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先天性训练免疫在疾病中的作用*

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摘要 先天免疫系统可通过预先与微生物或微生物产物接触，促进先天免疫系统对后续触发因素的反应增强，该过程被称为“训练免疫”。训练免疫是一种基本的保护机制，增强对继发感染的保护，其可被多种诱导剂诱导，主要分子机制为表观遗传重编程和代谢重编程。在对抗肿瘤和感染等疾病中，通过训练先天免疫可发挥治疗疾病的作用，但是在部分慢性炎症性疾病中，训练免疫会引起不良效应，导致过度炎症和疾病的发展。

关键词 训练免疫，先天免疫系统，表观遗传学，免疫代谢
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1 训练免疫

免疫系统分为先天免疫系统和适应性免疫系统[1]。通常认为机体的先天免疫应答不存在记忆性，即机体再次感染同一病原体时免疫反应并不会增强。2005年，Kurtz等[2]在缺乏适应性免疫的植物和无脊椎动物中均发现，先天免疫系统可发挥再感染的持续保护作用。Quintin等[3]研究也表明，哺乳动物机体对于不同病原体的感染有交叉保护作用，缺乏功能适应性免疫细胞的小鼠体内接种某些疫苗后，机体也具有部分免疫保护作用。由此说明，先天免疫系统可通过预先与微生物或微生物产物接触，促使先天免疫系统对后续触发因素的反应增强，该过程被称为“训练免疫”[4]。

与经典免疫记忆相比，训练免疫具有许多不同的特征。首先，训练免疫与经典免疫记忆中涉及的分子不同。训练免疫主要涉及先天性免疫细胞（如髓样细胞、自然杀伤细胞、先天淋巴样细胞）及其编码的相关效应分子（如模式识别受体（pattern recognition receptor，PRR）、多种细胞因子等）。其次，训练免疫期间对次级刺激的反应性增加并非针对某一特定病原体，而是通过影响细胞中转录因子和表观遗传重编程的信号，导致转录过程的持续变化，最终影响细胞的生理学变化，但并不涉及永久性的遗传变化（如基因突变和重组）。最后，训练免疫依赖于先天免疫细胞功能状态的改变，这种状态在消除初始刺激后可持续数周至数月[5]。

2 训练免疫的诱导剂

研究表明，在先天淋巴细胞群中诱导训练免疫需要相应的诱导剂，这些诱导剂可分为外源性刺激物（包括疫苗）和内源性刺激物等[6]。

2.1 外源性刺激物

病原体（细菌[7-8]、真菌[9]或病毒[10]）及其内在成分是外源性触发训练免疫的重要因素。其中，真菌病原体白色念珠菌及其细胞壁成分β葡聚

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糖[11]（β-glucan，β-Glu）是最早且使用最多的体内外训练免疫诱导剂之一。小鼠腹膜内注射低浓度β-Glu在骨髓造血祖细胞中可诱导训练免疫，β-Glu通过激活树突状细胞相关C型凝集素受体1-蛋白激酶B-雷帕霉素靶蛋白（Dectin-1-Akt-mTOR）信号通路，增加有氧糖酵解，从而增强脂多糖（lipopolysaccharide，LPS）攻击前的细胞免疫能力，改善骨髓抑制[12]。疟原虫[13]和乙型肝炎病毒[14]也可作为训练免疫的诱导剂。

LPS作为细菌细胞壁成分，通过与Toll样受体（Toll-like receptor，TLR）结合激活免疫细胞[15]，激活TLR4以触发细胞内信号转导途径，包括髓样分化因子88（MyD88）依赖途径，进一步激活转录因子（如核因子κB（NF-κB）），增强细胞糖酵解和氧化磷酸化，进而发生表观遗传层面的改变，包括组蛋白修饰（如乙酰化、甲基化）和DNA甲基化，调节下游基因的表达。与内源性刺激物相比，经微生物诱导剂（β-Glu和LPS）诱导训练免疫的细胞，受二次刺激时具有更强的炎症诱导潜力[16]。

疫苗通过对继发感染的交叉保护可诱导先天免疫系统的训练免疫。可发挥免疫训练作用的疫苗主要是减毒活疫苗，如卡介苗[17]（Bacillus Calmette-Guérin，BCG）、结核分枝杆菌减毒活疫苗[17]、口服脊髓灰质炎疫苗[18]和麻疹疫苗[19]。BCG通过与TLR4结合激活免疫细胞，增强细胞糖酵解和三羧酸循环（tricarboxylic acid cycle，TCA cycle）等代谢途径，进一步影响表观遗传修饰酶的活性。重组BCG不仅可以诱导对人类呼吸道合胞病毒（hRSV）和人类偏肺病毒（hMPV）抗原的特异性适应性免疫反应，还可以诱导对其他呼吸道病原体的训练免疫[20]。麻疹疫苗也被证实可以预防非特异性再感染，降低感染患者的死亡率[21]。

