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Exploring the metabolism and toxicity of amino sugars and 2-deoxyglucose in *Streptomyces*

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Stellingen

Behorende bij het proefschrift

Exploring the metabolism and toxicity of amino sugars and 2-deoxyglucose in *Streptomyces*

1. Amino sugar utilization has diversified among bacteria, which presumably reflects their different lifestyles and environmental niches (**Chapter 2**).
2. The ROK-family regulator RokL6 is involved in GlcN toxicity by controlling the transcription of the adjacent MFS transporter gene SCO1448, which likely encodes a detoxifying exporter (**Chapter 3**).
3. Streptomycetes have evolved a toxicity pathway to control the onset of programmed cell death (PCD). This involves the conversion of GlcNAc-6P into a cytotoxic metabolite that resembles ribose, by the action of NagS that governs a reaction that does not occur in the textbooks, and by a promiscuous activity of NagA (**Chapter 4**).
4. In *Streptomyces* the toxicity of 2-deoxyglucose (2-DG) is not connected to glycolysis but to the pentose phosphate pathway, whereby 6-phospho-2-deoxyglucono-1,5-lactone is the key to cytotoxicity. This discovery may also impact the application of 2-DG as a chemotherapeutic (**Chapter 5**).
5. While scientists may be inclined to believe that the core primary metabolism does not have any true secrets anymore, previously unrecognized metabolic routes can still be discovered.
6. Considering the complexity of the classical *Streptomyces* life cycle and newly discovered growth strategies, there is still much to learn about the cellular mechanisms and signalling pathways that govern these distinct developmental stages and the transitions between them (Schlimpert & Elliot, 2023, *J Bacteriol* **205**: e0015323).
7. Most contemporary clinical antibiotics are derived from natural products initially discovered in soil microorganisms, and the soil-to-clinic axis continues to inspire natural product chemists in their search for and design of new drugs (Perry *et al.*, 2022, *Nat Rev Microbiol* **20**: 129-142).
8. With the rapidly accumulating sequences of biosynthetic gene clusters (BGCs) and the development of large-fragment cloning technologies, heterologous expression is becoming increasingly important for the discovery of novel natural products in the post-genomic era (Zhang *et al.*, 2019, *Nat Prod Rep* **36**: 1313-1332).
9. Being bold enough to try is the most fundamental way to solve any problem.
10. Living abroad reshapes one's sense of distance, making the world feel more accessible than initially perceived.

Chao Li
Leiden, 30 oktober 2024