergy:mechanisms and role in management [J]. **Clinical and Experimental Allergy**,2015,45(2):368-383.

[87] NOVAK N,GROS E,BIEBER T,et al. Human skin and oral mucosal dendritic cells as 'good guys' and 'bad guys' in allergic immune responses[J]. **Clinical and Experimental Immunology**,2010,161(1):28-33.

[88] MOUSALLEM T,BURKS A W. Immunology in the clinic review series;focus on allergies:immunotherapy for food allergy[J]. **Clinical and Experimental Immunology**,2012,167(1):26-31.

[89] NOIREY N,ROUGIER N,ANDRE C,et al. Langerhans-like dendritic cells generated from cord blood progenitors internalize pollen allergens by macropinocytosis,and part of the molecules are processed and can activate autologous naive T lymphocytes [J]. **Journal of Allergy and Clinical Immunology**,2000,105(6):1194-1201.

[90] VAN-WILSEM E J G,BREVE J,SAVELKOUL H,et al. Oral tolerance is determined at the level of draining lymph nodes[J]. **Immunobiology**,1995,194(4/5):403-414.

[91] AOYAMA-KONDO T,YOSHIDA T,ISOBE K I,et al. Characterization of antibody responses of local lymph nodes to antigen given under the oral submucosa[J]. **Immunobiology**,1992,184(4/5):372-383.

[92] VAN-HELVOORT J M L M,SAMSOM J N,CHANTRY D,et al. Preferential expression of IgG2b in nose draining cervical lymph nodes and its putative role in mucosal tolerance induction [J]. **Allergy:European Journal of Allergy and Clinical Immunology**,2004,59(11):1211-1218.

[93] BOUSQUET J. Sublingual immunotherapy:from proven prevention to putative rapid relief of allergic symptoms [J]. **Allergy**,2005,60(1):1-3.

[94] SMITH H,WHITE P,ANNILA I,et al. Randomized controlled trial of high-dose sublingual immunotherapy to treat seasonal allergic rhinitis[J]. **Journal of Allergy and Clinical Immunology**,2004,114(4):831-837.

[95] PASSALACQUA G,ALBANO M,RICCIO A,et al. Clinical and immunologic effects of a rush sublingual immunotherapy to Parietaria species:a double-blind,placebo-controlled trial [J]. **Journal of Allergy and Clinical Immunology**,1999,104(5):

964-968.

[96] VOLTOLINI S, MODENA P, MINALE P, et al. Sublingual immunotherapy in tree pollen allergy. Double-blind, placebo-controlled study with a biologically standardised extract of three pollens (alder, birch and hazel) administered by a rush schedule[J]. **Allergologia et Immunopathologia**, 2001, 29(4): 103-110.

[97] RIENZO V D, MARCUCCI F, PUCCINELLI P, et al. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study[J]. **Clinical and Experimental Allergy**, 2003, 33(2): 206-210.

[98] NOVEMBRE E, GALLI E, LANDI F, et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis[J]. **Journal of Allergy and Clinical Immunology**, 2004, 114(4): 851-857.

[99] WILSON D R, LIMA M T, DURHAM S R. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis [J]. **Allergy**, 2005, 60(1): 4-12.

[100] AGOSTINIS F, TELLARINI L, CANONICA G W, et al. Safety of sublingual immunotherapy with a monomeric allergoid in very young children[J]. **Allergy**, 2005, 60(1): 133.

[101] ARASI S, PASSALACQUA G, CAMINITI L, et al. Efficacy and safety of sublingual immunotherapy in children [J]. **Expert Review of Clinical Immunology**, 2016, 12(1): 49-56.

[102] MARCUCCI F, SENSI L, FRATI F, et al. Sublingual tryptase and ECP in children treated with grass pollen sublingual immunotherapy (SLIT): safety and immunologic implications[J]. **Allergy**, 2001, 56(11): 1091-1095.

[103] MARCUCCI F, SENSI L, DI CARA G, et al. Sublingual reactivity to rBET V1 and rPHL P1 in patients with oral allergy syndrome[J]. **International Journal of Immunopathology and Pharmacology**, 2006, 19(1): 141-148.

[104] GROSCLAUDE M, BOUILLOT P, ALT R, et al. Safety of various dosage regimens during induction of sublingual immunotherapy: a preliminary study[J]. **International Archives of Allergy and Immunology**, 2002, 129(3): 248-253.

[105] GONZALEZ-ESPINOSA C, ODOM S, OLIVERA A, et al. Preferential signaling and induction of allergy-promoting lymphokines upon weak stimulation of the high affinity IgE receptor on mast cells [J]. **Journal of Experimental Medicine**, 2003, 197(11): 1453-1465.

[106] COX L S, LINNEMANN D L, NOLTE H, et al. Sublingual immunotherapy: a comprehensive review [J]. **Journal of Allergy and Clinical Immunology**, 2006, 117(5): 1021-1035.

[107] RODRIGUEZ-PEREZ N, AMBRIZ-MORENO M D J, CANONICA G W, et al. Frequency of acute systemic reactions in patients with allergic rhinitis and asthma treated with sublingual immunotherapy [J]. **Annals of Allergy, Asthma and Immunology**, 2008, 101(3): 304-310.

