动物营养学报 2020,32(4):1508-1515
Chinese Journal of Animal Nutrition

doi:10.3969/j.issn.1006-267x.2020.04.006

乳铁蛋白生物学功能研究进展

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摘　要: 乳铁蛋白(LF)是一种由外分泌腺和中性粒细胞分泌的多功能阳离子糖蛋白,广泛存在于大部分生物体液中,具有调节机体的铁代谢、增强机体的抗菌抗病毒能力、调节机体免疫力等多种功能。乳铁蛋白主要通过3种方式发挥其生物学功能:1)与铁紧密结合发挥营养免疫功能;2)与革兰氏阴性菌细胞壁外壁的脂多糖(LPS)结合进而使细菌溶解发挥杀菌作用;3)作用于免疫因子和各种免疫细胞以发挥其免疫调节作用。为了进一步挖掘乳铁蛋白的功能、促进其产品开发及其在食品与饲料工业中的应用,本文对乳铁蛋白的生物学功能进行了综述。

关键词: 乳铁蛋白;抗微生物作用;免疫调节作用

中图分类号:S816.7　　**文献标识码:**A　　**文章编号:**1006-267X(2020)04-1508-08

乳铁蛋白(LF)于1939年首次在牛奶中发现,是哺乳动物中普遍存在的糖蛋白[1]。它的分子质量为70~80 ku,大约由700个氨基酸组成[1]。乳铁蛋白主要由哺乳动物黏膜上皮细胞合成和分泌[2],广泛存在于牛奶、消化道、泪液等大部分生物体液中[3],血液中的乳铁蛋白主要来源于中性粒细胞,骨髓和子宫内膜也可分泌少量乳铁蛋白[4-6]。正常情况下,血液中性粒细胞的含量为0.4 mg/L,但在炎症情况下,其含量是正常情况的5 000倍[7]。人初乳中乳铁蛋白含量最高(7 g/L),其次是人常乳和牛奶[8-9]。商用乳铁蛋白主要包括牛乳铁蛋白(bLF)、人乳铁蛋白和重组乳铁蛋白,机体主要通过口服、注射等方式摄入。

乳铁蛋白有2种状态,即铁饱和状态的乳铁蛋白(Fe-LF)与无铁状态的乳铁蛋白(Apo-LF)[10]。天然bLF铁饱和度为15%~20%,而Fe-LF铁饱和度约为90%,Apo-LF铁饱和度<5%[11-12]。与Apo-LF相比,Fe-LF具有结构稳定、抗蛋白水解能力强、对机体肠道消化抵抗力高等优点。因此,它在肠道内不易降解,可以以完整分子的形式被吸收[12-13]。乳铁蛋白是转铁蛋白家族中铁结合能力最强的蛋白质,其对铁的亲和力是转铁蛋白的260倍,在pH中性条件下与铁结合能力最强[14]。它的结构由2个与α螺旋连接的对称结构域(N叶和C叶)组成,每个结构域可以高亲和力地、可逆地结合1个铁离子[10]。铁离子可与乳铁蛋白的4个氨基酸残基(2个酪氨酸、1个天冬氨酸、1个组氨酸)共价连接。在乳铁蛋白与铁离子结合前,球蛋白结构可以随意拉伸,铁离子与乳铁蛋白结合后,乳铁蛋白构象发生改变,即乳铁蛋白的分子结构更加致密。铁离子进入结构域的开放间隙内部,然后该区域相应地关闭[15]。除铁离子外,每个结构域还能结合铜离子(Cu^{2+})、锌离子(Zn^{2+})、锰离子(Mn^{2+})[16]。目前检测乳铁蛋白的分析方法主要包括理化分析、免疫分析、生物电化学和表面等离子体共振等[17-18]。

1　乳铁蛋白的抗微生物作用

乳铁蛋白有3种同分异构体(α、β和γ),所有这些都有相同的物理、化学和抗原性质[19-20],具有调节机体的铁代谢、增强机体的抗菌抗病毒能力、促进机体免疫力等多种生物学功能[21-22]。乳

收稿日期:2019-10-13

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铁蛋白的三维结构在抗病原微生物和促进宿主防御过程中起着至关重要的作用[23],从而保护宿主免受病原微生物(细菌、病毒、真菌)的侵害。

