Iron is an essential element for all organisms as it is required for vital biological processes. To circumvent the low bioavailability of iron in the environment, microorganisms biosynthesize and excrete high-affinity iron chelators, known as siderophores, to scavenge iron by forming soluble complexes that can be imported into the cell. Because iron overload is toxic, siderophore synthesis is tightly regulated in order to maintain strict homeostasis. In this work, we challenge the authoritative dogma according to which siderophore biosynthesis is inexcusably tied to iron availability. Indeed, our in silico predictions suggest the existence of a regulatory mechanism independent of environmental iron concentration, in which siderophore-mediated iron uptake would be repressed by the peptidoglycan subunit N-acetylglucosamine (GlcNAc) in Streptomyces coelicolor. Furthermore, we propose an evolutionary-oriented explanation for this regulatory mechanism that might at first seem fortuitous. This approach could, in line, bring to light alternative biological functions exerted by coelichelin and desferrioxamine, the siderophores of S. coelicolor.

### Introduction

Iron is an essential element for all organisms as it is required for vital biological processes. To circumvent the low bioavailability of iron in the environment, microorganisms biosynthesize and excrete high-affinity iron chelators, known as siderophores, to scavenge iron by forming soluble complexes that can be imported into the cell. Because iron overload is toxic, siderophore synthesis is tightly regulated in order to maintain strict homeostasis. In this work, we challenge the authoritative dogma according to which siderophore biosynthesis is inexcusably tied to iron availability. Indeed, our in silico predictions suggest the existence of a regulatory mechanism independent of environmental iron concentration, in which siderophore-mediated iron uptake would be repressed by the peptidoglycan subunit N-acetylglucosamine (GlcNAc) in Streptomyces coelicolor. Furthermore, we propose an evolutionary-oriented explanation for this regulatory mechanism that might at first seem fortuitous. This approach could, in line, bring to light alternative biological functions exerted by coelichelin and desferrioxamine, the siderophores of S. coelicolor.

### Conclusion

In previous investigations, we demonstrated that actinorhodin and prodigiosin, the pigmented metabolites produced by S. coelicolor, were under the control of DasR and GlcNAc via pathway specific regulators. In this work, we provide evidence that biosynthesis of another category of microbial 'small molecules', the tri-hydroxamates siderophore coelichelin and desferrioxamine, is also controlled by the cell wall component GlcNAc. Our results demonstrate the existence of a siderophore production inhibitory pathway that is entirely independent of environmental iron availability but is part of a genetically programmed cell death (PCD) mechanism associated with Streptomyces development.

We propose that the oxidative stress (ROS formation) generated by iron accumulation could initiate the PCD process. This hypothesis is strongly supported by the occurrence of siderophore biosynthetic proteins within PCD-induced dying cells but not in the surviving cells as well as by the role played by siderophores in triggering Streptomyces development. Streptomyces require both a programmed growth arrest - the transition phase - as a key step in morphological and physiological differentiation; as well as preset extensive cell lysis that liberates nutrients, thereby allowing the development of aerial hyphae. We propose that one of the strategies used by S. coelicolor to enter PCD could be auto-induced iron poisoning. The physiological meaning of this relationship between GlcNAc utilization and siderophore biosynthesis is that it would enable streptomycetes to control the iron-mediated PCD. Indeed, the amino sugar GlcNAc released during autolytic cell wall dismantling is a logical parameter for cell wall integrity, with its extracellular ion concentration acting as an indicator of the degree of cell lysis. The PCD process needs to be limited in order for S. coelicolor to reach the later stages of its developmental program. GlcNAc could play the role of PCD-limiting agent by reducing the biosynthesis of siderophores and, as a consequence, shutting down iron auto-poisoning.

The conservation of the GlcNAc/siderophore relationship in distantly related streptomycetes species provides strong validation for the siderophore regulatory pathway model we propose, and suggests that this regulatory event is the consequence of a successful evolutionary process. Investigations are underway to assess if the PCD/siderophore-mediated iron poisoning occurs in other streptomycete species.

### References

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N-Acetylglucosamine-Mediated Inhibition of Siderophore Biosynthesis Counteracts the Suicidal Tendencies of Streptomyces coelicolor

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