[108] BENHAMOU P H, DIOSZEGHY V, PUTEAUX E, et al. Long term protection against new sensitization after milk-epit in mice sensitized to milk is mediated by tregs[J]. **Journal of Allergy and Clinical Immunology**, 2014, 133(2): AB47.

[109] DIOSZEGHY V, MONDOULET L, DHELFT V, et al. Epicutaneous immunotherapy-induced regulatory T cells could migrate to more various sites of allergen exposure compared to sublingual or subcutaneous immunotherapy in mice sensitized to peanut[J]. **Journal of Allergy and Clinical Immunology**, 2014, 133(Suppl. 2): AB48.

[110] MONDOULET L, DIOSZEGHY V, LIGOUIS M, et al. Epicutaneous immunotherapy on intact skin using a new delivery system in a murine model of allergy[J]. **Clinical and Experimental Allergy**, 2010, 40(4): 659-667.

[111] MONDOULET L, DIOSZEGHY V, VANOIRBEEK J A J, et al. Epicutaneous immunotherapy using a new epicutaneous delivery system in mice sensitized to peanuts[J]. **International Archives of Allergy and Immunology**, 2011, 154(4): 299-309.

[112] STRID J, TIGELAAR R E, HAYDAY A C. Skin immune surveillance by T cells-a new orde?[J]. **Seminars in Immunology**, 2009, 21(3): 110-120.

[113] TOKURA Y, KOBAYASHI M, KABASHIMA K. Epidermal chemokines and modulation by antihistamines, antibiotics and antifungals[J]. **Experimental Dermatology**, 2008, 17(2): 81-90.

[114] PALMER C N A, IRVINE A D, TERRON-KWIATKOWSKI A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis[J]. **Nature Genetics**, 2006, 38(4): 441-446.

[115] THYSSEN J P,KEZIC S. Causes of epidermal filaggrin reduction and their role in the pathogenesis of atopic dermatitis[J]. **Journal of Allergy and Clinical Immunology**,2014,134(4):792-799.

[116] THYSSEN J P,TANG L,HUSEMOEN L L N,et al. Filaggrin gene mutations are not associated with food and aeroallergen sensitization without concomitant atopic dermatitis in adults [J]. **Journal of Allergy and Clinical Immunology**,2015,135(5):1375-1378.

[117] BROWN S J,ASAI Y,CORDELL H J,et al. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy[J]. **Journal of Allergy and Clinical Immunology**,2011,127(3):661-667.

[118] IRVINE A D,MCLEAN W H I,LEUNG D Y M. Filaggrin mutations associated with skin and allergic diseases[J]. New England **Journal of Medicine**,2011,365(14):1315-1327.

[119] BROUGH H A,SIMPSON A,MAKINSON K,et al. Peanut allergy:effect of environmental peanut exposure in children with filaggrin loss-of-function mutations[J]. **Journal of Allergy and Clinical Immunology**,2014,134(4):867-875.

[120] VENKATARAMAN D,SOTO-RAMIREZ N,KURUKULAARATCHY R J,et al. Filaggrin loss-of-function mutations are associated with food allergy in childhood and adolescence [J]. **Journal of Allergy and Clinical Immunology**,2014 134(4):876-882.

[121] HEIMALL J,SPERGEL J M. Filaggrin mutations and atopy:consequences for future therapeutics [J]. **Expert Review of Clinical Immunology**,2012 8(2):189-197.

[122] DUPONT C,KALACH N,SOULAINES P,et al. Cow's milk epicutaneous immunotherapy in children:a pilot trial of safety, acceptability,and impact on allergic reactivity[J]. **Journal of Allergy and Clinical Immunology**,2010,125(5):1165-1167.

[123] WASSERMAN R L,FACTOR J M,BAKER J W,et al. Oral immunotherapy for peanut allergy:multipractice experience with epinephrine-treated reactions[J]. **Journal of Allergy and Clinical Immunology-in Practice**,2014,2(1):91-96.

[124] NELSON H S,LAHR J,RULE R,et al. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract[J]. **Journal of Allergy and Clinical Immunology**,1997,99(6):744-751.

## 科 技 信 息

**欧盟续批酿酒酵母 MUCL 39885 制剂作为饲料添加剂**

2021 年 3 月 23 日,欧盟发布条例(EU) 2021/508,续批酿酒酵母 MUCL 39885(*Saccharomyces cerevisiae* MUCL 39885)制剂作为饲料添加剂用于断奶仔猪,本条例自发布之日起第 20 天生效。

该添加剂所属类别为"畜牧学添加剂",功能组别为"肠道菌群稳定剂";识别号为 4b1710;在含水率 12%全价饲料中的最低含量为 $3\times10^9$ CFU/kg;批准期限至 2031 年 4 月 13 日。

[信息来源] 江苏省技术性贸易措施信息平台. 欧盟续批酿酒酵母 MUCL 39885 制剂作为饲料添加剂[EB/OL].(2021-3-24).http://www.tbtguide.com/xwdt/gwxw/202103/t20210324_1540507.html