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专论与综述

食品加工过程中丝状形态食源性致病菌的形成及防控研究进展

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摘　要：食源性致病菌引起的食源性疾病已成为我国头号食品安全问题，对公众的健康产生了严重的威胁。在食品加工过程中，渗透压、温度和 pH 等不利环境的胁迫作用会诱导细菌的“抵抗机制”，引发细菌异常分裂、菌体丝状化伸长。丝状形态的食源性致病菌胁迫耐受性增强且在适宜条件下会迅速恢复分裂，使得细菌数量被严重低估，进而对食品安全造成重大影响。本文通过介绍细菌的丝状化诱导机制，为进一步控制食源性致病菌丝状化提供理论指导。

关键词：食源性致病菌；丝状化；异常分裂；食品安全

Formation and control of filamentous foodborne pathogens during food processing: a review

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Abstract: Foodborne diseases caused by foodborne pathogens have become the primary issue of food safety in China, posing serious threats to public health. During food processing, osmotic pressure, temperature, pH, and other unfavorable conditions can induce the protective responses of

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bacteria, leading to abnormal division and filamentous growth. The filamentation of foodborne pathogens enhanced the stress tolerance, enabling the pathogens to rapidly resume division under favorable conditions. It results in a significant underestimation of bacterial count and thus has an adverse impact on food safety. This article introduces the mechanism of inducing bacterial filamentation, aiming to provide theoretical guidance for controlling filamentous foodborne pathogens.
Keywords: foodborne pathogens; filamentation; abnormal division; food safety

据世界卫生组织估计，全球每年约有 6 亿人因食用受污染的食物而患病，约 42 万人死亡，其中多数由食品中致病微生物污染引起(https://www.who.int/news-room/fact-sheets/detail/food-safety)。根据 2010−2016 年中国家庭食源性疾病暴发事件流行特征分析，细菌性食物中毒事件所占比例最大，引起食源性疾病前 5 位的致病菌分别为沙门氏菌(59.2%)、副溶血性弧菌(18.4%)、金黄色葡萄球菌(7.4%)、变形杆菌(5.0%)和蜡样芽孢杆菌(4.7%)[1]。我国在 2006−2010 年共发生 2 023 起食源性疾病暴发事件，累计发病 62 920 人，死亡 967 人，其中因微生物引起的暴发事件数目和患者数目分别占 40.09%和 61.92%，以副溶血性弧菌、沙门氏菌等致病菌引起的微生物性食物中毒为主[2]。2010−2020 年全国共报告学校食源性疾病暴发事件 2 101 起，累计发病 44 510 例，住院 15 193 例，死亡 6 例，微生物性因素引起的暴发事件数最多，占已知病因暴发事件的 65.7% (678/1 032)[3]。以上数据表明，食源性致病菌已成为严重的公众健康威胁。

食源性致病菌一旦进入食品则很难去除，并且可以在食品上存活较长时间[4-7]。此外，食品加工过程中亚致死剂量的饥饿、极端 pH、高渗透压、低水分活度、低温、低氧和光照等胁迫条件均会导致细菌丝状化[8-9]。例如，单增李斯特菌接种在氯化钠(NaCl)含量为 1.35%和 2.35%的猪火腿上冷藏 2 个月后形成丝状形态[10]；沙门氏菌在 8 °C 的脱脂牛奶和鸡汤中储存 4 d 后，超过 70%的沙门氏菌发生丝状化[11]；模拟太阳光处理后，单增李斯特菌和大肠杆菌在储藏过程中均有丝状形态形成[12]。丝状形态是细菌对抗环境胁迫和保护其免受吞噬的生存策略之一(图 1)，丝

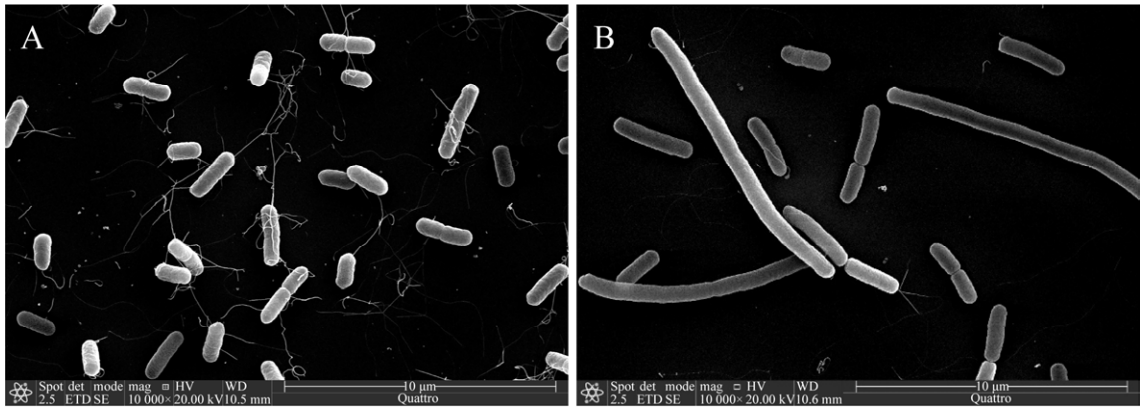

图 1 光动力处理下的大肠杆菌 O157:H7 的细胞形态变化[12] A：大肠杆菌 O157:H7 的正常形态细菌. B：模拟太阳光照射 30 min 后，37 ℃培养 12 h 的丝状形态细菌

Figure 1 Morphological changes of *Escherichia coli* O157:H7 after photodynamic treatment[12]. A: Normal morphology of *E. coli* O157:H7. B: Filamentous morphology of *E. coli* O157:H7 after simulated sunlight exposure for 30 min followed by incubation at 37 °C for 12 h.