2.2 内源性刺激物

研究表明，内源性刺激物也可诱导免疫训练，包括干扰素（interferon，IFN）、白介素（interleukin，IL）、氧化低密度脂蛋白（oxidized low density lipoprotein，oxLDL）[22]、儿茶酚胺类激素[23]、高浓度血糖等[24]。Arts等[25]研究发现，IL-1β在体外[26]和小鼠体内诱导训练免疫，对不同病原体（如金黄色葡萄球菌等）具有非特异性的机体保护作用[27-28]。IL-3也可调节细胞训练免疫效应[29]。IL-4通过转录激活因子6（signal transducer and activator of transcription 6，STAT6）发挥急性抗炎功能，同时还通过胰岛素受体底物2-磷酸肌醇3-激酶-雷帕霉素靶蛋白信号通路（IRS-2-PI3K-mTOR）诱导单核/巨噬细胞的训练免疫能力[30]。Groh等[31]研究表明，oxLDL可诱导训练单核细胞/巨噬细胞。儿茶酚胺类激素如肾上腺素和去甲肾上腺素与单核细胞作用24 h，随后用LPS进行二次刺激，单核细胞中促炎细胞因子表达增加，且其炎症通路上的多种基因表达发生变化，表明儿茶酚胺可诱导单核细胞训练免疫[32]。醛固酮与单核细胞作用24 h，静息5 d后使用TLR2/4的配体重刺激细胞，可促进细胞中促炎因子的表达增加[33]。高浓度血糖作用下，免疫细胞内糖酵解途径被增强，导致细胞内ATP产生增加及代谢中间体（如丙酮酸和乳酸）的积累[34-35]。经高血糖训练后的免疫细胞在二次刺激下，其炎症因子（如TNF-α、IL-1β、IL-6）表达增强[35]。

3 具有训练免疫功能的细胞

多种细胞具备训练免疫的功能，包括巨噬细胞、单核细胞、NK细胞和非免疫细胞。不同细胞经过不同刺激物干预后能引起不同信号通路的变化，进而引起不同的表观遗传和代谢的改变（表1）。

3.1 骨髓来源细胞（髓样细胞）

髓样细胞是主要的先天性免疫细胞，由巨噬细胞、单核细胞、粒细胞和树突状细胞组成[36]，主要是促进免疫细胞募集和分化，介导抗原递呈，并控制炎症反应[36]，在组织结构、重塑细胞外基质[37]、指导器官发育[38]和血管形成[39]等方面发挥着关键作用。β-Glu、oxLDL和BCG均可训练巨噬细胞的免疫记忆。在产气荚膜梭菌攻击前用热灭活的白色念珠菌预处理，可显著增强骨髓巨噬细胞杀死胞外菌的能力[12]。Lechner等[40]提出，巨噬细胞在过敏原致敏方面也展示出训练免疫表型。屋尘螨过敏原致敏小鼠的巨噬细胞再暴露时，细胞可表达更高水平的IL-6[40]。

白色念珠菌感染、BCG或麻疹疫苗接种后[3, 41-42]可增加单核细胞对继发感染的抵抗能力。研究表明，单核细胞在感染和疫苗接种后会表现出训练免疫能力[3, 11, 41-42]。急性炎症也可导致单核细胞的免疫能力和功能变化。念珠菌感染后的单核细胞会保留先前遭遇的“免疫疤痕”，进入反应性增强状态，形成训练免疫[11]。新型冠状病毒感染（COVID-19）恢复阶段的单核细胞也具有获得性训

练免疫的能力[43-45]。

中性粒细胞也可进行训练免疫。健康人接种BCG几周后，血液中嗜中性粒细胞的数量增加。接种疫苗后3个月，中性粒细胞计数重新平衡恢复正常，但细胞中整合素alpha M（ITGAM）表达增加，L选择素（L-selectin）和程序性死亡受体配体1（programmed death-ligand 1，PD-L1）的表达减少，其在体外杀死白色念珠菌的能力增强[46-47]。这是由于中性粒细胞的脱颗粒和吞噬能力得到增强，在二次刺激下，细胞中IL-8、弹性蛋白酶和活性氧类（ROS）的表达增强[46-47]。来源于真菌细胞壁的β-Glu对中性粒细胞同样具有训练作用。

除了循环髓系细胞外，驻留在组织中的免疫细胞也具有增强次级反应的能力。Kain等[48]研究发现，鸟分枝杆菌训练的骨髓来源巨噬细胞，其对胞外细菌的清除能力增强。小胶质细胞是中枢神经系统中驻留的组织巨噬细胞，在受到β-Glu预处理后产生训练免疫效果，细胞中TNF-α、IL-6和CCL3表达增强，细胞形态改变，其表观遗传发生重编程[49]。肺泡巨噬细胞（即驻留在肺部的巨噬细胞）在鼻内LPS暴露后也可建立训练免疫，用于抗细菌感染[50]。

3.2　NK细胞

自然杀伤细胞（natural killer cell，NK）属于先天淋巴样细胞，在防御病毒感染[51]和抑制肿瘤细胞生长方面起着关键作用。通过IL-12、IL-15或IL-18等细胞因子的短暂刺激，NK细胞会改变其代谢活性，从静息状态转变为激活状态，使NK细胞表现出记忆样特征，产生训练免疫[52-55]。由病毒感染、接触性超敏反应或LPS导致的内毒素血症诱导的具有不同的适应性和记忆样的NK细胞模型中，存在与免疫训练后的其他髓样细胞同样的表观遗传重塑[56]。

3.3　非免疫细胞

训练免疫首先发现于骨髓细胞中，但成熟的髓系细胞寿命十分短暂，平均半衰期为5~7 d[57]，可能无法将记忆表型传递给其后代并提供长期保护。因此，训练免疫更可能依赖长寿命细胞完成，如上皮干细胞[58]、间充质基质细胞[59]和成纤维细胞[24]等非免疫细胞。这些非免疫细胞通常在产生和维持组织稳态方面具有独特的功能，还可通过释放炎症因子在防御病原体方面发挥重要作用[60]，被认为具有持久的免疫记忆。在咪喹莫特诱导皮肤炎症的小鼠模型中，与野生型小鼠相比，经诱导后的小鼠暴露于炎症因子的皮肤对未知的继发性威胁的反应更快，具有更好的伤口愈合能力[61]。在糖尿病大鼠模型中，首先用LPS预处理间充质干细胞（mesenchymal stem cells，MSCs），随后用TNF-α再刺激MSCs，发现MSCs可释放大量细胞因子（包括IL-8、IL-6和单核细胞趋化蛋白1（MCP-1）等），诱导型一氧化氮合酶的表达增加，LPS训练后MSCs的免疫调节能力增强[62-63]。

