



脂滴在病原菌感染中的阴与阳: 从免疫屏障到病原劫持

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摘要 脂滴(lipid droplets, LDs)是由中性脂的疏水性核心、磷脂单层外壳和各种相关蛋白组成的一种动态和多功能细胞器, 在脂质储存、能量代谢、膜运输和细胞信号传导中起着重要作用。因此, LDs与多种疾病, 包括代谢紊乱、癌症和感染性疾病等密切相关。在宿主与病原菌的相互作用中, LDs展现出“阴阳”双重角色: 一方面, 作为宿主干扰素应答的核心组分, LDs不仅是激活干扰素信号通路的关键枢纽, 还通过调节免疫应答强度, 在病原感染早期协助建立有效的先天免疫防线; 另一方面, 多种病原菌可通过脂解调控、膜融合等机制主动劫持LDs, 将其作为营养来源和膜组分, 以建立其适于自身复制的细胞内生态位。目前已有的综述主要针对LDs的生物发生及其在细胞内的生理功能, 本文则重点综述了LDs在先天免疫及病原菌感染中的作用和分子机制, 为开发基于LDs的抗感染药物提供新思路。

关键词 脂滴, 病原菌感染, 天然免疫

脂滴(lipid droplets, LDs)是一种重要的脂质储存细胞器^[1]。在真核生物中, LDs起源于内质网(endoplasmic reticulum, ER), 在物理和功能上几乎与其他有膜细胞器均存在相互作用, 如ER、线粒体、高尔基体和溶酶体等^[2]。原核生物虽无ER, 但其LDs形成始于细胞质膜上的特定区域——相关酶(如WS/DGAT)在该处催化合成中性脂质, 随后形成被单层磷脂包裹的小LDs, 继而聚集融合并脱离质膜, 成为成熟的细胞质LDs^[3]。

1 脂滴的生物发生

LDs的生物合成过程涉及多个步骤, 包括中性脂

合成、LDs形成与成熟等(图1)。LDs形成的第一步发生在ER的LDs组装复合体(LD assembly complexes, LDAC)中, 这一复合体的核心是一个低聚体, 由源自ER的蛋白质和辅助蛋白共同构成^[4]。LDs的主要成分——中性脂质(如甘油三酯TAG和胆固醇酯SE)主要在真核生物的ER膜上合成, 其中TAG的合成由二酰基甘油酰基转移酶(DGAT1/DGAT2)催化, 而SE的合成则由酰基辅酶A-胆固醇酰基转移酶(ACAT1/ACAT2)催化。

LDs形成的第二步是在ER双层膜内形成中性脂质的透镜状结构(oil lens)。当合成的中性脂质在ER双层膜内积累至一定临界浓度(5~10 mol%TAG)时, 生物物

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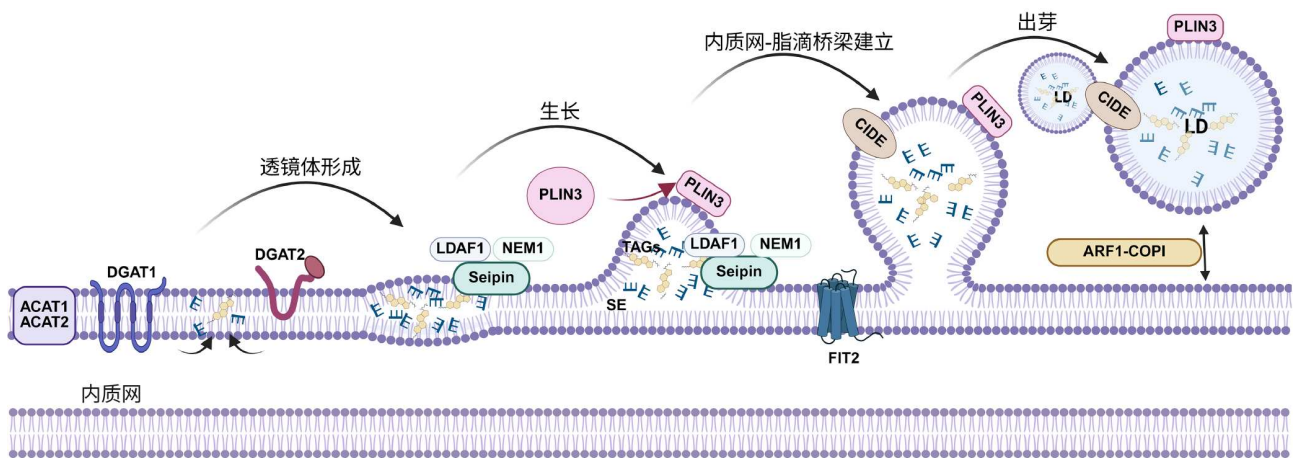


图 1 LDs的生物发生过程

Figure 1 Biogenesis process of LDs

理过程会驱动透镜状结构在ER膜的内、外小叶间形成^[5]。中性脂质成核和透镜结构形成的分子细节尚不清楚,但Seipin及其酵母同源物Sei1(亦称Fld1)在此过程中起关键作用^[6,7]。Sei1形成十聚体笼状结构,可能促进TAG的相分离^[8]。此外,Seipin及其相互作用蛋白(如LDs组装因子1(LADF1)及NEM1等)共同决定了细胞质LDs形成的起始位点,但Seipin仅是LDs生成的效率调控者而非绝对必需因子。在Seipin缺失时,细胞可通过FIT2, LADF1等蛋白维持LDs生成^[9~11]。其他蛋白如PLIN3、脂肪储存诱导跨膜蛋白2(FIT2)、网状蛋白4(reticulon 4)和Seipin 7也有助于启动细胞质LDs的形成^[11,12]。除蛋白质外,磷脂酸和二酰甘油等脂质也在TAG成核和透镜结构形成调控中发挥关键作用^[13]。

