*Streptomyces coelicolor* regulons: σR, GlnR, SoxR, Pho

σR

σR is a global regulator of redox homeostasis in *S. coelicolor* that is bound by its anti-sigma factor, RsrA, which retains σR in its inactive state (Li *et al.,* 2003). Disulphide bond formation in RsrA, induced by oxidative stress, causes σR to dissociate and activate transcription of genes that encode enzymes of the thioredoxin disulphide reductase pathway, initiating a response to the potentially lethal disruption of redox homeostasis (Kallifidas *et al.,* 2010). Over 30 target genes of σR which function in modulating the cellular response to disulphide stress, have been identified (Table1). Two genes, *ssrA* and *relA*, have suggested roles in sensing stalled ribosomes as a mechanism of inhibiting translation during disulphide stress. It has also been suggested that the transcriptional machinery is modified in response to disulphide stress, as σR has been shown to induce expression of a novel RNA polymerase associated protein, RbpA (Paget *et al.,* 2001). Resemblance between elements of σR target genes and mycobacterial homologues of said genes indicates that there is conservation of the σR-RsrA system among actinomycetes (Li *et al.,* 2002).

GlnR

The GlnR regulon is regarded as central regulator of nitrogen metabolism in *S. coelicolor*. It acts in a bifunctional manner, either activating or repressing transcription of its target genes. GlnR activates the target genes *glnA* and *glnII*, required for nitrogen assimilation and *nirB* and *amtB*, required for ammonium supply. In addition, GlnR represses the target genes *ureA* (urea cleavage), *gdhA* (synthesis of central metabolic nitrogen donors) and SCO0255, SCO088 and SCO2404 (not fully biochemically characterised) (Tiffert *et al.,* 2008). See Table 2 for GlnR target genes. It has been demonstrated that *glnR* transcription is induced in nitrogen limiting conditions, suggesting that transcription of the gene depends on nitrogen concentration and ultimately, this impacts transcription of GlnR target genes (Tiffert *et al.,* 2011). It would be reasonable to suggest that depletion of GlnR would result in reduced growth of *S. coelicolor* and this has been observed in Δ*glnR* mutants on a number of occasions, which displayed both reduced growth and reduced antibiotic production (He *et al.,* 2016).

SoxR

The SoxR regulon, conserved amongst actinomycetes, is responsible for eliciting a global response to oxidative stress in *S. coelicolor*. This response is generated through oxidation of the [2Fe-2S] cluster in SoxR in response to molecules such as superoxide and nitric oxide species (Shin *et al.,* 2010). Cluster oxidation mediates structural changes in the soxS promoter, which SoxR is bound to, initiating structural changes in the promoter that allows activation of expression of a small number of genes by SoxR (Table 3) (Dela Cruz *et al.,* 2010). These genes include *ecaA-ecaD* and SCO2478, the five members of the previously identified SoxR regulon. In addition, a number of further genes have been identified, SCO0319, SCO0320, SCO0321, SCO1734, SCO4021 that are also targets of the SoxR regulon (Naseer *et al.,* 2014). Activity of the SoxR regulon and expression of SoxR target genes is induced during stationary phase production of the antibiotic Actinorhodin. It has been demonstrated that target genes of SoxR are relatively well-conserved amongst *Streptomyces* species (Sheplock *et al.,* 2012).

Pho

The pho regulon controls the regulation of intracellular phosphate levels and allows a response to phosphate starvation (Santos-Beneit, 2015). The PhoP-PhoR two-component system governs intracellular phosphate levels that control primary and secondary metabolism in *S. coelicolor* (Allenby *et al.,* 2012). The PhoP-PhoR system consists of a DNA-binding response regulator, PhoP and a membrane-bound sensor histidine kinase, PhoR (Barreiro and Martínez-Castro, 2019). In response to phosphate starvation, PhoR phosphorylates PhoP, inducing its binding to the consensus sequence GTTCACC in the PHO boxes (promoter regions) of pho regulon genes. This two-component system is well-conserved among streptomyces species (Martín *et al.,* 2012). There are over 100 target genes of the response regulator phoP, that can be either activated or repressed in the presence of the regulator (Sola-Landa *et al.,* 2008). See Table 4 for specific *S. coelicolor* genes under PhoP regulation. A third gene, phoU also has a role in this system, acting to modulate the response to phosphate by negatively regulating target genes that are upregulated by PhoP (Martín-Martín et al., 2018).