状形态的形成还提高了细菌的耐药性，使得单一使用抗生素已难以达到灭菌效果[12-14]。例如，食品加工中的亚致死环境胁迫会影响沙门氏菌的耐药性，在低温或高温环境处理后，沙门氏菌对常见的6种抗生素的最低抑菌浓度增长了2−4倍[15]。同时丝状还有助于细菌黏附或定殖到生物或非生物表面，形成生物被膜[16]。细菌异常分裂后仍会继续生长并进行DNA复制，形成多核细胞，当外在应激条件消除时会快速分裂成多个细胞，从而造成食品中致病菌数量被严重低估[8]。本文对食品加工过程中丝状形态食源性致病菌的形成机制、危害性及控制思路进行阐述，以期为防控食品加工环节中的丝状形态致病菌提供指导。

1 细胞分裂调控机制

细菌丝状形态形成的根本原因是细胞分裂功能受损，无法进行正常分裂。细胞分裂是一个由多蛋白参与调控的复杂生物学过程，主要包括分裂部位的准确识别、Z环(Z-ring)的定位、内膜和细胞壁的协调收缩，这一过程需要复杂的蛋白质网络在空间和时间上协调细丝温度敏感蛋白Z (filamentous temperature-sensitive protein Z, Fts Z)的组装和活性[17]。FtsZ是细菌中一种含量丰富且结构稳定的蛋白质，在大多数原核生物和质体的胞质分裂中起关键作用，能在胞质分裂位点组装成Z环，并募集其他分裂蛋白形成一个跨越细胞膜的大型分裂体(divisome)[18-20]。

1.1 革兰氏阴性菌

革兰氏阴性菌的分裂调控机制研究主要以大肠杆菌为模型。在大肠杆菌中，分裂体上含有超过30种不同类型的蛋白质，其中12种是细菌分裂必需的，包括FtsZ、FtsA、ZipA、FtsE、FtsX、FtsK、FtsQ、FtsL、FtsB、FtsW、FtsI和FtsN，它们的缺失会导致细胞变成细长的丝状形态并最终死亡；其余的20多种蛋白质通常不是保守的，它们的缺失只会导致轻微的分裂缺陷[20-21]。如图2所示，大肠杆菌的分裂需要完成3个步骤：(1) Z环在细胞膜上的精确定位和组装：FtsZ通过FtsA和ZipA锚定在细胞膜上，从而形成Z环的初始复合物，并通过ZapA等提高稳定性[22-23]。(2) 募集大量分裂蛋白，形成分裂体：在原始环结构基础上，以FtsEX→FtsK→FtsBLQ→FtsW→FtsI→FtsN的线性顺序募集下游的保守分裂蛋白，形成功能性分裂体[17,21]。(3) 在分裂位点合成和重塑肽聚糖层，收缩并分裂成两个子细胞：FtsN的积累标志着所有必需蛋白的成功结合，即分裂体的更成熟形式——间隔环的形成[20,24]。大多数非必需蛋白随后开始加入组装，分裂体被激活，并在MreB的协同作用下由肽聚糖合成酶如PBP1a、PBP1b等合成隔膜肽聚糖[23-25]。新合成的肽聚糖被均匀插入Z环周围，使Z环逐渐向内收缩，最终形成新的细胞壁，完成细胞分裂[17,25]。

在正确的时间和位置进行Z环的定位对细胞分裂和遗传信息的完整传递至关重要，该过程主要由Min系统和类核闭塞(nucleoid occlusion, NO)系统控制，以防止Z环在除细胞中心以外的位置进行组装[26]。在大肠杆菌等革兰氏阴性菌的Min系统中，*minB*操纵子编码MinC、MinD和MinE三种基因产物，其中MinC作为真正的抑制子，与MinD互作充当细胞分裂的抑制剂，阻碍FtsZ发挥骨架作用，而MinE将这种抑制活性限制在细胞极，作为拓扑特异性因子起作用[27-28]。MinD是一种单体ATP酶，在Mg^{2+}存在时与膜磷脂相互作用，覆盖一个细胞极至细胞中心[29]。接着，膜结合的MinD将MinC募集到细胞质膜上并形成活性抑制剂复合物，从而抑制除细胞中部以外任何地方的Z环组装[26]。此后，MinE与MinC竞争MinD的结合位点，刺激MinD的ATP水解以驱动振荡，使MinD被释放到细胞质中，重新连接上ATP，在另一极组装[28-29](图3A)。

