

Figure S1. Functional distribution of the unexpressed proteins in both MDR and XDR strains, when compared to the RR strain, according to the TubercuList Functional Category (<http://svitsrv8.epfl.ch/tuberculist/>). RR, rifampin-resistant; MDR, Multidrug-resistant; XDR, extensively drug-resistant.

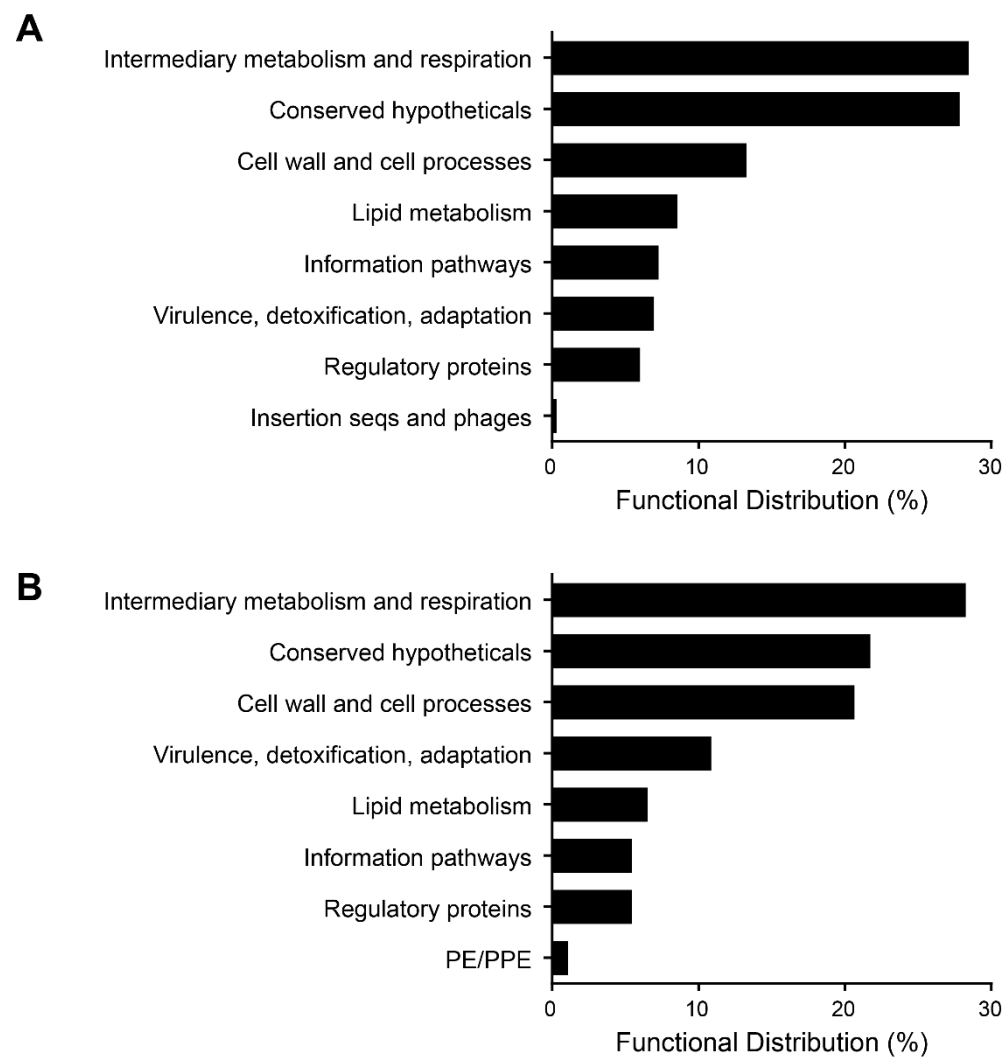


Figure S2. Functional distribution of the specially expressed proteins in either the XDR (**A**) or MDR (**B**) strains, according to the TubercuList Functional Category (<http://svitsrv8.epfl.ch/tuberculist/>). MDR, Multidrug-resistant; XDR, extensively drug-resistant.

Table S1. The DST patterns of the RR-TB, MDR-TB and XDR-TB clinical isolates.

Drugs	Concentrations (mg/L)	RR-TB	MDR-TB	XDR-TB
RIF	40.0	R	R	R
INH	0.2	S	R	R
EMB	2.0	S	S	R
LFX	2.0	S	S	R
MOX	2.0	S	S	R
KAN	30.0	S	S	R

Table S2. Biological Process enrichment in the PPI network of the up-regulated proteins of DR strains and other predicted functional partners.