4　训练免疫的分子机制

表观遗传重编程是诱导训练免疫的分子机制之一[64]。表观遗传重编程包括DNA修饰、非编码RNA、组蛋白修饰和染色质重塑[65]。除表观遗传重编程外，不同的细胞代谢途径也参与训练免疫的调控。

4.1　表观遗传重编程

研究表明，先天免疫细胞接收外界刺激后，会在基因水平留下“表观遗传疤痕”，从而改变细胞的长期反应性，表现为具有训练性的免疫能力[66-67]。在骨髓来源细胞中，许多编码炎症的基因在体内平衡期处于抑制状态，经初次刺激后，细胞的染色质可及性和乙酰化显著增加，募集大量RNA聚合酶，促进下游炎症基因的表达上调。这些炎症因子的持续刺激进一步诱导组蛋白修饰，从而导致染色质长期开放[68]。在被训练的巨噬细胞中可以观察到与基因激活相关的非永久性组蛋白修饰，包括组蛋白三号亚基4位赖氨酸的单甲基化（H3K4me）和三甲基化（H3K4me3）以及组蛋白三号亚基27位赖氨酸的乙酰化（H3K27ac）[69]。H3K27ac存在于携带H3K4me1的远端增强子中，而H3K4me3标记激活基因的启动子。基因转录的初始激活伴随着特异性染色质标记的丢失和获得，如H3K27me3和H3K4me3在消除刺激后有部分维持。先天免疫细胞状态的增强与“潜伏增强子”中组蛋白标记（如H3K4me3和H3K4me1）的持续存在密切相关，从而导致面对再次攻击时，细胞对次级刺激产生更强的非特异性反应。这些区域与转录因子的结合是随机的，但先天免疫细胞中多个快速反应基因主要集中在拓扑相关结构域（TAD）并相互作用，从而降低基因转录的随机性，这些结构也能使免疫相关基因与一些长链非编码RNA（lncRNA）相互作用并激活转录[70-72]。β-Glu或BCG刺激可上调骨髓来源祖细胞中的lncRNA，进而导致免疫基因的启动子上募集更多H3K4me3

标记。

表观遗传调控先天免疫细胞的非特异性先天免疫记忆过程[73]，是先天免疫细胞在二次刺激时增强反应的基础和分子机制，也是先天免疫细胞在训练免疫期间的适应性特征和记忆适应性反应放大的基础，使得细胞在受到二次刺激后促炎因子的分泌增加，如脓毒症中BCG诱导的非特异性（或异源）保护作用。经β-Glu诱导的巨噬细胞，H3K27ac、H3K4me1和H3K4me3修饰在参与训练免疫的基因启动子上大量募集，导致染色质转录活性发生变化，使转录程序重新连接先天免疫细胞内的信号转导，诱导细胞代谢从氧化磷酸化转变为有氧糖酵解，增加巨噬细胞对刺激的反应能力[74]。流感疫苗接种可诱导单核细胞动态染色质重塑[75]。BCG可改变单核细胞中的免疫和代谢基因[76]。IL-1β体外预处理人单核细胞，在LPS再刺激时可观察到细胞中IL-6和TNF-α的表达水平更高[5, 77]。进一步研究发现，单核细胞中TNF-α启动子区域的组蛋白甲基化水平H3K4me3和H3K9me3发生改变，这与BCG诱导后的单核细胞中观察到的表观遗传修饰一致[5, 77]。醛固酮与人单核细胞作用24 h，随后静息5 d，在第6天使用TLR2/4重刺激，通过盐皮质激素受体使经二次刺激的细胞中促炎因子的表达增加，并在脂肪酸合成途径核心基因的启动子处富集H3K4me3修饰[33]。

4.2　代谢重编程

诱导、维持和调节训练免疫的分子机制依赖于许多不同的代谢途径和细胞的表观遗传机制之间的复杂相互作用，细胞代谢是先天免疫细胞及其祖细胞训练免疫表观遗传重编程的关键介质[17]。激活代谢重编程并维持训练免疫表观遗传机制不仅仅与增强细胞内ATP有关，不同的代谢途径作为连续的能量来源和构建体系，为细胞表观遗传机制的主动重塑提供动力，也提供必要的底物用于修饰染色质和基因组相应区域的结构。因此，为了寻找诱导训练免疫背后的表观遗传机制，还需要了解特定代谢物和代谢网络在此过程中的作用。

当细胞处于静息状态时，通常表现出较低的生物合成需求。在这种状态下，细胞主要依赖于高效但缓慢的代谢途径，如氧化磷酸化和脂肪酸氧化。经刺激物激活后，免疫细胞需要快速获得底物供应，以补充触发免疫反应所需的许多生物过程。因此，训练免疫的诱导和维持涉及多种代谢途径的参与，包括有氧糖酵解、谷氨酰胺分解、胆固醇代谢和脂肪酸合成等。在受到初次攻击时[4]，PRR对特定配体的识别触发一系列细胞内级联反应，导致不同代谢途径的上调，如糖酵解、三羧酸循环和脂肪酸代谢，这些代谢物对表观遗传过程发挥直接调节作用，包括作为辅助因子以及表观遗传修饰的供体或受体基团，如延胡索酸（fumaric acid）和乙酰辅酶A（acetyl-CoA），激活或抑制一系列参与重塑细胞表观遗传特征的酶，如组蛋白去甲基化酶5（KDM5）或组蛋白乙酰转移酶（histoneacetyltransferase，HAT），诱导细胞中组蛋白甲基化和参与先天免疫反应的基因乙酰化（图1）。