1.1　乳铁蛋白的抗细菌作用

铁是生物体不可缺少的微量元素,参与许多重要的生命活动,细菌也需要适量的铁来生长。乳铁蛋白具有较高的铁结合能力,能竞争病原微生物的铁源,抵御病原微生物的侵袭,保护机体免受损伤[24]。此外,它是转铁蛋白家族中唯一不受环境酸碱度影响的蛋白质,始终保持高铁结合活性,具有抗水解能力。在感染过程中,乳铁蛋白迅速降低了微生物对铁的生物利用度,不饱和乳铁蛋白对铁有很强的亲和力,可以固定铁,使其不被缺铁微生物带走[25]。吞噬性粒细胞在炎症部位释放大量乳铁蛋白与铁结合,清除了受感染病原菌的细胞铁,局部抑制了细菌的生长。

同时,乳铁蛋白具有阳性的氨基酸基团,可通过其与革兰氏阴性菌表面的脂多糖(阳离子区)相互作用,进而破坏革兰氏阴性菌细胞膜的通透性。通过此机理,乳铁蛋白可直接作用于某些致病微生物上,起到裂解细菌杀菌的作用[26-28]。研究表明,乳铁蛋白会破坏肠道革兰氏阳性和革兰氏阴性致病菌,减少其入侵肠道上皮和黏膜,并调节小肠细胞的生长。同时促进双歧杆菌和乳酸菌的增殖,且保护肠道的有益菌[29]。此外,乳铁蛋白在炎症部位也具有抗氧化作用。乳铁蛋白能清除损伤部位的组织,释放出铁离子和二价铁离子,降低自由基的生成[30],减轻生物体的氧化应激[31]。

解伟纯等[32]的研究已证实,在断奶仔猪中,表达猪乳铁蛋白肽的重组屎肠球菌对其生长性能有极显著改善作用,且起到了抗产肠毒素大肠杆菌(ETEC)感染的保护作用。在婴幼儿腹泻研究中发现,肠道内乳铁蛋白可以通过促进益生菌生长、免疫调节作用和抗炎作用对其起到缓解效果[33]。

1.2　乳铁蛋白的抗真菌作用

真菌感染是世界上导致死亡的主要原因之一,早期研究表明,抗菌肽具有广泛的抗真菌作用[34]。乳铁蛋白可以水解得到乳铁素,为抗菌肽之一。与乳铁蛋白的抗细菌作用机理不同,乳铁蛋白的抗真菌作用机理不是与真菌竞争铁源,而是其 N-末端抗真菌活性。一方面,乳铁蛋白直接作用于真菌,通过 N-末端对其进行杀灭;另一方面,乳铁素通过增加宿主血液中干扰素(IFN)-γ 的水平进行抗菌作用[35]。再者,乳铁素与抗真菌药物具有协同作用。在 Velliyagounder 等[36]的研究中发现,在抗生素中添加人乳铁蛋白(hLF)具有较好的抗真菌效果。且在 Tanida 等[37-38]的研究中发现,铁调素通过促进假丝酵母细胞中 ATP 的流出以及降低药物的流失,增强了抗真菌药物的杀菌活性。

1.3　乳铁蛋白的抗病毒作用

乳铁蛋白在某些病毒感染的早期阶段具有抗病毒作用。乳铁蛋白通过阻断细胞受体或病毒颗粒的组合来防止病毒直接进入宿主细胞,如巨细胞病毒(CMV)、单纯疱疹病毒(HSV)、人类免疫缺陷病毒(HIV)和丙型肝炎病毒(HCV)[39]。然而,在最近的研究中,已发现乳铁蛋白不仅在病毒与细胞表面相互作用的早期阶段起抗病毒作用,而且也在一些病毒的细胞中起抗病毒作用。乳铁蛋白通过干扰病毒的复制来抑制病毒的活性。体外研究表明,在人血浆和牛奶中,乳铁蛋白通过抑制宿主细胞中的病毒复制,从而抑制艾滋病(AIDS)病毒活性[40]。主要表现在抑制逆转录酶活性[41]与抗原的表达[42]。如乙型肝炎病毒(HBV)、副流感病毒(PIV)和人类免疫缺陷病毒(HIV)[43]。