#term ID	Description	Observed Gene Count	Background Gene Count	FDR	Matching Proteins
GO:0042364	water-soluble vitamin biosynthetic process	11	44	9.43E-07	Rv1417,cmk,folB,folK,folP1,panB,ribA1,ribA2,ribC,ribG,ribH
GO:1901564	organonitrogen compound metabolic process	31	563	9.43E-07	Rv1417,Rv2851c,ackA,acs,cmk,dop,folB,folE,folK,folP1,folP2,glmU,mpa,mtrA,mtrB,pafA,panB,prcA,prcB,pta,pup,pykA,ribA1,ribA2,ribC,ribG,ribH,rplA,rplJ,rplL,rplM
GO:0010498	proteasomal protein catabolic process	6	6	1.79E-06	dop,mpa,pafA,prcA,prcB,pup
GO:0019941	modification-dependent protein catabolic process	6	6	1.79E-06	dop,mpa,pafA,prcA,prcB,pup
GO:0006771	riboflavin metabolic process	6	7	2.19E-06	Rv1417,ribA1,ribA2,ribC,ribG,ribH
GO:0009231	riboflavin biosynthetic process	6	7	2.19E-06	Rv1417,ribA1,ribA2,ribC,ribG,ribH
GO:0043604	amide biosynthetic process	14	130	5.66E-06	ackA,acs,cmk,folB,folE,folK,folP1,folP2,panB,pta,rplA,rplJ,rplL,rplM
GO:0042398	cellular modified amino acid biosynthetic process	7	21	1.10E-05	cmk,folB,folE,folK,folP1,folP2,panB
GO:0017144	drug metabolic process	14	144	1.50E-05	Rv1417,acs,folB,folE,folK,folP1,mutA,mutB,pykA,ribA1,ribA2,ribC,ribG,ribH
GO:0009108	coenzyme biosynthetic process	11	88	2.62E-05	ackA,acs,cmk,folB,folE,folK,folP1,folP2,panB,pta,pykA
GO:0009396	folic acid-containing compound biosynthetic process	5	7	2.62E-05	folB,folE,folK,folP1,folP2
GO:0006575	cellular modified amino acid metabolic process	7	27	3.52E-05	cmk,folB,folE,folK,folP1,folP2,panB
GO:1901566	organonitrogen compound biosynthetic process	22	401	5.71E-05	Rv1417,ackA,acs,cmk,folB,folE,folK,folP1,folP2,glmU,panB,pta,pykA,ribA1,ribA2,ribC,ribG,ribH,rplA,rplJ,rplL,rplM
GO:0044271	cellular nitrogen compound biosynthetic process	23	443	7.53E-05	Rv1417,ackA,acs,cmk,folB,folE,folK,folP1,folP2,glmU,mtrA,panB,pta,pykA,ribA1,ribA2,ribC,ribG,ribH,rplA,rplJ,rplL,rplM
GO:0006760	folic acid-containing compound metabolic process	5	11	0.00011	folB,folE,folK,folP1,folP2
GO:0046654	tetrahydrofolate biosynthetic process	4	6	0.00029	folB,folE,folK,folP1
GO:0040007	growth	24	541	0.00046	Rv1711,Rv3371,cmk,engA,folB,folE,folP1,ftsZ,glmU,lpqB,lpqW,mtrA,mtrB,panB,prcA,prcB,pup,pykA,ribA2,ribG,ribH,rplJ,rplL,rplM