Table 1　The mechanism of trained immunity in different kinds of cells

表1　不同细胞类型的训练免疫机制

细胞类型	刺激物	受体	信号通路	表观遗传改变	代谢改变	参考文献
巨噬细胞	β-Glu	Dectin-1	PI3K-AKT, syk	H3K4me3, H3K27me3	糖酵解	[11, 69, 78]
	BCG	TLRs/CLRs	NF-κB, PI3K-AKT	H3K4me3	琥珀酸和富马酸	[17, 25]
	OxLDL	LOX, CD36	MAPK, PI3K-AKT, NF-κB	H3K4me3, H3K27me3	糖酵解和氧化磷酸化	[23, 31, 79-81]
单核细胞	β-Glu	Dectin-1	AKT-mTOR-HIF-1α	H3K4me1	糖酵解	[11, 82-84]
	BCG	NOD2	AKT-mTOR, IL-32	H3K9me3	糖酵解	[25, 26, 85-86]
	OxLDL	TLR	mTOR依赖的ROS	H3K4me3	糖酵解	[87-88]
	LPS	TLR4	NF-κB, PI3K-AKT	H3K9me3, H3K4me3	葡萄糖和胆固醇代谢	[6, 42, 89]

续表1

细胞类型	刺激物	受体	信号通路	表观遗传改变	代谢改变	参考文献
自然杀伤细胞	LPS IL-12/IL-15	TLR4	MyD88-NF-κB, PI3K-AKT JAK-STAT, MAPK, PI3K-AKT	H3K4me3, H3K27me3 H3K4me3	糖酵解 糖酵解和氧化磷酸化	[90-91] [53, 92-93]
内皮细胞	GM-CSF, IL-1β, TNF-α	TLRs, CLRs	MyD88-NF-κB, MAPK	H3K27ac, H3K4me3	糖酵解	[17, 94]

BCG：卡介苗；β-Glu：β-葡聚糖；OxLDL：氧化型低密度脂蛋白；LPS：脂多糖；IL-12/15：白介素-12/15；IL-1β：白介素-1β；GM-CSF：粒细胞-巨噬细胞集落刺激因子；TNF-α：肿瘤坏死因子α；Dectin-1：树突状细胞相关C型凝集素受体1；TLR2/4：Toll样受体2/4；LOX：赖氨酰氧化酶；CD36：白细胞分化抗原36；PI3K：磷脂酰肌醇激酶；AKT：蛋白激酶B；syk：脾酪氨酸激酶；NF-κB：核因子κB；MyD88：髓样分化因子88；MAPK：丝裂原活化蛋白激酶；STAT：信号转导及转录激活蛋白；H3K4me3：组蛋白三号亚基4位赖氨酸三甲基化；H3K9me3：组蛋白三号亚基9位赖氨酸三甲基化；H3K27me3：组蛋白三号亚基27位赖氨酸三甲基化。