此外,有研究表明,服用乳铁蛋白能增强腺瘤性结直肠息肉患者自然杀伤(NK)细胞活性[44],增加小鼠 NK 细胞的数量[45]。口服乳铁蛋白诱导小鼠巨噬细胞和 B 淋巴细胞中 *IFN-α/β* 的表达,干扰宿主细胞中的病毒复制[45-46]。在小鼠皮肤感染 HSV-1 后,乳铁蛋白可以预防体重减轻并增加辅助性 T(Th)细胞 1 细胞因子的产生,包括 IFN-γ、白细胞介素(IL)-12 和 IL-18。这些细胞因子的产生可能有助于宿主抵抗 HSV-1。由此说明,乳铁蛋白还可以通过作用于机体的免疫细胞,如 NK 细胞、巨噬细胞、B 淋巴细胞和 Th 细胞,发挥免疫调节作用,增强机体的抗病毒能力。

综上,乳铁蛋白的抗微生物作用可见一斑。然而乳铁蛋白的抗微生物作用不是百发百中,最新关于早产儿迟发型感染的临床试验结果发现,极早产儿肠内补充 bLF 不能降低迟发感染风险及其相关的其他疾病的发病或死亡风险[47]。再有,口服重组人乳铁蛋白(rhLF)对 HIV 感染者虽然是安全的,但其对血浆 IL-6 含量、单核细胞和 T 细胞的活化、肠黏膜完整性及肠道菌群多样性的影响

并不显著[48]。这充分说明乳铁蛋白不是对于所有的疾病均有抗炎作用,在很多方面,将乳铁蛋白运用到实际生产中需要进一步的探究。

2 乳铁蛋白的免疫调节作用

随着研究的深入,越来越多的研究证实了乳铁蛋白的免疫调节功能。在免疫系统中,乳铁蛋白主要作用于免疫细胞和细胞因子,发挥免疫调节作用[49]。

乳铁蛋白受体(LFRs)存在于免疫细胞表面,如 T 细胞、B 细胞、NK 细胞、巨噬细胞和树突状细胞[50-51]。乳铁蛋白一方面通过刺激未成熟的 B 淋巴细胞促进抗原特异性 T 细胞的增殖,增强 B 细胞的抗原表达能力[52];另一方面通过作用于 T 淋巴细胞的成熟过程诱导 $CD4^+$表达,进一步将未成熟 T 淋巴细胞分化为 $CD4^+$ T 淋巴细胞亚群,从而调节 T 淋巴细胞的功能[53]。Artym 等[54]研究表明,采用 rhLF vin-120 治肠炎小鼠,体内调节 T 细胞的数量增加,激活调节性 T 细胞(Tregs)分泌 IL-17 缓解炎症;在同一项研究中,他们还在体外进行了 rhLF 对 $CD4^+$细胞的作用的检测,进一步证实了 rhLF 诱导 $CD4^+$ T 细胞分化为 Tregs,导致 Tregs 数量升高[54]。乳铁蛋白通过促进 $CD4^+$ T 淋巴细胞分化成 Th1,改变 Th1 和 Th2 之间的平衡,减少炎症因子的释放[55]。除此之外,乳铁蛋白使中性粒细胞在炎症部位积聚,促进细胞与细胞相互作用,并激活多核白细胞(PMN)和巨噬细胞的吞噬作用,以增强 NK 细胞的活性。研究表明,Apo-LF 储存在嗜中性粒细胞的细胞质二级颗粒中,在炎症期间,乳铁蛋白被释放并且其在炎症部位的浓度从 0.4~2.0 μg/mL 增加至 200 μg/mL,其在炎症反应的反馈机制中起主要作用[56]。

细胞因子在乳铁蛋白的免疫调节过程中承担着重要的角色。口服乳铁蛋白可以促进肠上皮中 IL-18 的产生,NK 细胞表达 IL-18 受体,IL-18 与其受体的结合直接增强 NK 细胞对肿瘤和病毒感染细胞的杀伤活性[57]。乳铁蛋白促进巨噬细胞中 IL-12 的合成,IL-12 是一种主要由巨噬细胞分泌的细胞因子[58-59],可以引导巨噬细胞迁移到炎症部位,激活 $CD4^+$ T 淋巴细胞[60]。而乳铁蛋白诱导树突状细胞成熟后,一方面,成熟的树突状细胞可增强 IL-8 和趋化因子配体 10(CXCL10)的释放,降低 IL-6、IL-10 和趋化因子配体 20(CXCL20)的生成[61];另一方面,成熟的树突状细胞可以诱导 T 细胞分化,增强 T 细胞的活性[62-63]。

