

**Pathway-specific regulation revisited: cross-regulation of multiple disparate gene clusters by PAS-LuxR transcriptional regulators**

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The control of secondary metabolites in *Streptomyces* has multiple levels like global regulators and pathway specific regulators. Pathway specific regulators are considered to be at lowest level of regulation and are encoded within respective biosynthetic gene cluster. PAS-LuxR regulators have been described to be pathway-specific regulators and responsible to monitor changes in light, redox potential, oxygen and over all energy of cell. This paper has demonstrated that pathway specific regulators could have some “Pleiotropic” effect and can cross regulate some other gene clusters. So, PAS-LuxR regulators cannot be categorized as pathway-specific regulators. The findings of this paper are valuable for secondary metabolite manipulation in *Streptomyces* as introduction of PAS-LuxR regulatory genes into *Streptomyces* may prove useful for expression of sleeping gene clusters for secondary metabolism.

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Appl Microbiol Biotechnol. 2015 Jun; 99(12):5123-35. doi: 10.1007/s00253-015-6472-x. Epub 2015 Feb 26. Vicente CM, Payero TD, Santos-Aberturas J, Barreales EG, de Pedro A, Aparicio JF. Area of Microbiology, Faculty of Biology, University of León, León, 24071, Spain.

**Abstract**

PAS-LuxR regulators are highly conserved proteins devoted to the control of antifungal production by binding to operators located in given promoters of polyene biosynthetic genes. In this study operator of PimM, has been used to search for putative targets of orthologous protein PteF in the genome of *Streptomyces avermitilis*, and 97 putative operators were found outside the pentaene filipin gene cluster (*pte*). These operators are supposed to affect genetic information processing; energy, carbohydrate, and lipid metabolism; DNA replication and repair; morphological differentiation; secondary metabolite biosynthesis; and transcriptional regulation, among others. In this paper they showed that PimM bound to all predicted operators suggesting a direct control over targeted processes. As a proof of concept, they analysed biosynthesis of the ATP-synthase inhibitor oligomycin whose gene cluster included two operators. The results demonstrated that PteF is able to cross regulate the biosynthesis of two related secondary metabolites, filipin and oligomycin, but might be extended to all the processes indicated above. This study highlights the complexity of the network of interactions in which PAS-LuxR regulators are involved and opens new possibilities for the manipulation of metabolite production in *Streptomyces*.