GO:0044267	cellular protein metabolic process	13	181	0.00047	Rv2851c,dop,mpa,mtrA,mtrB,pafA,prcA,prcB,pup,rplA,rplJ,rplL,rplM
GO:0006807	nitrogen compound metabolic process	32	900	0.001	Rv1417,Rv1711,Rv2851c,ackA,acs,cmk,dop,folB,folE,folK,folP1,folP2,glmU,mpa,mtrA,mtrB,pafA,p anB,prcA,prcB,pta,pup,pykA,ribA1,ribA2,ribC,ribG,ribH,rplA,rplJ,rplL,rplM
GO:0018130	heterocycle biosynthetic process	18	355	0.001	Rv1417,ackA,acs,cmk,folB,folE,folK,folP1,folP2,glmU,mtrA,pta,pykA,ribA1,ribA2,ribC,ribG,ribH
GO:0046653	tetrahydrofolate metabolic process	4	10	0.001	folB,folE,folK,folP1
GO:0009987	cellular process	40	1278	0.0011	Rv1417,Rv1711,Rv2851c,Rv3371,ackA,acs,bpa,cmk,dop,fadD21,folB,folE,folK,folP1,folP2,ftsZ,glm U,lpqW,mpa,mtrA,mtrB,mutA,mutB,pafA,panB,prcA,prcB,pta,pup,pykA,ribA1,ribA2,ribC,ribG,ri bH,rplA,rplJ,rplL,rplM,sepF
GO:0006084	acetyl-CoA metabolic process	3	3	0.0012	ackA,acs,pta
GO:0006085	acetyl-CoA biosynthetic process	3	3	0.0012	ackA,acs,pta
GO:0071704	organic substance metabolic process	38	1203	0.0015	Rv1417,Rv1711,Rv2851c,Rv3371,ackA,acs,chn2,cmk,dop,fadD21,folB,folE,folK,folP1,folP2,glmU,lp qW,mpa,mtrA,mtrB,mutA,mutB,pafA,panB,prcA,prcB,pta,pup,pykA,ribA1,ribA2,ribC,ribG,ribH,r plA,rplJ,rplL,rplM
GO:0046655	folic acid metabolic process	3	4	0.0019	folB,folK,folP1
GO:0046656	folic acid biosynthetic process	3	4	0.0019	folB,folK,folP1
GO:0070490	protein pupylation	3	4	0.0019	dop,pafA,pup
GO:0044237	cellular metabolic process	37	1182	0.0021	Rv1417,Rv1711,Rv2851c,Rv3371,ackA,acs,cmk,dop,fadD21,folB,folE,folK,folP1,folP2,glmU,lpqW, mpa,mtrA,mtrB,mutA,mutB,pafA,panB,prcA,prcB,pta,pup,pykA,ribA1,ribA2,ribC,ribG,ribH,rplA ,rplJ,rplL,rplM
GO:0044283	small molecule biosynthetic process	15	284	0.0021	Rv1417,cmk,fadD21,folB,folE,folK,folP1,folP2,panB,pykA,ribA1,ribA2,ribC,ribG,ribH
GO:1901362	organic cyclic compound biosynthetic process	18	388	0.0021	Rv1417,ackA,acs,cmk,folB,folE,folK,folP1,folP2,glmU,mtrA,pta,pykA,ribA1,ribA2,ribC,ribG,ribH
GO:0044281	small molecule metabolic process	22	552	0.003	Rv1417,Rv3371,ackA,acs,cmk,fadD21,folB,folE,folK,folP1,folP2,glmU,mutA,mutB,panB,pta,pykA,r ibA1,ribA2,ribC,ribG,ribH
GO:0043412	macromolecule modification	8	101	0.0052	Rv1711,Rv2851c,dop,mtrA,mtrB,pafA,pup,ribG
GO:0044249	cellular biosynthetic process	26	755	0.0063	Rv1417,Rv3371,ackA,acs,cmk,fadD21,folB,folE,folK,folP1,folP2,glmU,lpqW,mtrA,panB,pta,pykA,r ibA1,ribA2,ribC,ribG,ribH,rplA,rplJ,rplL,rplM
GO:0008152	metabolic process	40	1416	0.0072	Rv1417,Rv1543,Rv1711,Rv2851c,Rv3371,ackA,acs,chn2,cmk,dop,fadD21,folB,folE,folK,folP1,folP2, glmU,lpqW,mpa,mtrA,mtrB,mutA,mutB,pafA,panB,prcA,prcB,pta,pup,pykA,ribA1,ribA2,ribC,rib G,ribH,rplA,rplJ,rplL,rplM,yfiH
GO:1901576	organic substance biosynthetic process	26	767	0.0077	Rv1417,Rv3371,ackA,acs,cmk,fadD21,folB,folE,folK,folP1,folP2,glmU,lpqW,mtrA,panB,pta,pykA,r ibA1,ribA2,ribC,ribG,ribH,rplA,rplJ,rplL,rplM
GO:0034641	cellular nitrogen compound metabolic process	24	686	0.0083	Rv1417,Rv1711,ackA,acs,cmk,folB,folE,folK,folP1,folP2,glmU,mtrA,panB,pta,pykA,ribA1,ribA2,rib C,ribG,ribH,rplA,rplJ,rplL,rplM
GO:0019678	propionate metabolic process, methylmalonyl pathway	2	2	0.0116	mutA,mutB
GO:0006464	cellular protein modification process	6	71	0.0154	Rv2851c,dop,mtrA,mtrB,pafA,pup