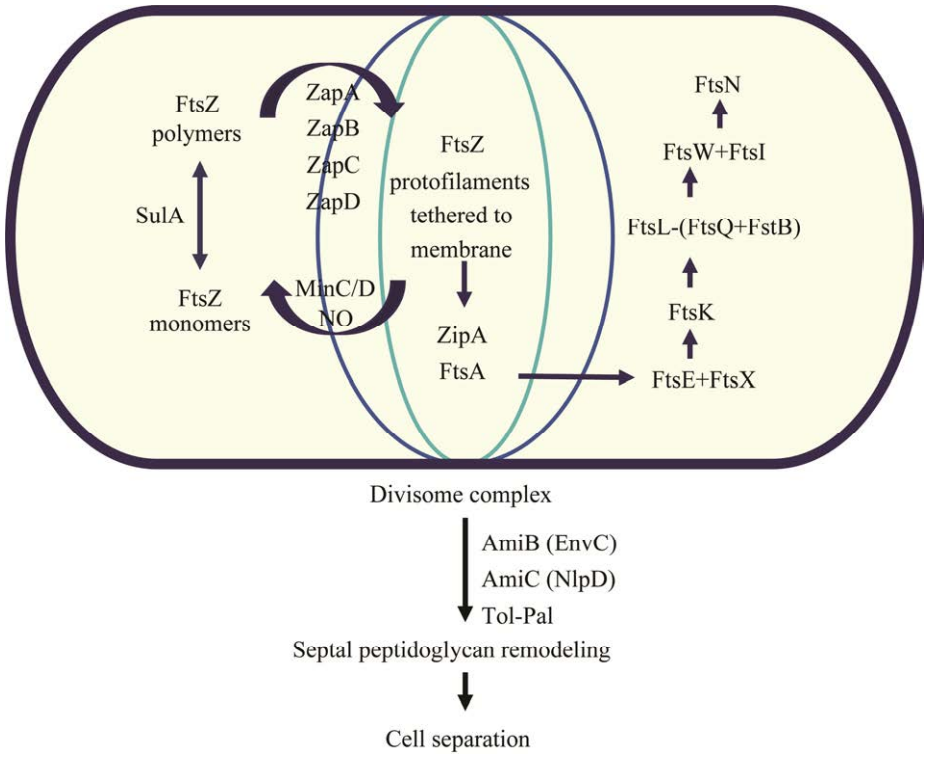

图 2　大肠杆菌细菌细胞分裂示意图　Z 丝在细胞中部聚合形成 Z 环(蓝绿色)，然后募集分裂体复合物的其他蛋白质，使 Z 环转变为间隔环(septal ring, SR) (深蓝色). 抑制分裂体在错误位置组装的负调节因子主要包括 Min 系统(MinC、MinD 和 MinE 蛋白)和 NO 系统(SlmA). ZipA 等通过正向调节促进 Z 环的定位和分裂. 分裂体成熟后，在存在分裂相关蛋白(如 EnvC、AmiB、AmiC 等)的情况下进一步进行隔膜肽聚糖的合成和外膜的有效内陷. 最终，Z 环收缩，细胞分裂产生子细胞

Figure 2　Schematic diagram of *Escherichia coli* cell division. Cell division starts with the polymerization of Z filaments at mid-cell to form the Z ring (blue-green) followed by recruitment of other proteins of the divisome complex, resulting in the transition of Z ring into a septal ring (SR) (dark blue). Negative regulators that inhibit the assembly of splitters at the wrong location mainly include the Min system (MinC, MinD, and MinE proteins) and the NO system (SlmA). ZipA promotes the localization and splitting of the Z-ring. After the maturation of the splitter, septum peptidoglycan synthesis and efficient invagination of the outer membrane are further carried out in the presence of division-related proteins (e.g. EnvC, AmiB, AmiC). Eventually, the Z ring contracts and the cell divides, producing daughter cells.

当 MinC 的表达过量时，无论 MinCDE 是否完整，都会抑制 FtsZ 在整个细胞上的组装，从而抑制细胞分裂，导致细胞丝状化[30-31]。

控制 FtsZ 动态定位的另一个系统 NO 能有效阻止 FtsZ 在类核附近的定位[32]。在大肠杆菌等革兰氏阴性菌中，NO 系统由 DNA 结合蛋白 SlmA 介导，SlmA 可通过与 FtsZ 直接结合耗竭 FtsZ，因而阻碍 Z 环的形成[33]。当 SlmA 过表达时不仅会引起细胞分裂异常的丝状化，还会在一定程度上增强 Min 系统的稳定性[33-34]。

1.2　革兰氏阳性菌

革兰氏阳性菌的细胞分裂总体上与革兰氏阴性菌相似，但分裂蛋白不尽相同，目前以枯草芽孢杆菌为模型研究得最透彻。革兰氏阳性

菌中尚未发现 ZipA 的同源物，在 Z 环组装过程中，一种在革兰氏阳性菌中高度保守的蛋白质 SepF 可作为将 FtsZ 与细胞膜相连的 FtsA 非必需替代因子，当枯草芽孢杆菌缺乏 FtsA 时，SepF 含量的增加使细胞分裂仍可进行，但是分裂水平较差[22,35-36]。另外，在革兰氏阳性菌中高度保守的蛋白 EzrA 作为 Z 环形成的负调节因子，在金黄色葡萄球菌和枯草芽孢杆菌中可直接与 FtsZ 作用，抑制 FtsZ 的聚合并破坏 Z 环的稳定[19,37]。

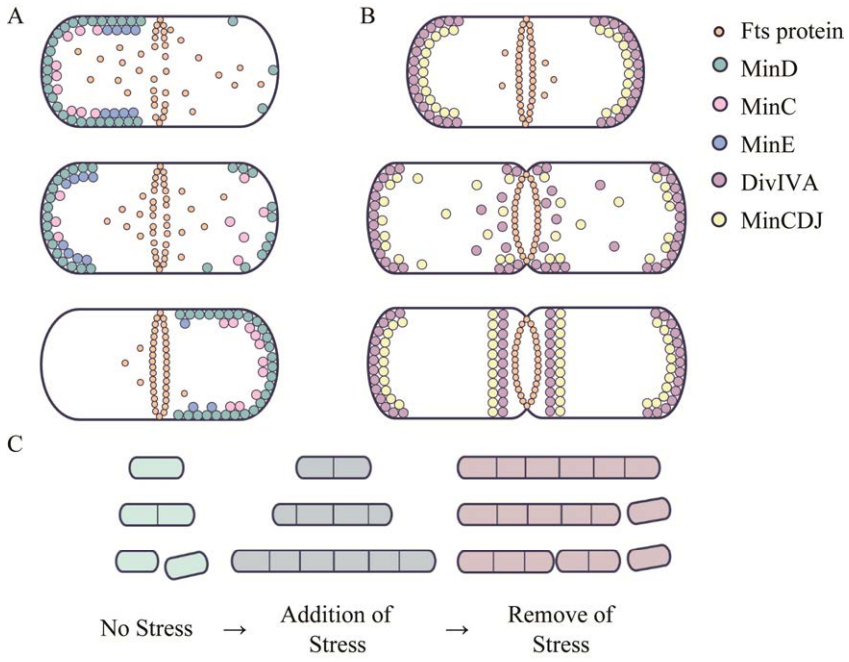

图 3　细菌的 Min 系统及丝状细菌的分裂情况示意图　A：革兰氏阴性菌的 Min 系统，如大肠杆菌，由 MinC、MinD 和 MinE 蛋白组成，称为 MinCDE 系统. MinD (绿色)优先与膜结合，MinE (蓝色)刺激 MinD 的 ATPase 活性，从膜中释放 MinD，驱动 MinD 从细胞的一端振荡到另一端，导致细胞中 MinD 的明显浓度梯度，平均浓度在细胞中间最低，在两极附近最高. MinC (粉色)作为 FtsZ 抑制剂，与 MinD 结合并随着 MinD 的运动而移动. B：革兰氏阳性菌的 Min 系统，如枯草芽孢杆菌. 由 MinC、MinD、MinJ 和 DivIVA 蛋白组成，称为 MinCDJ 系统. 当 DivIVA (紫色)主要结合在细胞的两端时，MinD 表现出静止的双极梯度模式. 一旦膜内陷开始，DivIVA 蛋白会在细胞中重新定位，而 MinCDJ 蛋白(黄色)在分裂细胞中同时定位到分裂位点和极点，以防止新一轮分裂和/或可能作用于 Z 环组装的一些下游蛋白质. C：丝状细菌在不同胁迫状态下的分裂情况