**Table 1. σR target genes**

|  |  |  |  |
| --- | --- | --- | --- |
| Gene | Locus tag | Gene | Locus tag |
| SCF73.11c | SCO0564 | SCH24.11c | SCO3889 |
| rpmJ | SCO0569 | trxB | SCO3890 |
| rpmG | SCO0570 | SCH24.12c | SCO3890 |
| SCM1.15 | SCO0882 | 2SCD60.05c | SCO4039 |
| trxC | SCO0885 | 2SCD46.12 | SCO4198 |
| SCM1.18 | SCO0885 | 2SCD46.13 | SCO4199 |
| 2SCG61.22 | SCO1340 | 2SCD46.18 | SCO4204 |
| SC1A8A.04c | SCO1384 | SCD95A.30 | SCO4297 |
| SC1A8A.12c | SCO1392 | SCD95A.49c | SCO4316 |
| RbpA | SCO1421 | SCD35.08c | SCO4501 |
| SC6D7.18c | SCO1421 | SC6G4.41c | SCO4736 |
| relA | SCO1513 | guaB | SCO4770 |
| SCI8.16 | SCO1831 | 2SCK31.16 | SCO4956 |
| SCI8.24c | SCO1839 | 2SCK31.27 | SCO4967 |
| SCI39.16c | SCO1869 | 2SCK31.28 | SCO4968 |
| SCC22.01c | SCO1919 | fumC | SCO5042 |
| SCC22.02c | SCO1920 | SCP8.26c | SCO5163 |
| uvrA | SCO1958 | 2SC3B6.01 | SCO5177 |
| SC7H2.09c | SCO1995 | moeB | SCO5178 |
| coaE | SCO1996 | 2SC3B6.02 | SCO5178 |
| SC7H2.11c | SCO1997 | 2SC3B6.11c | SCO5187 |
| SC6G10.34c | SCO2161 | sigR | SCO5216 |
| SCC77.04c | SCO2537 | rsrA | SCO5217 |
| clpP2 | SCO2618 | lon | SCO5285 |
| clpP1 | SCO2619 | rpmE | SCO5359 |
| SC8E4A.04c | SCO2634 | SC3D11.22 | SCO5465 |
| pepN | SCO2643 | SC1C2.26 | SCO5545 |
| SCE20.23 | SCO2849 | SC6A9.12 | SCO5655 |
| SCE19A.10c | SCO2910 | cinA | SCO5754 |
| SCE19A.11c | SCO2911 | SC7C7.09 | SCO5754 |
| SCE19A.12c | SCO2912 | SC7C7.10 | SCO5755 |
| SCE25.24c | SCO3083 | hflX | SCO5796 |
| SCE25.32c | SCO3091 | SC4H2.17 | SCO5796 |
| SCE87.13 | SCO3162 | SC9B1.08 | SCO6061 |
| SCE22.04 | SCO3187 | SC1A6.12c | SCO6423 |
| hrdD | SCO3202 | SC1A6.13c | SCO6424 |
| SCE22.23c | SCO3206 | SC4B5.01c | SCO6551 |
| SCE94.24c | SCO3373 | SC3F9.12 | SCO6577 |
| folE | SCO3403 | SC6A5.08 | SCO6759 |
| SCE9.22 | SCO3415 | SC4B10.18c | SCO7117 |
| SCH63.11c | SCO3764 | SC2H12.02 | SCO7203 |
| trxA | SCO3889 | SC10F4.05 | SCO7632 |