LDs形成的第三步:出芽与新生LDs的形成。当TAG在ER双层中积累到一定程度时,LDs就会通过出芽方式进入细胞质基质。细胞质中的特定蛋白(如PLIN3, FIT2, Seipin)以及ER衍生蛋白促进LDs在ER膜小叶处形成初始的凸曲率,从而驱动LDs向细胞质方向出芽,而非留在ER内^[14]。此外,蛋白质和脂质也参与促进细胞质LDs出芽过程。如Seipin十聚体笼状结构在ER膜上创造了一个独特的微环境:它通过腔内侧的疏水斑块选择性“捕获”并浓缩中性脂质前体(如磷脂酸PA和二酰甘油DAG),极大地促进TAG的局部生成与相分离,从而启动LDs成核。同时,Seipin的刚性环状结构作为一个分子模板和测量器,通过限制中性脂质透镜的过早扩张来控制新生LDs的大小,并协同下

游因子(如LADF1)确保LDs正常生长与定向出芽^[15~17]。近年来的研究已明确,ER定位的FIT2蛋白凭借其保守的磷酸酶结构域,可特异性水解磷脂酸生成二酰甘油;这一过程在LDs形成部位促使DAG局部积累,进而可能通过改变膜曲率或招募LDs组装相关蛋白,调控LDs向ER腔出芽的方向^[18,19]。

LDs形成的第四步:LDs的生长和扩张。出芽的细胞质LDs可能通过多种生物物理及蛋白质辅助的机制继续生长。其中的一个关键机制是Ostwald熟化,这是一个重要的热力学驱动过程:由于表面曲率差异,小LDs内部中性脂质(如TAG和SE)的化学势高于大LDs,其更易溶解于胞质并通过浓度梯度扩散,最终沉积于更大、更稳定的LDs中,从而实现脂质从小LDs向大LDs的定向转移,该过程促进中性脂质从小LDs向更大、更稳定的LDs转移^[20]。同时,该转移过程由LDs相关的细胞死亡诱导DFFA样效应(CIDE)蛋白家族CIDEA, CIDEB和CIDECD协助完成,LDs表面的磷脂酰肌醇-4-磷酸(PI(4)P)是CIDE蛋白定位的关键信号。PI(4)P特异性富集于部分LDs表面,通过直接结合CIDE蛋白(如CIDECD),引导CIDE蛋白从ER转运并富集于LDs-LDs接触位点(LDCS),通过介导中性脂从小LDs向大LDs的定向转移,促进LDs融合与增大。这一过程是细胞内脂质储存和脂稳态维持的关键步骤^[21]。另外,连接细胞质LDs与ER的膜桥是LDs的另一种生长方式。在此过程中,ARF1-COPI复合物的激活可触发膜桥形成^[22],使TAG合成酶(如GPAT4)能够从ER迁移至

LDs^[23]。除CIDE蛋白和GPAT4外, 还有其他蛋白可通过ER-LDs(ERTOLD)或细胞质-LDs(CYTOLD)途径到达并附着于LDs, 促进LDs生长^[24-26]。

LDs的异常生物发生通常由细胞暴露于过量脂质的环境中、营养过剩及氧化应激等条件触发, 也与能量代谢紊乱和氧化还原失衡等多种病理或生理状态密切相关^[27]。然而, LDs的功能远不止于脂质存储与代谢调控, 它更是细胞应激响应中的核心参与者。这一角色在病原菌感染过程中尤为突出, 呈现出复杂的“阴”与“阳”双重特性: 一方面, LDs可作为天然免疫屏障, 通过隔离毒性脂质与异常蛋白(如游离脂肪酸、脂质过氧化物、过度炎症信号蛋白)、维持能量与氧化还原稳态、保护膜结构完整性以及提供脂质信号分子等方式, 增强细胞对入侵病原的防御能力; 另一方面, 诸多病原菌也可劫持LDs的生物发生与功能, 利用其作为营养来源和复制场所, 从而促进自身存活与扩散。因此, LDs在感染界面中同时扮演着保护者与被利用者的双重角色, 其平衡状态直接影响感染的进程与结局^[27,28]。

2 脂滴在细胞先天免疫中的作用

天然免疫受体(包括TLR2, TLR4和核受体)在感染驱动的LDs生物发生中起主要作用。由病原体及病原体来源的分子激活的Toll样受体(Toll-like receptors, TLRs)能够通过触发受感染宿主细胞内的信号通路参与LDs的形成, 又能通过宿主产生的细胞因子和趋化因子间接激活旁观者扩增诱导系统(bystander amplification-induced system)。

2.1 脂滴与天然免疫

作为重要的细胞器, LDs是宿主干扰素(IFN)应答的核心参与者, 既作为信号传导通路关键枢纽参与IFN通路激活, 又通过调节应答效能影响免疫反应。在病原体感染早期, LDs促进感染细胞中干扰素的合成, 以建立有效的先天免疫防线。干扰素作为庞大的信号蛋白家族, 不仅调控宿主多种抗感染蛋白质的表达, 而且也是LDs蛋白质组成的关键调节因子^[29]。在宿主免疫应答过程中, LDs充当了干扰素诱导GTP酶(INF-inducible GTPases, IRGs)的组织中心。多种干扰素诱导IRGs在LDs上富集, 将其转化为先天免疫枢纽。其主