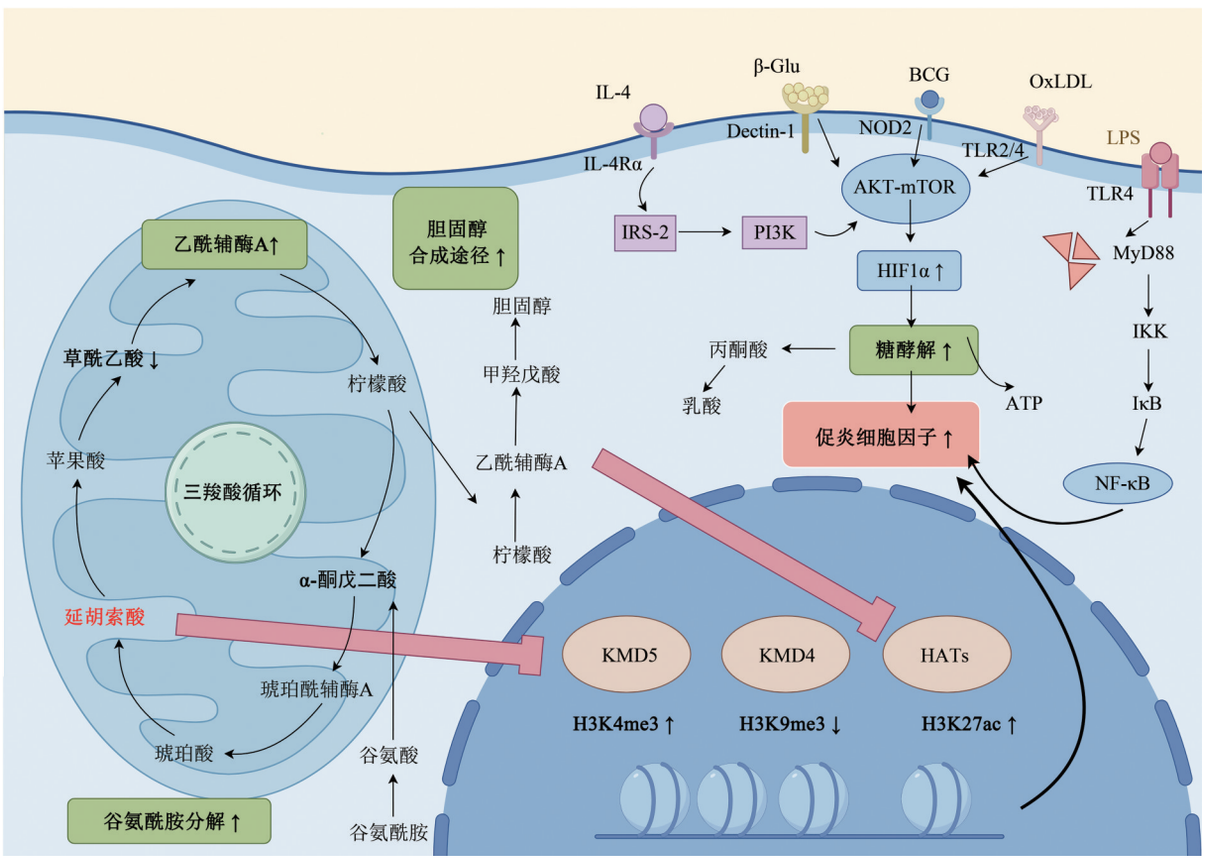

Fig. 1　Trained immunity−related signaling pathways and molecular mechanisms (created with Figdraw)

图1　训练免疫相关信号通路及分子机制（使用Figdraw制作）

训练免疫的长期保护作用依赖于细胞内的代谢变化和表观遗传重编程，从而促进促炎基因的表达和细胞因子的分泌。BCG：卡介苗；β-Glu：β-葡聚糖；OxLDL：氧化型低密度脂蛋白；LPS：脂多糖；Dectin-1：树突状细胞相关C型凝集素受体1；AKT-mTOR：蛋白激酶B-雷帕霉素靶蛋白；HIF1α：缺氧诱导因子1亚基α；IL-4：白介素-4；TLR2/4：Toll样受体2/4；IRS-2：胰岛素受体底物；PI3K：磷脂酰肌醇激酶；MyD88：髓样分化因子88；IκK：κB抑制因子激酶；IL-4Rα：白介素-4R亚基α；IκB：核因子κB抑制蛋白；NF-κB：核因子κB；KMD5：组蛋白去甲基化酶5；KMD4：组蛋白去甲基化酶4；HATs：组蛋白去乙酰化酶；H3K4me3：组蛋白三号亚基4位赖氨酸三甲基化；H3K9me3：组蛋白三号亚基9位赖氨酸三甲基化；H3K27ac：组蛋白三号亚基27位赖氨酸乙酰化。

5 免疫训练与疾病

训练免疫与多种病理状态有关，既是疾病恢复的关键决定因素，也是疾病进展的驱动因素。在大多数动物中，经过训练的免疫很可能进化为一种原始的免疫记忆形式，更有效地保护宿主免受再次感染。但是，在部分疾病中训练免疫却可能具有致病作用。

5.1 肿瘤

大量研究表明，先天免疫细胞的训练免疫具有抗肿瘤作用[50, 95-97]。Chen等[98]通过改造灭活的大肠杆菌，使其负载肿瘤抗原和β-Glu，制备出癌症疫苗。皮下注射该疫苗可在注射部位高度积累，并通过巨噬细胞吞噬疫苗诱导巨噬细胞产生训练免疫[98]。经训练的巨噬细胞可招募树突状细胞，进一步促进疫苗的吞噬作用和树突状细胞的成熟，激活T细胞。此外，该疫苗还可显著增加循环中的经训练的单核细胞/巨噬细胞数量，促进其在肿瘤组织中分化为M1样巨噬细胞，发挥抗肿瘤作用[98]。Ding等[95]发现，经β-葡聚糖颗粒（WGP）训练的巨噬细胞不仅对LPS的反应性增强，且对肿瘤来源因子的反应性也增强。WGP能在人单核细胞中诱导训练免疫，产生抗肿瘤活性[95]。流感病毒感染也可训练肺泡巨噬细胞，使其在面对肿瘤细胞时具有更强的吞噬和杀伤能力，且这种训练效果具有长期性和组织特异性[50]。在非小细胞肺癌患者体内，具有训练免疫特征的肺泡巨噬细胞与抗肿瘤免疫微环境相关[99]。因此，先天性训练免疫无论是作为单一疗法还是作为辅助疗法，已被认为是一种新的预防性或治疗性抗癌策略。

5.2 感染

训练免疫的治疗性调节可增强感染急性期的保护性免疫反应，阻止感染性疾病的发展。Gu等[100]研究发现，灭活的鲍曼不动杆菌鼻内给药可训练肺泡巨噬细胞。*Rag1*缺陷小鼠在接种灭活的鲍曼不动杆菌全细胞疫苗几天后再接收二次刺激时，体内TLR4和TNF-α的表达增加[100]。对于其他抗生素耐药的革兰氏阴性菌，免疫训练也具有抗再感染的作用[100-101]。此外，训练免疫还可通过增强RIG-I样受体（RLRs）的活性，提高宿主细胞对病毒RNA的识别能力，增强细胞的抗病毒作用[102-103]，通过提高TNF-α和IL-17等抗真菌细胞因子的产生，增强巨噬细胞对真菌孢子的吞噬和杀伤能力[11, 23]，通过增强宿主对寄生虫抗原的免疫应答，提高特异性抗体的产生，增强细胞毒性T细胞的活性[104-105]。训练免疫的这些作用通常不依赖于特定的病原体识别，而是通过增强先天免疫细胞的一般性反应能力，提高宿主对多种病原体的防御能力，从而在一定程度上减少感染的严重性和持续时间。然而，训练免疫的具体机制因病原体类型和宿主的免疫状态而异，并且受到多种因素的影响。