Figure 3　Min system of bacteria and the division of filamentous bacteria. A: Min system of Gram-negative bacteria, such as *E. coli*. The MinCDE system is composed of MinC, MinD, and MinE proteins. MinD (green) preferentially binds to the membrane, and MinE (blue) stimulates the ATPase activity of MinD, releasing MinD from the membrane, driving MinD to oscillate from one end of the cell to the other, resulting in a distinct concentration gradient of MinD in the cell, with the lowest concentration in the middle of the cell and highest near the poles. MinC (pink) acts as an FtsZ inhibitor, binding to and moving with MinD. B: Min systems of Gram-positive bacteria, such as *Bacillus subtilis*. The MinCDJ system is composed of MinC, MinD, MinJ, and DivIVA proteins. When DivIVA (purple) binds mainly to both ends of the cell, MinD exhibits a quiescent bipolar gradient pattern. Once membrane invagination begins, the DivIVA protein relocates in the cell, and the MinCDJ protein (yellow) locates to both the division site and the pole in the dividing cell to prevent a new round of division and/or some downstream proteins that may act on the Z-ring assembly. C: Morphology and division of bacteria under different conditions.

在第二阶段招募分裂蛋白的过程中，枯草芽孢杆菌的分裂体组装与大肠杆菌不同。FtsQ 和 FtsB 在革兰氏阳性菌中被称为 DivIB 和 DivIC，与 FtsL 和 PBP2b 之间具有很强的相互依赖性[38]。即使缺乏其他分裂蛋白如 FtsN 的典型结合结构域时，金黄色葡萄球菌中 DivIB 的胞外结构域仍可以与肽聚糖结合[19,39]。DivIC 在金黄色葡萄球菌的分裂和存活中，还可通过影响主要肽聚糖合酶 PBP2 和 FtsW 的募集在空间上调节肽聚糖合成，从而调节细胞壁结构[40]。

与革兰氏阴性菌相比，革兰氏阳性菌有更厚的细胞壁。因此，与大肠杆菌不同，在枯草芽孢杆菌中 FtsZ 在 Z 环上的踏车效应(treadmilling)不仅控制肽聚糖合成的分布，而且还控制整个间隔肽聚糖的合成速率[41]。这可能是由于二者具有不同水平的细胞壁前体，也可能是因为大肠杆菌中肽聚糖的合成还与外膜的插入偶联[21,41]。

此外，防止细胞两极附近 Z 环组装的 Min 控制 Z 环动态定位的系统在革兰氏阴性菌和革兰氏阳性菌中也不同。在大肠杆菌和大多数革兰氏阴性细菌中，调节因子是 MinE，它与细胞两极之间的 MinC/MinD 一起发生耦合振荡；而在枯草芽孢杆菌等大多数革兰氏阳性细菌中，Min 系统包括 MinC、MinD、MinJ 和 DivIVA[42]。区别于革兰氏阴性菌中的振荡模式，Min 系统在革兰氏阳性菌中表现为由 DivIVA 调节的静止双极梯度模式[42]。DivIVA 起初定位于细胞极处，通过 MinJ 与 MinD 结合并调节其分布，形成两极高中间低的浓度梯度，使 Z 环得以在细胞中间组装[42-43]。在分裂开始后，DivIVA 会迅速到达新的分裂位点，形成位于隔膜两侧的双环以调节 MinCD 的活性，防止 Z 环在新完成的隔膜附近异常组装[44](图 3B)。当 Min 系统缺损或 MinC 过度表达时，革兰氏阳性菌同样也会呈现丝状形态[45]。

枯草芽孢杆菌等革兰氏阳性菌中的类核闭塞因子是 Noc，其与 SlmA 无相似的结构和序列，通过不同的 DNA 结合域与类核结合，抑制分裂体的方式也存在差异[28]。Noc 通过与膜蛋白结合将 DNA 富集到细胞膜上，Noc-DNA 复合物的挤压使 FtsZ 只能在类核之间形成并限制了其迁移，当 Noc 过表达时会抑制或延迟细胞分裂，使细胞的长度增加，但 FtsZ 的水平不受影响[32,46-47]。

2 诱导细菌异常分裂机制

2.1 SOS 应答

SOS 应答是细菌在胁迫条件下形成丝状最广泛且研究最明确的机制之一。SOS 应答是细菌对 DNA 损伤的全面反应，因此，可以诱导细菌 DNA 损伤的环境条件(如抗生素、饥饿、活性氧自由基、pH 变化等)均可通过该机制诱导细菌成丝[48-49]。

SOS 反应系统最早在大肠杆菌模型中发现，主要涉及 RecA 和 LexA 蛋白[50-51]。在 DNA 受损后，RecA 作为 SOS 系统的“传感器”获得蛋白酶活性[48,52]，随后这种活化的 RecA 刺激转录抑制蛋白 LexA 的裂解[53-54]。在 LexA 蛋白裂解后，其原本抑制的 SOS 基因编码的蛋白质转录合成，这些蛋白在保护稳定复制叉的同时，可通过核苷酸切除或重组修复机制来处理损伤[55]。这一系列蛋白中存在一种能抑制 FtsZ 聚合的蛋白，它能阻止细胞分裂，并避免受损 DNA 传递到子细胞[56-57]。例如，在大肠杆菌中，LexA 抑制的 SOS 基因不仅编码 DNA 修复过程的 DNA 聚合酶，也编码细胞分裂抑制剂 SulA[58]。DNA 损伤后，SulA 迅速积累；一旦 DNA 修复完成，SulA 被 Lon 蛋白酶消除，细胞就会恢复正常分裂[59]。然而 SulA 在细菌中并不广泛保守。SOS 诱导的分裂抑制蛋白也已在枯草芽孢杆菌(YneA)、新月柄杆菌(SidA)、谷氨酸棒状杆菌(DivS)和结核分枝杆菌(Rv2719c)中被鉴定[60-62]。