要抗菌机制包括: 第一, 促进吞噬细胞氧化酶(PHOX)复合体组装以增强活性氧(ROS)产生; 第二, 协助抗菌肽(cathelicidin)的动员; 第三, 直接驱动自噬以清除胞内病原体^[30,31]。

LDs参与先天细胞自主抗感染过程涉及两种抗菌蛋白——抗菌肽和蝮蛇毒素(viperin)。抗菌肽是具有抗菌和免疫调节功能的阳离子肽, 能结合并诱导细胞膜损伤, 导致受病原感染的细胞死亡^[32]。抗菌肽的杀菌机制与果蝇LDs上抗菌组蛋白的作用机制相似。蝮蛇毒素则是一种S-腺苷甲硫氨酸(SAM)酶, 其表达受病毒感染干扰素反应调控^[33]。该蛋白与多种病毒蛋白相互作用, 同时催化内源性抗病毒分子3'-脱氧-3',4'-双脱氢胞苷三磷酸(ddhCTP)的生成, 从而抑制病毒入侵、复制、组装和出芽^[34]。此外, 蝮蛇毒素可作为TLR7, TLR9和干扰素基因刺激蛋白(STING)通路的支架蛋白, 促进免疫细胞中I型干扰素的产生(图2)。蝮蛇毒素以刺激依赖性方式将IRAK1和TNF受体相关因子6 (TRAF6)募集至LDs, 促使TRAF6对IRAK1进行泛素化修饰, 最终通过干扰素调节因子7(IRF7)介导的途径诱导I型干扰素生成^[35]。研究还发现蝮蛇毒素在STING信号通路中对双链DNA(dsDNA)应答时发挥类似作用——通过劫持TANK结合激酶1(TBK1)和STING蛋白, 促进TBK1活化进而触发干扰素产生^[36]。有意思的是, 蝮蛇毒素和抗菌肽都是脂代谢的关键调节因子, 暗示着LDs在代谢功能与免疫作用之间的内在关联。

2.2 LDs与免疫代谢

在炎症环境中, LDs的形成是促炎性白细胞合成代谢和糖酵解代谢程序的重要组成部分。研究表明, Toll样受体的激活(特别是TLR2, TLR3, TLR4, TLR5, TLR6和TLR9)是诱导白细胞中LDs积累的关键机制^[37]。此外, TLR驱动的LDs积累是一个多因素介导的过程, 包括: 上调参与脂质摄取和运输的多种受体表达、下调脂解酶表达、抑制线粒体 β -氧化以及促进LDs生物发生相关通路。TLR激活下游的LDs生物发生过程依赖于从头脂质合成途径, 抑制脂质合成则显著降低LDs的积累。最新研究表明, 不同TLR可在巨噬细胞中诱导形成具有特征性差异的脂质组。由于TLR家族成员能够特异性识别不同种类的病原体, 这种脂质组多样性可能与LDs在脂质的特异性重塑有关^[38]。