**Table 2. GlnR target genes**

|  |  |  |  |
| --- | --- | --- | --- |
| **Gene** | **Locus tag** | **Gene** | **Locus tag** |
| glnR | SCO4159 | SCD78.28c | SCO3961 |
| glnA | SCO2198 | fusA | SCO4661 |
| amtB | SCO5583 | tuf | SCO4662 |
| glnK | SCO5584 | SCF62.19 | SCO0393 |
| glnD | SCO5585 | SCF62.20 | SCO0394 |
| glnII | SCO2210 | SC7H2.35 | SCO2021 |
| gdhA | SCO4683 | rph | SCO2904 |
| nirB | SCO2486 | SCBAC28G1.01 | SCO5075 |
| SC7A8.26 | SCO2487 | actVA3 | SCO5078 |
| SC7A8.27 | SCO2488 | SC4H2.10c | SCO5789 |
| ureA | SCO1236 | metE | SCO0985 |
| SCF20.01c | SCO0255 | SC10A9.20c | SCO1378 |
| SCM1.21 | SCO0888 | trpB | SCO2037 |
| SC4A7.28c | SCO2400 | SC8D9.27 | SCO5515 |
| SC4A7.32 | SCO2404 | SC5F7.20 | SCO2181 |
| SCI39.10c | SCO1863 | ppc | SCO3127 |
| SC5F7.06 | SCO2195 | SC5A7.10c | SCO6660 |
| SC9A4.17 | SCO7155 | SC5A7.11c | SCO6661 |
| nnaR | SCO2958 | tal1 | SCO6662 |
| nasA | SCO2473 | gap2 | SCO7511 |
| SC7A8.11 | SCO2472 | pyrB | SCO1487 |
| msdA | SCO2726 | purL | SCO4079 |
| aspC | SCO4645 | SCC80.05c | SCO2620 |
| SC1G7.05 | SCO6279 | SCE94.24c | SCO3373 |
| SCBAC8D1.05 | SCO6292 | clpB | SCO3661 |
| SCC22.17 | SCO1935 | groEL2 | SCO4296 |
| pdhL | SCO2180 | groEL1 | SCO4762 |
| SCE50.06 | SCO2978 | SCF85.17c | SCO0289 |
| acsA | SCO3563 | SCC22.04c | SCO1922 |
| SC8F4.03 | SCO5399 | glmS2 | SCO2789 |
| SC7H2.22 | SCO2008 | SCH18.11c | SCO3874 |
| SC2A11.11 | SCO5477 | cysA | SCO4164 |
| SCC117.02 | SCO2529 | SCD65.14 | SCO4471 |
| SCH35.53 | SCO3671 | SCBAC1A6.26c | SCO6102 |
| terD | SCO0641 | SC1A9.12 | SCO6148 |
| SCC54.25c | SCO1965 | SCI39.11 | SCO1864 |
| SCC8A.26c | SCO2368 | SCI39.12 | SCO1865 |
| SC7H2.12c | SCO1998 | ectC | SCO1866 |
| SCAC2.03c | SCO3795 | SCI39.14 | SCO1867 |

**Table 3. SoxR target genes**

|  |  |
| --- | --- |
| **Gene** | **Locus tag** |
| SC5G9.28c | SCO0319 |
| SC5G9.29 | SCO0320 |
| SC5G9.30 | SCO0321 |
| ecaC | SCO1178 |
| soxR | SCO1697 |
| SCI11.23 | SCO1734 |
| ecaB | SCO1909 |
| SC7A8.15c | SCO2476 |
| SC7A8.16c | SCO2477 |
| SC7A8.17c | SCO2478 |
| 2SC10A7.25 | SCO4021 |
| SCD49.05c | SCO4264 |
| SCD86A.02c | SCO4265 |
| ecaD | SCO4266 |
| ecaA | SCO7008 |