2.2 细胞周期调节

细菌的丝状化还与细胞周期的调节有关。细胞周期调节的主要因子 CtrA 控制着多个细胞周期事件，并将形态变化与细胞周期进程结合了起来[63]。此外，CtrA 通过直接结合复制起点来控制染色体复制的起始，防止细胞周期 G1 中复制体的形成[64]。Heinrich 等[65]发现在新月柄杆菌中存在一种不依赖于 SOS 应答和 FtsZ 蛋白调节的丝状化机制，由磷酸化信号系统调节细胞分裂所需的主细胞周期调节剂的稳定性和活性。双功能组氨酸激酶 CckA 在该调节中起着核心作用，它通过将细胞周期与环境信息相结合来决定是否进行细胞分裂[66]。在适宜条件下，CckA 通过在其激酶和磷酸酶活性之间动态切换来驱动主细胞周期调节因子 CtrA[67-68]。环境压力将 CckA 锁定在其磷酸酶模式，通过蛋白酶 ClpXP 降解，导致 CtrA 快速失活，从而阻断 CtrA 调节细胞分裂的功能[69-70]。同时，盐、乙醇和高温会引起膜特性的变化，例如改变膜流动性或脂质成分，这些变化可能直接引起 CckA 构象和活性的变化[71-73]。另外，虽然盐胁迫、乙醇胁迫和轻度热休克会导致 CtrA 快速降解，但“碳饥饿”可通过小信号分子(p)ppGpp 的传导机制导致 CtrA 稳定性增加[74-76]。尽管饥饿依赖性 CtrA 稳定性增加的确切机制尚不清楚，但它可能与 DNA 复制启动子 DnaA 的下调有关，确保在这种情况下阻断 DNA 复制启动[74,77]。

2.3 σ 因子调控

在大肠杆菌中，RpoS 是一种替代性的 σ 因子，负责全基因组十分之一基因的调控，在大肠杆菌等革兰氏阴性菌中，它能调控在渗透、酸、热和饥饿胁迫等一般抗逆性中发挥作用的多种基因[78]。Dong 等[79]研究结果显示 *rpos* 基因突变后，糖原代谢相关基因(*glgCAP*, *glgX*)、醋酸盐合成相关基因(*pta*, *ackA*)、糖酵解相关基因(*fbaB*, *pfkB*)、精氨酸合成相关基因(*argB*)、三羧酸循环中所有基因及乙醛酸支路的基因表达水平均有所提高。然而，饥饿条件下成丝的机制可能与(p)ppGpp 通路相关的 RpoS 蛋白表达有关。在不利条件下，(p)ppGpp 不断积累，同时进行适当的 RpoS 表达，抑制细菌主要的生化反应，使其能够适应极端环境并存活下来[80]。随着胁迫条件的加剧，(p)ppGpp 合成随之受到抑制，核糖体 RNA 积累速率降低，碳水化合物、脂质和核苷酸等重要生命活动代谢产物减少，细胞转运大分子数目减少，导致生长停滞[81-82]。Mattick 等[11]的研究表明 RpoS 的含量与丝状化有相关性，渗透胁迫诱导的 OsmY 蛋白能指示 RpoS 水平的变化，而且在低温环境下表达会有所上升[83-84]。随着胁迫时间的延长，细胞丝化显著，RpoS 水平明显下降，因此推断丝状细胞可能含有相对较低水平的 RpoS[11]。

2.4 外源性抑制

外源性抑制由外源添加各类抗菌剂产生，影响细菌细胞的正常分裂。比如姜黄素作为姜黄的一种酚类物质，是植物性抗菌剂的代表之一，可抑制 Z 环以及 FtsZ 蛋白的组装，并且激活 FtsZ 的 GTP 酶活性，促进 GTP 消耗使得 FtsZ 分解成小单体，导致枯草芽孢杆菌和大肠杆菌的丝化[85]。动物中提取的抗菌剂以壳聚糖为例，作为甲壳素脱乙酰后的一种存在形式，壳聚糖现已成为食品和药品行业被广泛用于抑菌的一种物质。壳聚糖带正电荷的氨基与带负电荷的细胞膜的相互作用导致细胞包膜的干扰和细胞内化合物和蛋白质的泄漏，进而影响细菌分裂，导致细菌丝状化[86]。

2.5 其他

在食品中常用降低水分活度的方法来延长货架期，在高剂量渗透剂的环境条件下，为保证细胞膜内外渗透压平衡，相溶溶质通过主动运输进入、累积和自身生物合成，NaCl、甘油和糖等物质浓度提高，同时诱导食源性致病菌丝状

化[8]。受渗透压胁迫长成的细丝被发现其 PBP2 的活性比正常细胞高出 1.5−5.0 倍，推测或许存在 PBP2 作用成丝的机制，但缺乏研究[87]。

3 细菌丝状化的危害性

细菌成丝的本质是细胞长度因间隔形成和细胞分裂受到抑制而显著增加的过程，丝状细菌的活力与细菌长度密切相关，细菌长度越长越容易失活死亡[88-89]。丝状细胞的活力可以分为三类：第一类在胁迫消失后从丝状细胞一端开始迅速分裂成多个细菌，导致当前的评估和预测模型低估食品中的致病菌数量，引入新的安全隐患(图 3C)[8,90]；第二类丝状细胞长度已经达到了无法恢复生长的停滞点(point of no return, PONR)，丝状细胞仍具有细胞膜完整性和代谢活力，但胁迫消失后无法恢复分裂[91]；第三类长度较长的丝状细胞则会直接失去细胞活性[49,88]。当第一类丝状细胞恢复分裂能力后，分裂将从尖端开始，并在短时间内快速产生大量恢复正常生长的子代活细胞，其分裂速度可达到非丝状细胞的三倍[92-93]。