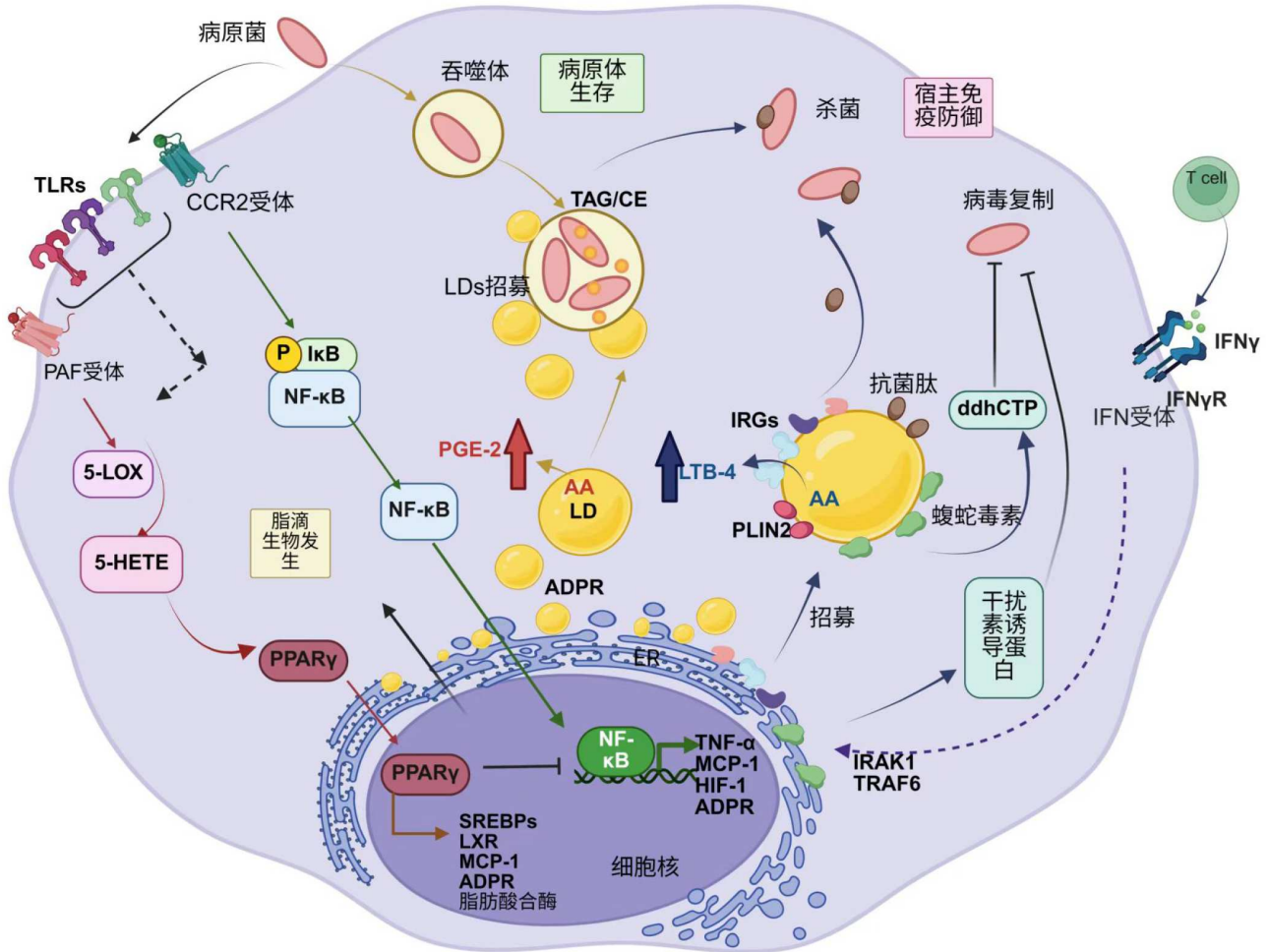


图 2 LDs在病原体感染中的作用

Figure 2 The role of lipid droplets in pathogen infection

TLR驱动的信号通路还涉及多种转录因子的激活,例如缺氧诱导因子(HIF)、肝X受体(LXR)、过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptors, PPARs)和固醇调节元件结合蛋白(SREBPs)。这些核受体亚家族成员是细胞内脂质代谢状态的重要传感器,同时也是脂质合成、脂肪酸摄取、胆固醇外流及LDs生物合成等关键基因表达的重要调节因子,但其具体路径和功能因细胞类型而异。多项研究表明,在巨噬细胞中,PPAR γ 的激活通常与免疫抑制和病原体劫持相关^[39]。例如,在卡介苗(BCG)或结核分枝杆菌感染中,病原体成分通过CD36-CD11b/CD14受体复合物信号轴激活PPAR γ ,进而上调脂肪酸合酶(FASN)和LDs蛋白Plin2的表达,驱动LDs大量生成。这些LDs为

胞内菌提供了丰富的营养来源,同时,PPAR γ 会抑制iNOS表达和炎症小体活化,削弱巨噬细胞的杀菌能力,从而促进感染建立与持续^[40]。同时,PPAR γ 激活后能抑制NF- κ B等通路,缓解过度炎症并促进巨噬细胞向M2修复表型极化,从而减轻组织损伤,其最终效应取决于感染阶段与细胞微环境——早期激活削弱宿主防御,而后期调控则有利于炎症消退。而在中性粒细胞中,LDs的形成更依赖于脂肪酸摄取和糖酵解-HIF-1 α 轴。在此环境下,LDs作为快速产生促炎脂质介质(如前列腺素和白三烯)的平台,能够增强抗菌防御^[41]。

此外,炎症反应过程中产生的多种分子以旁分泌的方式发挥作用,这些分子包括LDs、脂质介质、细胞因子和趋化因子,细胞的多种信号通路能够响应这

些信号分子的刺激而激活。例如, 血小板活化因子(platelet-activating factor, PAF)或类PAF物质通过与其G蛋白偶联受体(PAF-R)结合, 激活了脂滴生物发生的核心通路: 它首先促使细胞质磷脂酶A2(cPLA2)水解膜磷脂, 释放出大量花生四烯酸, 它被直接酯化并驱动新生脂滴的形成^[42]。这些花生四烯酸还可作为底物被5-脂氧合酶(5-lipoxygenase, 5-LO)代谢生5(S)-羟基二十碳四烯酸(5-HETE), 进一步促进脂滴生成^[42]。此过程依赖于新蛋白质的合成并可被转录因子PPAR γ 激活所放大, 并与趋化因子配体2(CCL2/MCP-1)信号通路相关: CCL2可直接通过其同源受体CCR2, MAP激酶, ERK和PI3K下游信号通路, 以剂量依赖的方式增加胞质LDs的数量^[43,44], 从而与PAF信号共同构成了一个精密且协同的调控网络, 共同调控炎症中脂滴的生成及其功能。

LDs也是产生多种宿主保护性类二十烷酸(eicosanoids), 如白三烯B4(leukotriene B4, LTB4)和前列腺素E2(prostaglandins E2, PGE2)的重要平台^[45]。作为不同类二十烷酸的合成场所, LDs还参与这些分子在免疫细胞中分泌及信号转导的过程。此外, LDs的积累与多种细胞因子(尤其是受类二十烷酸调控的细胞因子)的合成和/或分泌存在显著相关性。例如, 在中性粒细胞中, LTC4介导的旁分泌信号转导通路可调控嗜酸性粒细胞颗粒(包含细胞因子IL-4)的分泌。当LDs积累受阻时, LTC4的合成受到抑制, 从而导致IL-4分泌减少^[46]。类似地, 在促炎性巨噬细胞中, 抑制LD会降低IL-6和IL-1 β 的表达水平, 而补充PGE2可逆转这一现象; 在SARS-CoV-2感染的单核细胞中, DGAT1抑制剂导致的LDs合成障碍会减少cysLT和LTB4的合成, 并降低CXCL10, IL-6, IL-8和TNF的水平^[47]。

