A Possible Extended Family of Regulators of Sigma Factor Activity in *Streptomyces coelicolor*

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Morphologically complex, ecological adaptable and antibiotic-producing streptomycetes have large genomes and extraordinarily high numbers of RNA polymerase sigma factors. Among the 65 sigmas of *Streptomyces coelicolor,* eight are closely related to the stress-responsive sigma B of *Bacillus subtilis*. This sigma factor subfamily is exclusive to, but widespread among, Gram-positive bacteria. Its members are often regulated by interaction with anti-sigma factors, which, in low G+C Gram-positive bacteria, all belong to a family of paralogous proteins that have in common the ability to phosphorylate other, alternative, partner proteins of a third class of paralogues (anti-anti-sigmas, or anti-sigma antagonists) through the serine protein kinase activity of their HATPase_c domain. The balance between the two alternative interactions of these anti-sigmas determines the extent to which the sigma factor is free to interact with RNA polymerase and promoters.

Five anti-sigma factors have been identified experimentally in *S. coelicolor*, all encoded by genes adjacent to the genes for the target sigmas. Overall, about 40 proteins encoded in the genome have an HATPase_c domain, giving rise to speculation that they may all be anti-sigmas active against Group 3 sigmas, though they are generally rather highly diverged, with only a few being located close to genes for sigma factors or anti-anti-sigmas. One antagonist of such an anti-sigma factor has been experimentally identified (RsbV, which is antagonistic to RsbA: the σ^B-RsbA-RsbV interactions appear to be responsive to osmotic stress). RsbA and RsbV are both recognisably similar to their equivalents in other bacteria.

The SCO4677 product is one of the ca. 40 HATPase_c domain-containing putative anti-sigma factors. It is not located close to genes likely to encode either a sigma factor or an anti-anti-sigma. SCO4677 was found to regulate antibiotic production and morphological differentiation, both of which were significantly enhanced by the deletion of SCO4677. Through protein-protein interaction screening of candidate sigma factor partners using the yeast two-hybrid system, SCO4677 protein was found to interact with the developmentally specific σ^F, suggesting that it is an antagonistic regulator of σ^F. Two other proteins, encoded by SCO0781 and SCO0869, were found to interact with the SCO4677 anti-σ^F during a subsequent global yeast two-hybrid screen, and the SCO0869-SCO4677 protein-protein interaction was confirmed by co-immunoprecipitation. The SCO0781 and SCO0869 proteins resemble well-known anti-anti-sigma factors such as SpoIIAA of *Bacillus subtilis.* It appears that streptomycetes may possess an extraordinary abundance of anti-sigma factors, some of which may influence diverse processes through interactions with multiple partners: a novel feature for such regulatory proteins.

References

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