丝状形态对细胞毒力的影响尚不明确。Stackhouse 等[94]首次验证了低水分活度诱导的丝状形态沙门氏菌的毒力，结果显示丝状形态的沙门氏菌有侵入人肠上皮细胞 Caco-2 且在胞内繁殖的能力，灌胃感染小鼠后在其肠道中定殖水平较高，而扩散至脾脏和肝脏的能力均与普通沙门氏菌类似，但对其是以丝状还是非丝状形态侵入细胞仍有待探究。Chen 等[95]研究证明在头孢他啶作用下，丝状化后的伯克霍尔德菌同样具有裂解 THP-1 细胞的能力，同时内毒素水平增加；而在其他类别抗生素的作用下，伯克霍尔德菌丝状化后毒力会暂时降低，一旦减少或去除抗生素，细胞恢复分裂后毒力恢复。此外，在感染期间，例如尿路致病性大肠杆菌在膀胱环境中形成丝状细菌后可对多形核白细胞和巨噬细胞具有抵抗力，也能逃避免疫反应[96-97]。

虽然丝状细菌的分裂受到抑制，但胞内 DNA 复制仍可进行。Shogo 等[92]研究发现亚致死氯化钠胁迫诱导单增李斯特菌呈丝状形态后，单个丝状细胞中含有多个核区且分布不均。Bos 等[98]在环丙沙星诱导的大肠杆菌中也观察到了同样的现象，同时发现这些丝状大肠杆菌产生的子细胞耐药性显著提高。Chen 等[95]用头孢他啶诱导的丝状形态伯克霍尔德菌在抗生素被稀释或失去活性时，细胞分裂就会恢复，在恢复为正常大小的细胞后，细菌对头孢他啶和其他类别抗生素的耐药性均有所提升。这些现象表明，丝状化可使细菌的耐药性增强，其原因可能与 SOS 反应时 DNA 复制突变率提高或细菌的多核区基因重组有关[98-100]。

除耐药性外，丝状细菌的其他抗性也发生了改变。亚致死胁迫不仅可能诱导致病菌形成对同种胁迫的耐受性，还会通过交叉保护效应提高对其他胁迫的耐受性[101]。有研究报道低水分活度诱导的丝状形态沙门氏菌对有机酸的耐受性较普通细胞显著提高，但对低温、高温和胆盐的耐受性显著降低[94]。然而低水分活度诱导的丝状形态单增李斯特菌对有机酸的抗性则与普通细胞类似，但耐热性显著提高[8]。此外，弯曲杆菌丝状化还能提高其在水中的存活能力，这可能给食品安全带来严峻的挑战[102](表 1)。

4 丝状形态细菌的控制

丝状细菌的控制主要聚焦在两个方面：一方面，抑制 FtsZ 会使细胞无法正常分裂，可以继续伸长成丝，最终导致细菌死亡[91]。因此，FtsZ 可作为新一代抗生素开发的有效靶标[103]。另一方面，通过抑制细菌丝状化的形成，减少细菌的表面黏附和定殖，降低细菌在胁迫条件下的存活率，同时达到准确统计活细胞数的效果[16]。

表 1 细菌丝状化危害性研究

Table 1 Research on harm of filamentous bacteria

Harm	Bacteria	Treatment	Extent of filamentation	Description	Reference
Rapid division	*Escherichia coli*	Ultraviolet/ Cefazolin	92%/76% filamentation rate	Upon removal of the stressor, the rate of cellular division was accelerated by three times	[103]
	Listeria monocytogenes	Sublethal concentrations of sodium chloride	All tested strains' lengths exceeding 4 μm	Upon the removal of the stressor, there was a rapid increase in the initial colony-forming units with a rate approximately two times that of the untreated group	[92]
	Salmonella enterica	Pelargonic acid	79% filamentation rate	Upon the removal of the stressor, an increase of 2 $\log_{10}$ (CFU/mL) was observed within a 4-hour timeframe	[104]
	Escherichia coli	Ofloxacin	21% filamentation rate	Upon the removal of the stressor, the rate of cellular division within 5 hours was twice that of the untreated group	[105]
Metabolism	*Escherichia coli*	Ceftriaxone sodium	/ (Single-cell analysis, ranging from 67.5 to 119.7 μm)	Eight metabolites, namely γ-glu-GABA, proline, β-hydroxyarginine, serine, 3-sulfopyruvic acid, histidine, ADP-ribose, and mannitol-6-phosphate were observed to be closely associated with the filamentous morphology induced by antibiotic stimulation in bacteria	[14]
	Bacillus subtilis & *Staphylococcus aureus*	Genetics/ Benzamide derivatives	/ (Presence of filamentous without specific data)	Bacterial membrane integrity remained intact, and metabolic activity remained unchanged	[91]
Virulence	*Salmonella enterica*	Reduced water activity to 0.95	75% filamentation rat, over 20% of bacteria length exceed 30 μm, maximum length exceeds 100 μm	When an equivalent number of bacteria invaded Caco-2 cells, both the treated and control groups exhibited similar invasion and proliferation capacities. However, upon invasion with bacteria of the same weight, filamentous bacteria displayed weaker invasion and proliferation capabilities Following gastric infection in mice, filamentous bacteria established higher colonization levels in the intestinal tract	[94]
	Burkholderia pseudomallei	Cefotaxime, ofloxacin, or trimethoprim	Lengths of short filaments typically range from 7 to 10 μm, while long filaments can reach 20 to 30 μm; cefotaxime-induced filaments exhibit maximum length	Under the influence of cefotaxime, filamentous bacteria retained the capability to lyse THP-1 cells and concurrently induced the production of TNF-α and IL-1β Similarly, following treatment with ofloxacin or trimethoprim, the bacterial virulence temporarily diminished. However, upon reduction or removal of the antibiotics, bacterial virulence rebounded after cellular recovery and division	[95]