总之, 这些与细胞免疫相关的LDs多重触发机制表明, LDs是天然免疫应答不可或缺的组成部分。

3 LDs在病原微生物感染中的作用

在感染性疾病中, 研究表明LDs参与多种病原体的感染过程, 包括病毒、原虫、细菌和真菌。病原体利用LDs的方式多种多样, 胞内病原菌可以利用宿主LDs逃避免疫系统, 同时也将其作为细胞内存存复制所需营养物质和膜成分的来源^[48,49], 以建立其独特的细胞内存复制生态位^[50,51]。

3.1 结核分枝杆菌

结核分枝杆菌(*Mycobacterium tuberculosis*, *Mtb*)是一种全球性病原体, 引发的结核病每年导致超过125万人死亡^[52]。结核病的临床标志之一是在患者肺部形成肉芽结构, 这些肉芽含有“泡沫状”巨噬细胞, 其胞内大量积聚LDs^[53]。结核分枝杆菌主要感染巨噬细胞, 并需以宿主脂质作为碳源。研究表明, 在静息状态的巨噬细胞中, LDs可作为*Mtb*的营养来源^[54]; 然而, 当巨噬细胞被干扰素 γ (IFN- γ)激活后, 其所诱导的LDs则能有效阻止*Mtb*获取脂质^[55]。

在感染过程中, 结核分枝杆菌利用其非蛋白和蛋白毒力因子调控LDs的形成, 促进其生存^[53,56]。结核分枝杆菌利用长链脂肪酸调控宿主细胞的代谢途径, 诱导巨噬细胞向泡沫细胞方向分化^[54,57]。值得关注的是, 近期研究表明, 结核分枝杆菌的萜烯核苷1-结核菌萜腺苷具有诱导TAG和SE在溶酶体内积累的能力, 这一发现与泡沫巨噬细胞内溶酶体及其周围细菌周围的脂质积累模式高度吻合^[58]。而与结核分枝杆菌内部TAG合成密切相关的因子包括酰基辅酶A合成酶FacL6以及具有Perilipin样特性的蛋白PPE1^[59,60]。

结核分枝杆菌利用其Ⅶ型分泌系统(T7SS)转运效应蛋白, 在建立感染和宿主适应中发挥核心作用。其中, ESX-1系统是结核分枝杆菌最关键的一个T7SS亚型, 其分泌的效应蛋白是主要的毒力因子^[61], 且巨噬细胞LDs的形成依赖于结核分枝杆菌的ESX-1分泌系统。ESX-1分泌的毒力因子ESAT-6通过干扰糖酵解途径驱动“泡沫状”巨噬细胞的分化过程^[62]。HIF-1 α 及其靶基因*Hig2*对结核分枝杆菌感染小鼠肺部大部分LDs的形成是必需的, IFN- γ 驱动的LDs形成触发宿主保护性类二十烷酸(包括PGE2和LXB₄)的产生^[55]及过氧化物酶体增殖物激活受体 γ (PPAR γ)的表达上调^[63]。这些脂质通过脂质受体TLR2和TLR6相关信号传导, 促进宿主细胞内LDs的形成^[64]。然而, 也有研究表明, LDs的积累是巨噬细胞应对结核分枝杆菌感染的一种适应性的代谢模式, 这种模式不仅可增强巨噬细胞抵御结核分枝杆菌的能力, 同时迫使细胞内结核分枝杆菌向脂肪酸节约型的生存模式进行转变^[65]。有意思的是, 结核分枝杆菌通过其LDs的疏水核心靶向富集脂溶性抗生素(如贝达喹啉、利福平), 形成动态药物库, 显著提升感染部位局部药物浓度, 并借助LDs-细菌接触实现药物直接传递; 同时, LDs内低pH、高脂质浓度的

微环境可触发抗生素(如贝达喹啉)以非活性形式储存后释放,在游离脂肪酸改变局部pH时活化,通过抑制ATP合酶阻断细菌能量生成,且LDs动态过程加速药物向细菌细胞质的扩散;此外,脂溶性抗生素还可借助LDs渗透至休眠态*Mtb*体内,突破肉芽肿干酪样坏死核心的屏障,显著增强对代谢静止期细菌的杀伤效果,相关研究显示,经此途径,贝达喹啉的最低抑菌浓度可降低一半并缩短杀菌时间^[66,67]。这些证据恰恰证明了,LDs在病原菌感染过程中扮演的“阴”与“阳”的双重角色。

3.2 嗜肺军团菌

嗜肺军团菌(*Legionella pneumophila*)是一种革兰氏阴性胞内病原菌,可引起人类的严重肺炎,即军团病^[68,69]。嗜肺军团菌通过宿主细胞的胞吞作用进入细胞后,通过细菌Dot/Icm IV型分泌系统(T4SS)将300多种效应蛋白转运至宿主细胞^[70],干扰宿主的细胞进程^[71,72],以建立其胞内繁殖所需的复制场所——含军团菌液泡(*legionella-containing vacuole*, LCV)^[71]。大量研究表明,LCV形成及成熟过程涉及以下关键步骤:(i) 磷脂酰肌醇(PI)从PtdIns(3)P向PtdIns(4)P的转化,这一过程将LCV从内吞途径重新定向转变至分泌途径;(ii) 劫持Arf, Rab, Ran和Rap家族的小GTP酶,调控宿主的囊泡转运途径;(iii) 截获并与ER来源的囊泡发生融合。