**Table 4. Pho target genes**

|  |  |  |  |
| --- | --- | --- | --- |
| **Gene** | **Locus tag** | **Gene** | **Locus tag** |
| SCJ4.14c | SCO0033 | nuoM | SCO4574 |
| SCJ4.15 | SCO0034 | nuoN | SCO4575 |
| narG2 | SCO0216 | dhsB | SCO4855 |
| narH2 | SCO0217 | dhsA | SCO4856 |
| SCF20.01c | SCO0255 | SC5G8.25c | SCO4857 |
| katA | SCO0379 | SC5G8.26c | SCO4858 |
| SCG11A.27c | SCO1196 | SCK20.13c | SCO4872 |
| ureA | SCO1236 | SCK20.14c | SCO4873 |
| acsA | SCO1393 | SCK20.14c | SCO4873 |
| SC1A8A.14 | SCO1394 | SCK20.15 | SCO4874 |
| rpoZ | SCO1478 | SCK20.15 | SCO4874 |
| glpQ1 | SCO1565 | 2SCK8.01 | SCO4875 |
| pitH2 | SCO1845 | 2SCK8.02 | SCO4876 |
| SCI7.24c | SCO1906 | 2SCK8.03c | SCO4877 |
| glpQ2 | SCO1968 | 2SCK8.04c | SCO4878 |
| phoD | SCO2068 | 2SCK8.04c | SCO4878 |
| bfr | SCO2113 | 2SCK8.05 | SCO4879 |
| qcrA | SCO2148 | 2SCK8.05 | SCO4879 |
| SC6G10.22c | SCO2149 | 2SCK8.06 | SCO4880 |
| SC6G10.23c | SCO2150 | 2SCK8.07 | SCO4881 |
| SC6G10.24c | SCO2151 | 2SCK8.08 | SCO4882 |
| cox1 | SCO2155 | narG3 | SCO4947 |
| cox | SCO2156 | narH3 | SCO4948 |
| glnA | SCO2198 | narJ3 | SCO4949 |
| SC10B7.02 | SCO2207 | narI3 | SCO4950 |
| glnII | SCO2210 | ahpC | SCO5032 |
| SC10B7.12 | SCO2217 | bldKA | SCO5112 |
| SCC75A.08c | SCO2262 | bldKB | SCO5113 |
| SCC75A.09 | SCO2263 | bldKC | SCO5114 |
| PhoA | SCO2286 | bldKD | SCO5115 |
| hrdA | SCO2465 | bldKE | SCO5116 |
| SC7A8.05 | SCO2466 | atpI | SCO5366 |
| SCC88.05c | SCO2594 | atpB | SCO5367 |
| SCE6.15 | SCO2878 | atpE | SCO5368 |
| SCE8.09 | SCO3216 | atpf | SCO5369 |
| SCH63.37c | SCO3790 | atpH | SCO5370 |
| SCH63.38 | SCO3791 | atpA | SCO5371 |
| pstS | SCO4142 | atpG | SCO5372 |
| ppk | SCO4145 | atpD | SCO5373 |
| SCD84.19 | SCO4152 | atpC | SCO5374 |
| glnR | SCO4159 | SC3D11.04c | SCO5447 |
| gpmA | SCO4209 | SC2A11.10 | SCO5476 |
| PhoU | SCO4228 | SC2A11.11 | SCO5477 |
| PhoR | SCO4229 | SC2A11.12 | SCO5478 |
| PhoP | SCO4230 | SC2A11.13 | SCO5479 |
| SCD49.02c | SCO4261 | SC2A11.14 | SCO5480 |
| afsS | SCO4425 | amtB | SCO5583 |
| nuoA | SCO4562 | SCO5822 | SCO5822 |
| nuoB | SCO4563 | SC1C3.09 | SCO6021 |
| nuoC | SCO4564 | SC1C3.10 | SCO6022 |
| nuoD | SCO4565 | SC1C3.11 | SCO6023 |
| nuoE | SCO4566 | SC1C3.12 | SCO6024 |
| nuoF | SCO4567 | SC1C3.13 | SCO6025 |
| nuoG | SCO4568 | SC6C5.06 | SCO6170 |
| nuoH | SCO4569 | narH | SCO6534 |
| nuoI | SCO4570 | narG | SCO6535 |
| nuoJ | SCO4571 | SC10F4.03 | SCO7630 |
| nuoK | SCO4572 | SC1A4.05 | SCO7697 |
| nuoL | SCO4573 |  | |

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