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VERSATILITY OF TOXIN-ANTITOXIN SYSTEMS IN BACTERIAL PHYSIOLOGY AND STRESS RESPONSE MECHANISMS

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Natural toxins are diverse molecules produced by various organisms to benefit themselves, such as by inhibiting competitors, aiding in defense or predation, and promoting infection. Bacteria produce toxins, classified as exotoxins or endotoxins, which are either actively secreted or released upon bacterial death, respectively. Additionally, bacteria produce antibiotics and bacteriocins to inhibit the growth of competing microbes. Bacterial and archaeal species also encode toxin-antitoxin (TA) modules, where toxins disrupt cellular processes and antitoxins block their activity, functioning as intracellular time bombs that can incapacitate the host when activated. TA systems play roles in bacterial competitiveness, virulence, biofilm formation, antiphage activity, and the formation of persister cells, suggesting potential applications in plant disease management.

Toxin-antitoxin (TA) systems in bacteria are operons that contain toxin and antitoxin-encoding genes. TA modules consist of a stable toxin and a degradation-prone antitoxin, mostly encoded in an operon, resulting in tight co-transcription and co-translation of the toxin and antitoxin. The cognate antitoxin is either a protein or a small RNA molecule that counteracts the toxin activity by acting as a direct inhibitor or by controlling toxin production (Shidore & Triplett, 2017).

The toxin is relatively more stable than the antitoxin and the latter binds to and stabilizes the toxin under normal conditions. Under stress conditions, the antitoxin is selectively degraded allowing the free toxin to inhibit various cellular process thereby retarding the growth of bacteria.

Types of Toxin-Antitoxin System

Toxin-antitoxin (TA) systems are classified into eight types based on the nature of the toxin and antitoxin and their mode of action (Singh et al., 2021). Type I toxin-antitoxin (TA)

systems feature an antisense RNA as the antitoxin that inhibits toxin mRNA translation, exemplified by the hok-sok and tisB-istR modules. The toxins in Type I systems are typically small hydrophobic peptides targeting bacterial membrane integrity, leading to disruption in membrane potential and cell division.

Type II TA systems, the most extensively studied, involve both toxin and antitoxin as small proteins forming a tight-binding protein-protein complex for toxin neutralization. Examples include ccdAB and parDE, where under stress conditions, proteolytic degradation of antitoxin liberates the toxin, impacting bacterial survival.

Type III systems consist of RNA antitoxins that directly interact with toxin proteins, as seen in the toxIN module of Pectobacterium atrosepticum. ToxN toxin exhibits endoribonuclease activity and forms a macromolecular complex with RNA antitoxin ToxI, leading to toxin inhibition.

In Type IV systems, both the antitoxin and toxin are proteins but do not directly interact. Instead, the antitoxin competitively binds to the toxin, inhibiting its target interaction. An example is the cbeA-cbtA operon in E. coli.

Type V TA systems involve an enzyme antitoxin that degrades mRNAs of the corresponding toxin rather than directly binding to it, illustrated by the ghoST module. GhoS, the antitoxin, exhibits endoribonuclease activity towards GhoT toxin mRNA, which encodes a small protein damaging the cell membrane.

Type VI systems, exemplified by socAB, feature a protein toxin, SocB, that binds strongly with the β-sliding clamp, repressing replication elongation. The antitoxin, SocA, acts as a proteolytic adaptor protein, binding to SocB and facilitating its protease-mediated degradation.

Type VII TA systems involve antitoxins enzymatically modifying toxins, as seen in the hha-tomB module. Hha toxin, a hemolysin expression modulating protein, is inactivated by antitoxin TomB, which promotes oxidation of Hha, destabilizing it. This TA system acts as an oxygen sensor in biofilms, impacting bacterial growth under anoxic conditions.

Type VIII modules, represented by sdsR-ryeA, feature both antitoxin and toxin as small RNAs. SdsR toxin regulates multiple mRNA targets, acting as a multi-targeting sRNA, while RyeA antitoxin masks its activity through anti-sense binding. Modulation of RyeA

expression shifts the timing of sdsR expression, affecting cell viability, representing a novel type of TA module with small RNA components. Each type of TA system plays distinct roles in bacterial physiology and stress response mechanisms.

Role of Toxin-Antitoxin System

TA systems affect plant biome composition and activity through mechanisms like DNA maintenance, anti-addiction, pathogen virulence enhancement, dormancy induction, biofilm formation, and phage defence. They mediate entry into the persister state, a reversible dormant state aiding survival under stress. These systems, initially identified as stabilizers of plasmids through post-segregational killing, have since been implicated in stress management, persistence, gene regulation, and virulence enhancement. TA modules provide stability to mobile genetic elements like plasmids, preventing their loss and conferring a competitive advantage.

Wen et al. (2014) stated that TA systems are linked to dormancy states like persistence and the viable but nonculturable (VBNC) state, allowing bacteria to survive adverse conditions, including those encountered in plant hosts. TA systems also participate in antiphage activity, limiting bacteriophage infection through mechanisms like abortive infection, phage exclusion, and RNA degradation, with implications for the evolution and fitness of plant pathogens. Biofilms, formed by bacterial aggregates, aid survival in harsh environments, with TA systems influencing their formation and antibiotic tolerance. TA toxins like MqsR and HipA affect biofilm formation and cell death within biofilms. Additionally, TA systems limit phage infection through abortive infection mechanisms and other antiphage activities.

Conclusion

In summary, TA systems are versatile regulatory mechanisms influencing bacterial behaviour and survival, with implications for both bacterial ecology and pathogenesis, including interactions with plant pathogens and their environments. Moreover, in view of their emerging contributions to bacterial virulence, TAs are potential targets for novel prophylactic and therapeutic approaches that are required urgently in an era of expanding antibiotic resistance.

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