ER的大型融合GTP酶Sey1/atlastin3可促进嗜肺军团菌LCV的扩张及其胞内复制。最近的研究表明,在盘基网柄菌(*Dictyostelium discoideum*, *D. discoideum*)中,嗜肺军团菌LCV与棕榈酸酯诱导的LDs存在密切相互作用,而GTP酶Sey1和嗜肺军团菌效应蛋白LegG1可促进LCV与宿主LDs的相互作用。敲除*sey1*基因导致ER结构异常、LCV-ER相互作用及胞内细菌复制受损及其LCV-LDs相互作用显著减弱^[73]。

研究发现,当以脂肪酸(如棕榈酸酯)或特定细菌饲喂军团菌的天然宿主——盘基网柄菌时,其细胞内会出现LDs积累现象^[74]。类似地,军团菌感染巨噬细胞后导致细胞内LDs的积累并集聚在其LCV周围,这可能是由于盘基网柄菌的LDs与哺乳动物LDs具有相似的组成,包括TAG、SE、FA以及脂周蛋白,并被极性磷脂单层和特异性蛋白质所包裹^[74]。含有锚蛋白重复序列的嗜肺军团菌效应蛋白LegA15/AnkD^[75]可能参

与该过程。效应蛋白LegA15/AnkD直接定位于宿主LDs并募集宿主囊泡运输因子p115。在正常生理条件下,p115作为高尔基体囊泡运输因子定位于高尔基体,发挥维持高尔基体完整性的功能^[76]。LegA15与p115的AMR结构域相互作用,将p115劫持至LDs,一方面会导致宿主高尔基体碎片化(图3),损害宿主细胞的早期分泌途径,另一方面,将宿主LDs招募至LCV上,从而使嗜肺军团菌操纵宿主LDs以实现LCV的生物发生^[77]。

总之,嗜肺军团菌通过其分泌的效应蛋白LegG1和LegA15调控宿主LDs代谢,介导LDs与LCV的相互作用,并依赖GTPase Sey1介导的膜融合过程,促使LDs与LCV发生物理性融合,从而为其提供宿主来源的脂肪酸营养。

3.3 伤寒沙门氏菌

鼠伤寒沙门氏菌(*Salmonella enterica* Typhimurium)属于革兰氏阴性细菌,是引起急性胃肠炎的主要病原菌之一^[78]。在感染宿主细胞后,鼠伤寒沙门氏菌能够构建一个特殊的复制场所——含沙门氏菌的空泡(*Salmonella-containing vacuole*, SCV)^[79]。SCV的形成依赖于沙门氏菌携带的两个位于其致病岛(*Salmonella* pathogenicity island, SPI)基因组上的III型分泌系统(T3SS): SPI-1和SPI-2^[80]。SPI-1在细菌的初步侵袭阶段发挥着关键作用,而SPI-2则是在细菌被内化至细胞内后开始发挥作用^[80,81]。鼠伤寒沙门氏菌感染巨噬细胞后能够迅速诱导巨噬细胞内LDs的生成和积累,该过程依赖其SPI-1^[82]。通过抑制二酰甘油酰基转移酶1或磷脂酶A2(PLA2)的活性阻止LDs的形成,导致细胞内细菌的生长受到抑制^[82,83]。

此外, SPI-2所转运的效应蛋白SifA, SseJ和SseL在沙门氏菌调控宿主LDs积累过程中扮演着关键角色^[84]。效应蛋白SseJ具有脱酰酶活性,能够在宿主细胞内以及感染过程中促进胆固醇酯化,进而推动LDs的形成^[85,86]。SseJ基因缺失则会导致细胞内LDs数量降低^[84]。SseL是另一种由SPI-2编码的效应蛋白,与脂质代谢密切相关^[84,87]。ΔSseL突变株感染会导致宿主细胞脂质代谢发生显著改变,并引发感染细胞内LDs的大量积累,而这些现象归因于SseL的去泛素化酶活性, SseL通过调控宿主细胞的泛素化修饰改变感染细胞中的脂质代谢^[83]。总之, SPI-1和SPI-2转运的效应蛋白在鼠伤寒沙门氏菌调控宿主LDs、脂质代谢及其细胞内