动物试验表明,口服 bLF 增加了和仔猪体内的细胞因子[IL-10、IFN-γ、肿瘤坏死因子(TNF)-α 和 IL-6]含量,降低了仔猪的死亡率。TNF-α 和 IL-6 数量的增加意味着机体正在进行强烈的先天免疫反应,而 IFN-γ 数量的增加意味着给仔猪饲喂乳铁蛋白这一举措在 Th1 介导的适应性免疫反应中起重要作用[64]。经口服途径的乳铁蛋白可能通过 2 种可能的机制影响细胞因子的分泌。一种可能的机制是完整的 bLF 通过胃肠道被吸收到血液中,这可能通过受体介导的机制或间接的乳铁蛋白吸收对组织驻留细胞产生直接影响。这一机制已经在体外研究中得到证实,采用猪肠外植体观察到了固有层 T 细胞对乳铁蛋白的非特异性摄取[65]。另一种可能的机制是乳铁蛋白通过影响肠道中的淋巴细胞,使淋巴系统通过淋巴循环迁移到肠系膜淋巴结,并最终迁移到脾脏[66-67]。

3 乳铁蛋白的抗肿瘤作用

铁在许多细胞代谢过程中都是必不可少的,因此高铁水平在肿瘤微环境中是必不可少的[68],它促进细胞生长、增殖和血管生成。Apo-LF 因结合游离铁离子的能力和作为铁螯合剂的作用而具有增强的抗癌特性[69-70],竞争肿瘤细胞的铁源,发挥抗肿瘤作用。铁饱和状态的牛乳铁蛋白(FebLF)可以恢复化疗后的红细胞和白细胞[71],增加肿瘤对化疗药物的敏感性[72]。此外,有研究发现,乳铁蛋白在正常乳腺细胞中无细胞毒性,但在细胞癌化之后,其抑制癌细胞的迁移和侵袭能力,且通过增加凋亡蛋白抑制剂的表达,在凋亡过程中激活半胱天冬酶,诱导癌细胞凋亡[73-74]。

综上,乳铁蛋白抗肿瘤作用主要可能通过 2 种方式实现:其一,Apo-LF 与癌细胞争夺铁源进而抑制癌细胞的正常代谢;其二,乳铁蛋白保护凋亡蛋白的正常表达进而诱导癌细胞凋亡。

4 小 结

乳铁蛋白是通过自然选择形成的,在对抗感染的过程中发挥着多种重要的生物学功能。乳铁蛋白的抗病原微生物作用、免疫调节和防御功能及抗癌功能是近年来研究的热点,但乳铁蛋白的

免疫调节功能和抗癌功能是否与铁代谢直接有关尚不清楚,且其对于具体疾病的作用机制尚不完全清楚,需进一步深入研究。深入解析乳铁蛋白的作用机制对铁代谢相关疾病治疗与防控具有非常重要的实践意义。

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Research Progress on Biological Function of Lactoferrin

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Abstract: Lactoferrin (LF) is an multifunctional cationic glycoprotein which secreted by exocrine glandular and neutrophils, and widely distributed in most biological fluids. It has multiple functions, such as regulating of host iron metabolism, improving of host defenses in antibacterial and antivirals, and enhancing the host immunity function. Lactoferrin exerts its biological functions mainly in three ways: 1) close binding to the iron to play the role of nutrition and immunity; 2) binding to the lipopolysaccharide (LPS) of Gram-negative bacteria cytoderm, then make the bacteria dissolve and play an bactericidal role; 3) acting on immune factors and various immune cells and play a immunomodulatory role. This paper reviews the studies of lactoferrin and its biological functions in recent years, would help to better understand the function of lactoferrin, develop of related products and apply in area of food and feed industries. [***Chinese Journal of Animal Nutrition***, **2020**, **32**(**4**): **1508-1515**]

Key words: lactoferrin; antimicrobial activity; immunoregulat ion

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