5.3 免疫麻痹

免疫麻痹（immunological paralysis）是创伤、败血症或其他严重损伤引起的代偿性和持续性抗炎反应，其特征为在脓毒症等损伤后出现持续的先天性抗炎免疫反应[106]，使患者处于复发和继发感染的高风险中，经常导致器官功能障碍和死亡[107]。在髓系细胞中，IL-4可抑制急性炎症[108]，诱导训练免疫。Schrijver等[30]开发的一种载脂蛋白A1和IL-4融合蛋白纳米颗粒，在小鼠和非人灵长类动物中可直接靶向富含髓样细胞的造血器官，特别是脾脏和骨髓，缓解LPS诱导的小鼠免疫麻痹。

5.4 自身免疫性疾病

自身免疫性疾病是一组以免疫紊乱为特征的疾病[109]，病患者的单核细胞通过mTOR信号改变细胞代谢和表观遗传修饰，诱导细胞因子的大量产生，从而表现出被训练的特征[78]。

系统性红斑狼疮（systemic lupus erythematosus，SLE）是一种自身免疫疾病[110-112]，累及全身多个器官，其主要特征是免疫系统错误地针对自身组织产生自身抗体，促进促炎因子的分泌和免疫细胞积累[113-114]。有报道称，在SLE患者体内，促炎因子的表达增加与训练免疫中高表达的细胞因子相似，包括IL-6、TNF-α和IL-1β[115]。在*Il-1β*缺陷小鼠体内诱导SLE，小鼠表现出较轻的疾病症状，而IL-1β的表达与小鼠疾病的严重程度呈正相关[116]。SLE患者可能因IL-1β和其他促炎细胞因子的分泌而引起不利影响，且疾病本身可能会诱导患者先天免疫系统的训练。SLE患者体内的髓系细胞及其骨髓祖细胞表现出训练免疫的特征，持续促进炎症状态，促进疾病进展[117]。β-Glu诱导的刺激能激活细胞内mTOR通路，进一步促进患者SLE的发展[12]。

类风湿性关节炎（rheumatoid arthritis，RA）是一种累及关节的炎症性疾病[96]，其炎症由免疫细胞浸润关节滑膜引起[118]，并伴随着促炎细胞因子的分泌。这些细胞因子进一步诱导NF-κB受体激动剂、前列腺素和金属蛋白酶等高表达，促进损

伤。通常通过注射II型胶原蛋白（CII）和弗氏完全佐剂（FCA）诱导小鼠关节炎（CIA）模型，在Hida等[119-121]的研究中，使用β-Glu代替FCA，在小鼠体内注射β-Glu的OX-CA和CII混悬液，发现β-Glu可诱发RA，表明经训练的先天免疫细胞可能会促进RA的进程。

5.5　神经退行性疾病

阿尔茨海默病（Alzheimer's disease，AD）是一种常见的神经退行性疾病[122]，其主要特征包括：β淀粉样蛋白（Aβ）的胞外聚集、过度磷酸化微管相关蛋白组成的细胞内神经原纤维缠结（NFT）[123]及Aβ斑块被激活的神经胶质细胞包围后持续的神经炎症反应[124]。AD小鼠模型中，外周炎症刺激可导致小鼠的小胶质细胞被长期训练，从而加剧中枢神经系统的β淀粉样变性[125]。作为表观遗传重编程的结果，小胶质细胞也显示出转录和蛋白质表达的变化。在炎症早期，AD小鼠的小胶质细胞功能受损，而全身炎症可进一步诱导小胶质细胞的重编程，导致大脑免疫系统的记忆特征潜在增强反应，造成Aβ诱导的突触损伤和认知障碍，其中的机制与训练免疫不谋而合[126]。以上研究表明，全身炎症可诱导小胶质细胞重编程，导致大脑免疫系统的潜在高反应“训练”状态。

5.6　心血管疾病

训练免疫易促进心血管疾病的发展[127]。研究表明[128]，动脉粥样硬化会导致单核细胞/巨噬细胞处于持续性低炎性病理状态。这种状态下，当单核细胞/巨噬细胞被再次触发炎症反应时，会进一步促进疾病的发生发展[128]。Niels等[129]研究表明，在动脉粥样硬化易感小鼠中，通过高脂饮食诱导训练免疫导致骨髓中前体细胞和分化的单核细胞及巨噬细胞发生持久性的功能、转录和表观遗传重编程，这种重编程依赖于NOD样受体蛋白3（NLRP3）的激活。这表明，特定的饮食模式可以在小鼠体内诱导训练免疫，从而影响动脉粥样硬化的发展。在体外采用低浓度oxLDL预处理单核细胞，随后用TLR4/TLR2激动剂进行二次刺激，细胞中促动脉粥样硬化相关因子表达升高[130]。采用组蛋白甲基转移酶抑制剂甲硫腺苷预处理单核细胞后，oxLDL诱导的单核细胞训练失败[130]。不健康饮食以及炎症性疾病[129]也可在骨髓造血干细胞中激活类似训练免疫的机制。

5.7　杜氏肌营养不良症

杜氏肌营养不良症（Duchenne muscular dystrophy，DMD）是由编码抗肌萎缩蛋白的X染色体上的DMD基因突变引起的[131]，在缺乏抗肌萎缩蛋白后，肌肉纤维遭受重复性损伤，导致它们被纤维化和脂肪组织取代。DMD动物模型（mdx小鼠）的巨噬细胞H3K27me3的抑制性组蛋白标记减少，同时mdx小鼠中的整体TLR4缺乏会减少营养不良肌肉中促炎性单核/巨噬细胞的数量以及其他萎缩性肌肉的病理特征[132]。以上研究均表明，DMD动物模型的巨噬细胞表现出训练免疫的特征[133-134]，先天免疫系统的“记忆”，这种记忆反映在表观遗传变化和骨髓移植传递给健康非营养不良小鼠的持久性传递上[135]。通过靶向训练免疫，可能同时实现抑制有害炎症和防止抗炎反应过度“超调”的双重能力，这可能是理想的DMD免疫治疗方法。