(待续)

(续表 1)

Harm	Bacteria	Treatment	Extent of filamentation	Description	Reference
Virulence	*Escherichia coli*	Cefotaxime	/ (Presence of filamentous without specific data)	The bacterial endotoxin levels were 13.5 times higher than those in the control group. In mice following infection, there were elevated concentrations of endotoxin in both plasma and muscle tissues	[106]
	Escherichia coli & *Pseudomonas aeruginosa*	Cefotaxime, imipenem, amikacin	/ (Presence of filamentous without specific data)	At 400-fold MIC against *E. coli*, ampicillin led to a 19-fold increase in total endotoxin release within 4 hours, compared to the other two antibiotics. Meanwhile, at 40-fold MIC, cefotaxime resulted in an eight-fold increase in total endotoxin release. For *P. aeruginosa*, at 50-fold MIC, cefotaxime led to a three-fold rise in total endotoxin release compared to the control group	[107]
Colonization	*Escherichia coli*	Cefamandole	/ (Presence of filamentous without specific data)	Under physiological flow conditions, the filamentation of *E. coli* enables bridging of non-adherent distances exceeding 5 μm, markedly enhancing bacterial surface colonization rates	[108]
	Escherichia coli	Urinary tract infection model	Nearly 100% filamentation rate	Filamentous bacteria can adhere to host cells, and the surface-attached filaments can withstand fluid shear forces	[109]
Immunity	*Escherichia coli*	Streptomycin	74.2% filamentation rate after enrichment	Filamentous bacteria may evade macrophages and neutrophils, with regular rod-shaped bacteria being preferentially targeted for elimination	[110]
Drug resistance	*Escherichia coli*	0.125×MIC of ciprofloxacin	99.5% filamentation rate	At the minimum lethal concentration, the frequency of drug resistance increased by 250-fold	[98]
	Escherichia coli	Fluoroquinolone	26.4% bacteria lengths above the 95% confidence interval	Survival rates were elevated by 19.5-fold and 4.5-fold with ofloxacin and D-cycloserine, respectively	[111]
	Burkholderia pseudomallei	MIC of cefotetan	Lengths ranging from 20 to 30 μm	The MIC of cefotaxime increased fourfold, while that of ofloxacin and kanamycin increased two-fold	[95]
	Pseudomonas aeruginosa	Cefotetan, meropenem	/ (Presence of filamentous without specific data)	After 7 days, the MIC increased by more than tenfold	[112]
Other resistance	*Salmonella* enterica	Reduced water activity to 0.95	75% filamentation rate, over 20% of bacteria exceed 30 μm, maximum exceeds 100 μm	Enhanced acid resistance was observed, with the filamentous bacteria exhibiting a survival rate of 73.5% at pH 2.0, significantly surpassing the control group's rate of 40.6%	[94]
	Listeria monocytogenes	Sublethal concentration sodium chloride solution	All tested strains' lengths exceeding 4 μm	Increased heat resistance was evident, as the filamentous bacteria exhibited a reduction of only 1.5 $\log_{10}$ (CFU/mL) after exposure to 55 °C for 30 minutes	[92]

(待续)

(续表 1)

Harm	Bacteria	Treatment	Extent of filamentation	Description	Reference
Other resistance	*Campylobacter jejuni*	Starvation	2-fold lengths	Enhanced survival in water was observed, as the control group's viable bacterial count decreased to the detection limit after 96 hours at 4 °C, while the treated group only experienced a reduction of 1.5 $\log_{10}$ (CFU/mL)	[102]
	Vibrio parahemolyticus	Alkaline treatment	Lengths ranging from 1.6 to 8.8 μm	Enhanced heat resistance was evident, with a 350-fold increase in heat tolerance within 10 minutes at 47 °C. After 30 minutes, there was an approximate 470-fold difference in bacterial survival between groups. Additionally, the treated bacteria exhibited increased resistance to dissolved organic carbon (DOC), with an 8-fold increase within 10 minutes and a 10-fold difference after 30 minutes Moreover, their resistance to hydrogen peroxide (H_2O_2) was also elevated, with a 1 400-fold difference in bacterial survival after 20 minutes	[113]
	Caulobacter crescentus	Starvation	Over 95% of viable cells' lengths beyond 6 μm, with an average length of 20 μm	Enhanced alkaline resistance was observed, with a survival rate over 100 times higher after 2 hours at pH 9.5. Additionally, there was an increase in resistance to H_2O_2, as the bacterial count remained unchanged after treatment with 10 mmol/L H_2O_2	[114]

MIC: Minimal inhibitory concentration; /: Not mentioned.

4.1 诱导细胞成丝

随着抗生素耐药性问题的日益严峻,新一代抗生素的研发日益迫切。在目前已明确有效的靶点中，FtsZ 作为细菌细胞分裂的关键蛋白，具有在原核生物中高度保守且不存在于高等真核生物中的特点,是目前研究最热门的作用靶点之一[17]。FtsZ 抑制剂会导致细胞分裂异常，最初不抑制细胞生长形成丝状细胞,在经过几个质量倍增期后，细胞进入生长停滞期，由于细胞分裂受阻和 DNA 复制启动停滞的恶性循环，即使将丝状细胞转移到允许条件后,细胞仍无法恢复生长和分裂，最终死亡[91]。近年来，多种 FtsZ 靶向抑制剂已被报道可以通过抑制 FtsZ 组装、Z 环形成和细胞分裂等方式诱导细胞丝状化死亡，对多种不同的致病菌(如金黄色葡萄球菌、大肠杆菌等)有效[115]。FtsZ 靶向抑制剂主要包括天然产物类和合成类：天然产物类包括多酚、苯丙烷类和萜类化合物、生物碱，如血根碱、黄连素、白藜芦醇、肉桂醛、绿毛霉毒素等；合成类 FtsZ 抑制剂包括苯甲酰胺、芳香碳环、非芳香杂环(即奎宁)和芳香杂环衍生物，如喹诺酮类、紫杉烷类、嘧啶类、喹唑啉类、吲哚类和苯并咪唑类等[115]。但特定种类的苯甲酰胺 PC190723 在药理学和药代动力学上表现不佳,阻碍了其临床发展,最新的 TXA709 通过基团取代达到了更优的性能和杀菌活性，在 2016 年通过美国食品与