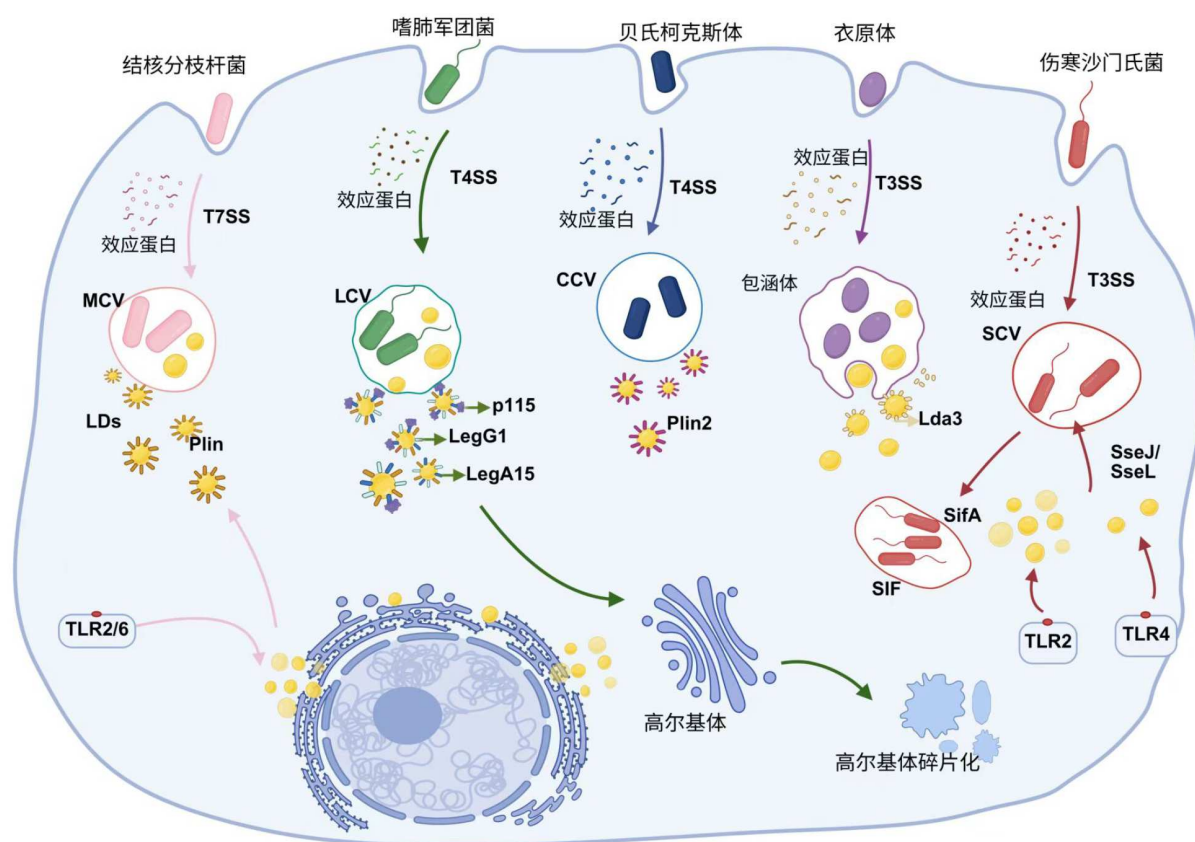


图3 细胞内细菌病原体与宿主LDs的相互作用

Figure 3 Interaction between intracellular bacterial pathogens and host lipid droplets

的生存和复制发挥着重要作用。

3.4 贝氏柯克斯体

贝氏柯克斯体(*Coxiella burnetii*)是一种革兰氏阴性专性胞内菌,可引起人畜共患的Q热^[88]。其致病核心在于它能成功感染肺泡巨噬细胞,并在此细胞内构建一个独特的、适于其复制的膜性囊泡——含柯克斯体液泡(*Coxiella*-containing vacuole, CCV)^[89]。CCV的成熟是一个主动劫持宿主细胞内膜运输系统的过程:它最终与溶酶体融合并维持其强烈的酸性环境(pH≈4.5)^[90],这一酸性环境是激活贝氏柯克斯体四型分泌系统的关键信号,促使它将超过130种效应蛋白注入宿主细胞质中,以操纵宿主各项细胞功能^[91,92]。有研究发现,由贝氏柯克斯体编码的CbEPF1蛋白含有FFAT基序,并定位于宿主LDs。CbEPF1通过与VAP家族蛋白的相互作用,成功地在宿主LDs与ER之间建立膜接触位点。更有趣的是,CbEPF1能够通过FFAT基序

依赖的方式调节宿主LDs的生长^[93]。此外,贝氏柯克斯体分泌的效应蛋白Vice通过促进巨胞饮作用和干扰内吞体分选转运复合体(ESCRT)机制,改变宿主细胞的膜运输和脂质组成,为CCV的发育和扩张提供膜脂和原料^[94]。而定位于ER的效应蛋白ElpA在感染过程中会破坏ER的结构和功能,但ElpA是否影响宿主LDs的稳态尚未明确^[95]。

贝氏柯克斯体最初会感染肺泡巨噬细胞,但也在心内膜炎患者心脏瓣膜的含LDs泡沫巨噬细胞内被检测到^[96,97]。进一步的研究表明,感染贝氏柯克斯体的巨噬细胞会上调LDs相关蛋白PLIN2的表达,并诱导宿主细胞内的LDs大量积累,该过程依赖于贝氏柯克斯体的T4SS^[98]。使用抑制剂或在巨噬细胞中敲除ACAT1抑制LDs的形成,则会促进细胞内贝氏柯克斯体的繁殖,而通过抑制剂Atglistatin阻断ATGL活性来阻止LDs的脂解作用,则会抑制细菌的生长^[98]。这些发现表明,宿主LDs的稳态对伯纳氏柯克斯体的细胞内生长

至关重要, 而贝氏柯克斯体通过T4SS分泌的效应蛋白维持LDs的稳态.

3.5 衣原体

衣原体(*Chlamydia*)是一类革兰氏阴性、专性细胞内寄生的微生物, 介于细菌和病毒之间. 它们依赖宿主细胞进行繁殖, 可引起人类和动物的多种疾病. 比如沙眼衣原体(*Chlamydia trachomatis*)可造成眼部及生殖道感染, 而肺炎衣原体(*Chlamydia pneumoniae*)则可引起人类呼吸道感染, 与罹患的社区获得性肺炎密切相关^[99].