5.8　器官移植

器官移植中，固有免疫系统在移植初期对非自身识别和移植物排斥反应起关键作用[136]，而巨噬细胞为此过程中发挥作用的主要细胞[137]。巨噬细胞可以根据环境中的信号（如细胞因子）采取特定的表型和功能程序（M1/M2极化）[43]。心脏移植小鼠模型[43，138]表明，巨噬细胞极化决定免疫反应结果，M1型巨噬细胞与器官排斥有关，而M2型巨噬细胞则与耐受诱导相关。训练免疫可以通过特定的模式识别受体（PRR）激活，导致巨噬细胞在遇到特定信号（如感染、oxLDL）时产生更强的免疫反应。训练免疫激活的巨噬细胞能够分泌更多的促炎细胞因子（如IL-6和TNF-α）。器官移植小鼠模型表明[139]，内源性刺激可以激活移植物浸润的单核细胞来源的细胞，并在同种异体移植物排斥反应期间导致细胞因子产生增加[140]。在使用mTOR高密度脂蛋白（HDL）纳米颗粒后，$CD8^+$T细胞介导的免疫被阻止，同时促进$CD4^+$调节性T细胞扩增，从而提高了同种异体移植物存活率[140]。因此，抑制训练免疫是预防器官排斥的新治疗选择。器官移植诱导巨噬细胞训练有助于降低同种异体移植物排斥反应。

6　展　　望

先天免疫系统在产生异源效应方面起着至关重要的作用，训练免疫是一种非特异性免疫记忆，由

骨髓或长寿命组织免疫祖细胞的表观遗传重编程介导，是先天免疫细胞长期功能编程的过程，是针对感染的进化保护过程，它也可能参与许多生理过程，包括诱导有效的抗肿瘤免疫反应和促进组织再生等。虽然过去的研究已了解部分先天免疫记忆，但训练免疫的分子机制和治疗潜力仍有待更多的新发现。目前，关于训练免疫所赋予机体非特异性保护过程中发生的细胞内代谢和表观遗传变化的潜在分子机制仍缺乏关键细节研究，包括这些修饰可以持续多久以及这种修饰是如何传递给子细胞等。有必要进一步研究初始刺激后发生的DNA甲基化和组蛋白修饰之间的相互作用，以阐明它们在调节训练免疫中的作用。进一步的研究还需要着眼于了解先天免疫记忆特征的跨代传递。先天免疫细胞的表观遗传和代谢重编程发生在生命早期[40, 74]，有助于过敏或自身免疫性疾病的发展。在无脊椎动物中观察到的训练免疫可以跨代遗传[141-142]，小鼠经过训练免疫后通过细胞、发育、转录和表观遗传重编程实现的非特异性再感染保护可以传递给后代[143]，表明不改变DNA序列的修饰更可能遗传。接下来应研究类似的过程是否发生在人类中，进一步研究训练免疫的跨代转移对全面了解以先天性免疫反应长期重编程为特征的疾病至关重要。

训练免疫的诱导是针对感染的进化保护过程，从进化的角度看免疫记忆是有利的。如BCG对COVID-19提供的保护作用，又如训练免疫提高寄生虫疫苗的保护率。训练免疫针对一系列病原微生物诱导了更广泛有效的免疫反应，因此了解参与激活训练免疫的途径和分子有助于开发针对传染病的潜在疫苗。传统疫苗旨在诱导抗原特异性适应性免疫反应，而基于训练免疫设计新型疫苗具有挑战性，了解训练免疫的分子和细胞过程中涉及的通路/网络的相互关联性，包括表观遗传修饰、代谢重编程和免疫反应，对于实现持久的免疫保护至关重要。虽然训练免疫细胞诱导的增强性炎症反应可以增强对感染性疾病或肿瘤的保护，但训练免疫并不总是具有保护作用，在某些情况下是病理性的，失调的训练免疫有助于炎症和自身免疫性疾病的发展。训练免疫提供了一种免疫记忆形式，当这种记忆被不适当激活时，可能导致对自身组织的攻击，引起自身炎症。在类风湿关节炎等自身免疫性疾病中，训练免疫可能导致关节炎症和组织损伤。在AD和帕金森病等疾病中，训练免疫可能导致微胶质细胞的过度激活，引发神经炎症。又比如肿瘤坏死因子在巨噬细胞中诱导促哮喘的先天免疫记忆。因此，未来研究应着眼于抑制促进训练免疫的机制来改善与训练免疫相关的慢性炎症和组织损伤。

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Role of Innate Trained Immunity in Diseases*