药物管理局审查，目前已完成I期临床试验，未出现严重不良事件[116-117]。现有研究大多集中在鉴定靶向特定分裂蛋白的天然或合成药物方面，仅比较不同化合物间最低抑菌浓度的关系，较少进行临床试验，距离大规模上市应用仍有较远距离。

4.2 抑制细胞成丝

在细菌 DNA 损伤后，SOS 应答能够快速修复进而减少损伤对细胞的负面影响，但由于 DNA 聚合酶在修复中可能会引入差错，使得细菌变异即获得一定的耐药性，提高了生存机会。RecA 介导的修复也会诱导一种超突变状态，促进抗生素耐药性的获得[118]。如果 DNA 损伤未能成功修复，则会诱发突变聚合酶(PolIV 和 PolV)，导致突变，使细菌产生抗生素耐药性[118]。同时，SOS 应答引导的细胞丝状化带来的细胞膜通透性改变等，也增强了对致死或亚胁迫条件的抵抗[119]。为了降低这两方面给杀菌带来的不利影响，以抑制细菌 SOS 应答为靶点开发新的药物是一条重要的思路。

目前，抑制细菌 SOS 应答主要有 3 种途径，分别作用于 RecA 蛋白、LexA 蛋白和 RecA-LexA 间相互作用[16]。RecA 蛋白作为 SOS 应答的初级诱导物，激活的 RecA 对与 LexA 相互作用及诱导 LexA 抑制物的自催化蛋白的水解活性至关重要，从而导致 SOS 相关基因的表达[120]。因此，RecA 介导的 SOS 基因表达的主要调节作用使其成为削弱细菌损伤修复的首要治疗靶点。经研究表明，抑制 RecA 蛋白的合成与表达可以阻止 SOS 应答的诱导，并有助于阻断 DNA 损伤修复、抑制水平基因转移途径以及 SOS 带来的基因突变[118]。目前已经发现了几种体外抑制 RecA ATP 酶活性的化合物，包括苏拉明[121]、金属阳离子[122]、核苷酸类似物[123]、α-螺旋肽[124]及其他复杂化合物。此外，据报道，多种天然酚类物质也有类似功效，姜黄素可抑制左氧氟沙星引起的 SOS 反应[125]；黄芩苷能够抑制 ATP 合成酶，进而抑制环丙沙星给金黄色葡萄球菌带来的 SOS 反应[126]；香豆素酸能与 ssDNA 结合，抑制李斯特菌在环丙沙星刺激下的 SOS 反应和丝状化[127]。

由于 RecA 与 Rad51 (一种在 DNA 修复机制中起关键作用的人类药物靶点)的高度序列相似性，脱靶效应带来的高风险引起了严重关注[128]。然而在无应激情况下，SOS 应答的所有基因都被 LexA 蛋白直接抑制，因此，LexA 蛋白可作为更有效的靶点[51]。现有研究对化合物进行了高通量筛选，发现 5-氨基-1-(氨基甲酰基甲基)-1H-1,2,3-三唑-4-甲酰胺对 LexA 蛋白有一定的抑制作用[123]。除此之外，含硼化合物[129]和纳米抗体[128]对抑制 LexA 蛋白也有显著作用。

SOS 应答中的 RecA/LexA 轴(即两种蛋白应答过程中的结合区域)是一个新颖且有前途的药物靶点[130]。Mo 等[131]通过一种新的荧光偏振分析筛选了 180 万种化合物，在其中鉴定出了特异性靶向 SOS 激活中 LexA 自溶步骤的小分子。另一种基于 SOS 应答的独特调节手段是抑制 Caspase-3，用 Caspase-3 抑制剂处理过的大肠杆菌在紫外线照射情况下呈丝状，SOS 反应下调，原因是其 RecA 蛋白活性降低并有 LexA 蛋白失活[131]。

5 总结与展望

丝状化是细菌为应对不利生存条件的一种异常分裂机制，并且在恢复到适宜环境时能快速分裂。正常的细胞分裂依赖于 FtsZ 蛋白的组装和活性，在革兰氏阴性菌和革兰氏阳性菌中行为模式大致相同，即 Z 环定位与组装、募集分裂蛋白、合成和重塑肽聚糖，但具体的分裂体蛋白有明显差异。丝状化的主要诱因是环境胁迫导致细菌 DNA 损伤，为避免 DNA 损伤传

递给子代细胞并给予 SOS 应答充足的修复时间，合成特定蛋白使细菌暂时停止分裂，但未停止进一步生长，逐渐伸长出现丝状化现象。此外，细菌还可以通过其他信号途径来实现丝状化，如细胞周期调整、σ 因子调控或靶向分裂体蛋白的外源性抑制驱动，其目的也是为了适应环境变化或降低抑制剂的影响。同时，由于丝状细菌分裂受到抑制，细胞体积的最大化可导致胞内聚羟基烷酸酯(PHA)的积累，因此丝状形态细菌也具有应用于生物合成领域的潜力[132]。

关于丝状形态细菌的现有研究主要基于丝状化现象的解释，关于其分子机制鲜有研究。此外，关于细菌分裂及丝状化的研究仍集中于模式细菌(大肠杆菌、枯草芽孢杆菌等)，对其他相关食源性致病菌的研究相对较少，不同菌种间的成丝调控机制是否相同也尚不明确，使得部分药物靶点杀菌的广谱性受到一定质疑。若能进一步明确不同刺激下细菌成丝在机制、条件和生理学特性等方面的异同点，探索丝状保护和丝状致死的关联，将会为细菌控制带来崭新的解决思路。

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