沙眼衣原体在感染黏膜上皮细胞后, 通过Ⅲ型分泌系统构建一个称为包涵体的病原体囊泡^[100]. 一些T3SS分泌的效应蛋白被称为包涵体膜(Inc)蛋白, 可嵌入包涵体膜中, 参与包涵体膜与宿主ER的直接相互作用^[101,102]. 当在真核细胞中异位表达时, 沙眼衣原体的Inc蛋白CT006与LDs及ER的发生有关, 这提示沙眼衣原体分泌的效应蛋白可能参与LDs与包涵体之间的相互作用^[103]. 沙眼衣原体的包涵体通过LDs获取宿主脂质^[104], 这些LDs会从宿主细胞质迁移至包涵体内部, 并与沙眼衣原体紧密结合. 该过程依赖于沙眼衣原体Ⅲ型分泌系统分泌的效应蛋白. 如效应蛋白Lda3在沙眼衣原体包涵体吸收LDs的过程中扮演着关键角色^[105], 它通过形成LDs-包涵体膜的接触点促进LDs被摄取进入衣原体包涵体, 并通过“内吞”进入机制形成膜包裹的包涵体腔内LDs^[104,106]. 在包涵体内, 效应蛋白IncA与LDs结合并在沙眼衣原体包涵体腔内积累^[104], 而富含IncA的包涵体区域可能构成了LDs转运的位点. 效应蛋白IncD与CERT相互作用, 而CERT能与ER上的VAP蛋白结合^[107]. 另外, 效应蛋白IncV通过两个FFAT基序直接与VAP相互作用, 并在ER-包涵体膜接触位点富集^[108]. CERT或VAP的缺失会导致衣原体包涵体变小, 并使其感染性后代数量显著减少^[78,109]. 总之, IncA, IncD-CERT-VAP复合物和IncV-VAP复合物共同促进ER-包涵体膜接触位点的形成. 鉴于细胞LDs的生物发生起源于ER, 因

此, 效应蛋白IncA, IncD和IncV也可能参与了LDs与包涵体膜接触位点的形成, 目前尚待进一步研究. 而相比之下, 肺炎衣原体缺乏沙眼衣原体中负责介导膜直接互作的IncA蛋白同源物, 导致其包涵体膜与LDs的直接相互作用显著减少^[110]. 研究表明, 肺炎衣原体在利用宿主LDs时采取一种以“间接调控”为核心的策略, 主要依赖对宿主信号通路的调控: 通过下调PPAR γ 、上调ACAT1, 并激活MAPK通路(包括JNK, ERK和p38), 促进宿主细胞(如巨噬细胞)中胆固醇酯的积聚, 从而诱导LDs的形成. 在肺炎衣原体中, 这些LDs仅围绕包涵体分布, 与之形成“间接接触”, 而未被其摄取; 同时, 也未观察到类似于沙眼衣原体中存在的ER-包涵体膜接触位点(MCSs)及其相关蛋白复合物(如 CERT-VAP)的形成; 其对LDs的利用不依赖宿主内质网蛋白(如CERT, VAP)的协同, 而是更侧重通过调控宿主脂质代谢稳态(而非直接分子结合)来实现^[111].

4 总结与展望

除参与细胞器互作、脂质存储及能量代谢调控外, LDs在细胞应激应答、信号转导及先天免疫等生物学过程中亦发挥关键作用. 胞内病原菌与宿主LDs的相互作用不仅体现了病原菌精巧的生存策略, 更体现了宿主脂质组分在病原菌感染过程中的关键作用. 对于胞内致病菌而言, 宿主LDs在感染过程中扮演双重角色: 既作为必需营养储备库, 又通过脂质信号分子调控病原体毒力因子的表达与分泌. 目前, 人们对细菌分泌效应蛋白来调控宿主细胞的LDs 还知之甚少. 同时, 病原体如何通过其液泡屏障与外部环境进行物质交换, 也是一个有待深入研究的课题. 特别是, LDs外层覆盖的脂质单层如何与病原体液泡膜的脂质双层发生相互作用并跨越其屏障, 这一机制仍尚未明晰. 总之, 尽管LDs的研究已历经半个多世纪, 但其生物学功能仍待全面挖掘, 众多基本的生物学问题仍有待进一步探索.

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The Yin-Yang of lipid droplets in pathogenic bacterial infection: from immunological guardian to pathogenic exploitation

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Lipid droplets (LDs) are dynamic and multifunctional organelles composed of a hydrophobic core of neutral lipids, a monolayer phospholipid shell, and various associated proteins. They play a critical role in diverse processes such as lipid storage, energy metabolism, membrane trafficking, and cellular signaling, thus linking them to a variety of diseases, including metabolic disorders, cancer, and infectious diseases. In host-pathogen interactions, LDs exhibit a “Yin-Yang” dual role: on the one hand, as a core component of the host interferon response, LDs not only serve as key hubs for activating interferon-signaling pathways but also help establish an effective innate immune defense by modulating the intensity of the immune response in the early stages of pathogen infection. On the other hand, various pathogens hijack LDs through mechanisms such as lipolysis regulation and membrane fusion, utilizing them as nutrient sources and membrane components to create an intracellular niche favorable for their own replication. While existing literature has reviewed the biogenesis and physiological functions of LDs within cells, this review focuses on the roles and molecular mechanisms of LDs in innate immunity and bacterial infections, thereby providing new perspectives for developing LD-based anti-infective therapeutics.

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