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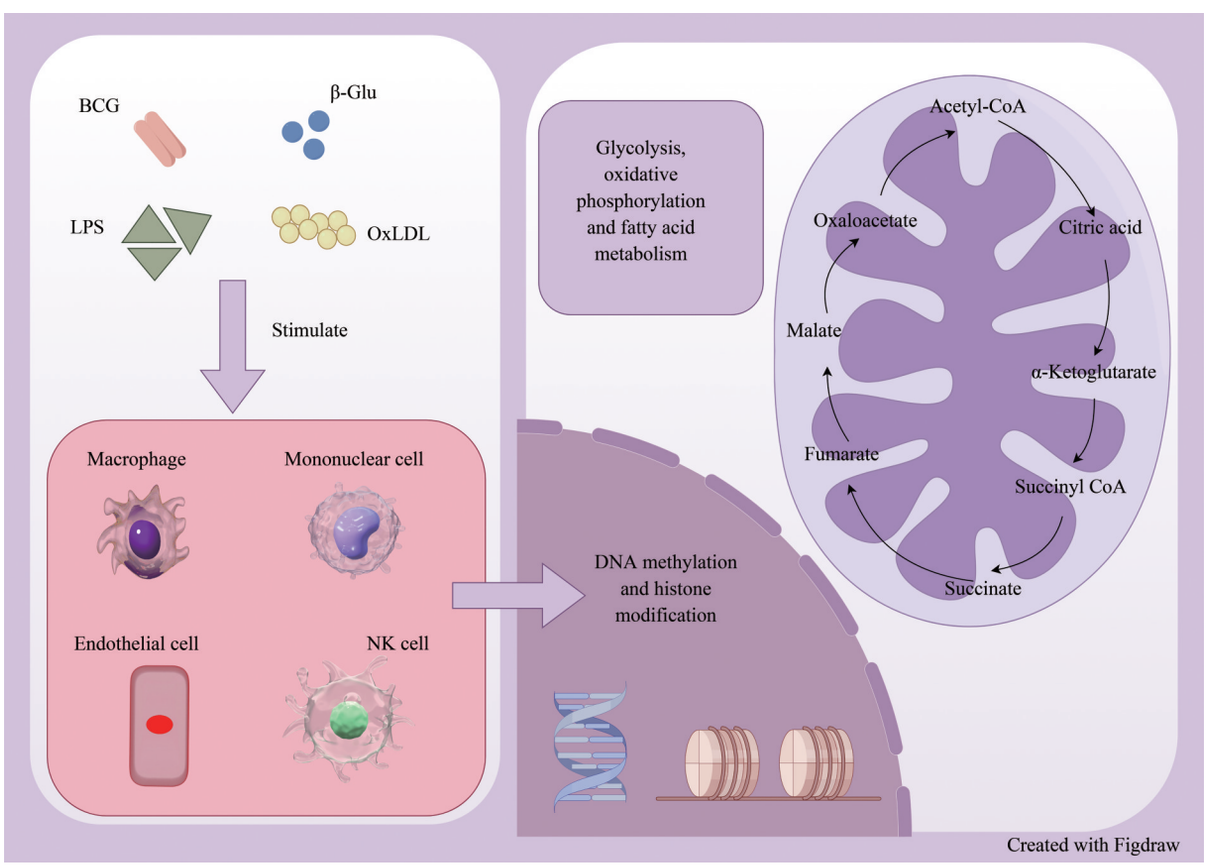
Graphical abstract



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Abstract The innate immune system can be boosted in response to subsequent triggers by pre-exposure to microbes or microbial products, known as “trained immunity”. Compared to classical immune memory, innate trained immunity has several different features. Firstly, the molecules involved in trained immunity differ from those involved in classical immune memory. Innate trained immunity mainly involves innate immune cells (*e.g.*, myeloid immune cells, natural killer cells, innate lymphoid cells) and their effector molecules (*e. g*., pattern recognition receptor (PRR), various cytokines), as well as some kinds of non-immune cells (*e.g*., microglial cells). Secondly, the increased responsiveness to secondary stimuli during innate trained immunity is not specific to a particular pathogen, but influences epigenetic reprogramming in the cell through signaling pathways, leading to the sustained changes in genes transcriptional process, which ultimately affects cellular physiology without permanent genetic changes (*e. g*., mutations or recombination). Finally, innate trained immunity relies on an altered functional state of innate immune cells that could persist for weeks to months after initial stimulus removal. An appropriate inducer could induce trained immunity in innate lymphocytes, such as exogenous stimulants (including vaccines) and endogenous stimulants, which was firstly discovered in bone marrow derived immune cells. However, mature bone marrow derived immune cells are short-lived cells, that may not be able to transmit memory phenotypes to their offspring and provide long-term protection. Therefore, trained immunity is more likely to be relied on long-lived cells, such as epithelial stem cells, mesenchymal stromal cells and non-immune cells such as fibroblasts. Epigenetic reprogramming is one of the key molecular mechanisms that induces trained immunity, including DNA modifications, non-coding RNAs, histone modifications and chromatin remodeling. In addition to epigenetic reprogramming, different cellular metabolic pathways are involved in the regulation of innate trained immunity, including aerobic glycolysis, glutamine catabolism, cholesterol metabolism and fatty acid synthesis, through a series of intracellular cascade responses triggered by the recognition of PRR specific ligands. In the view of evolutionary, trained immunity is beneficial in enhancing protection against secondary infections with an induction in the evolutionary protective process against infections. Therefore, innate trained immunity plays an important role in therapy against diseases such as tumors and infections, which has signature therapeutic effects in these diseases. In organ transplantation, trained immunity has been associated with acute rejection, which prolongs the survival of allografts. However, trained immunity is not always protective but pathological in some cases, and dysregulated trained immunity contributes to the development of inflammatory and autoimmune diseases. Trained immunity provides a novel form of immune memory, but when inappropriately activated, may lead to an attack on tissues, causing autoinflammation. In autoimmune diseases such as rheumatoid arthritis and atherosclerosis, trained immunity may lead to enhance inflammation and tissue lesion in diseased regions. In Alzheimer’s disease and Parkinson’s disease, trained immunity may lead to over-activation of microglial cells, triggering neuroinflammation even nerve injury. This paper summarizes the basis and mechanisms of innate trained immunity, including the different cell types involved, the impacts on diseases and the effects as a therapeutic strategy to provide novel ideas for different diseases.

Key words trained immunity, innate immune system, epigenetics, immunometabolism
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