GO:0018193	peptidyl-amino acid modification	4	31	0.0203	dop,mtrB,pafA,pup
GO:0042254	ribosome biogenesis	4	33	0.0245	Rv1711,engA,rplA,rplJ
GO:0044085	cellular component biogenesis	8	139	0.0261	Rv1711,bpa,engA,ftsZ,glmU,rplA,rplJ,sepF
GO:0071732	cellular response to nitric oxide	2	4	0.0261	mpa,pafA
GO:0015940	pantothenate biosynthetic process	2	5	0.0327	cmk,panB
GO:0071731	response to nitric oxide	3	19	0.0348	Rv3371,mpa,pafA
GO:0046483	heterocycle metabolic process	20	608	0.0356	Rv1417,Rv1711,ackA,acs,cmk,folB,folE,folK,folP1,folP2,glmU,mtrA,pta,pykA,ribA1,ribA2,ribC,ribG,ribH,rplA
GO:0043650	dicarboxylic acid biosynthetic process	3	20	0.0382	folB,folK,folP1
GO:0015939	pantothenate metabolic process	2	6	0.0406	cmk,panB
GO:0090407	organophosphate biosynthetic process	8	159	0.048	ackA,acs,cmk,folE,glmU,lpqW,pta,pykA
GO:0016310	phosphorylation	6	97	0.0485	ackA,cmk,folK,mtrA,mtrB,pykA
GO:0006082	organic acid metabolic process	13	343	0.05	ackA,acs,cmk,fadD21,folB,folE,folK,folP1,folP2,mutA,mutB,panB,pykA

Table S3. Molecular Function enrichment in the PPI network of the up-regulated proteins of DR strains and other predicted functional partners.

#term ID	Description	Observed Gene Count	Background Gene Count	FDR	Matching Proteins
GO:0070628	proteasome binding	3	3	0.0141	bpa,mpa,pup
GO:0003933	GTP cyclohydrolase activity	2	2	0.0236	folE,ribA2
GO:0004298	threonine-type endopeptidase activity	2	2	0.0236	prcA,prcB
GO:0004494	methylmalonyl-CoA mutase activity	2	3	0.0236	mutA,mutB
GO:0005525	GTP binding	5	30	0.0236	Rv1496,engA,folE,ftsZ,ribA2
GO:0008144	drug binding	14	331	0.0236	Rv1496,Rv2148c,Rv2850c,ackA,acs,cmk,dop,folK,mpa,mtrB,mutA,mutB,pafA,pykA
GO:0008686	3,4-dihydroxy-2-butanone-4-phosphate synthase activity	2	2	0.0236	ribA1,ribA2
GO:0016814	hydrolase activity, acting on carbon-nitrogen (but not peptide) bonds, in cyclic amidines	3	9	0.0236	folE,ribA2,ribG
GO:0032555	purine ribonucleotide binding	15	312	0.0236	Rv1496,Rv2850c,ackA,acs,cmk,dop,engA,folE,folK,ftsZ,mpa,mtrB,pafA,pykA,ribA2
GO:0035639	purine ribonucleoside triphosphate binding	15	307	0.0236	Rv1496,Rv2850c,ackA,acs,cmk,dop,engA,folE,folK,ftsZ,mpa,mtrB,pafA,pykA,ribA2
GO:0036094	small molecule binding	18	497	0.0245	Rv1496,Rv2148c,Rv2850c,ackA,acs,cmk,dop,engA,folE,folK,ftsZ,mpa,mtrB,mutA,mutB,pafA,pykA,ribA2
GO:0005488	binding	32	1122	0.0248	Rv1496,Rv1711,Rv2148c,Rv2850c,ackA,acs,bpa,cmk,dop,engA,folE,folK,folP1,ftsZ,glmU,mpa,mtrA,mtrB,mutA,mutB,pafA,panB,prcB,pup,pykA,ribA1,ribA2,ribG,rplA,rplJ,rplM,yfiH
GO:0016740	transferase activity	16	440	0.034	Rv2851c,Rv3371,ackA,chg2,cmk,fadD21,folK,folP1,glmU,mtrB,pafA,panB,pta,pykA,ribC,ribH
GO:0031419	cobalamin binding	2	5	0.034	mutA,mutB
GO:0043167	ion binding	25	821	0.034	Rv1496,Rv2148c,Rv2850c,ackA,acs,cmk,dop,engA,folE,folK,folP1,ftsZ,glmU,mpa,mtrA,mtrB,mut

					A,mutB,pafA,panB,pykA,ribA1,ribA2,ribG,yfiH
GO:0016810	hydrolase activity, acting on carbon-nitrogen (but not peptide) bonds	4	41	0.0382	dop,folE,ribA2,ribG
GO:0046872	metal ion binding	17	490	0.0382	ackA,acs,dop,folE,folP1,ftsZ,glmU,mtrA,mutA,mutB,pafA,panB,pykA,ribA1,ribA2,ribG,yfiH
GO:0016301	kinase activity	5	67	0.0389	ackA,cmk,folK,mtrB,pykA
GO:0016772	transferase activity, transferring phosphorus-containing groups	7	127	0.0389	ackA,cmk,fadD21,folK,glmU,mtrB,pykA
GO:0016866	intramolecular transferase activity	3	23	0.0389	Rv1711,mutA,mutB
GO:0043168	anion binding	16	465	0.0389	Rv1496,Rv2148c,Rv2850c,ackA,acs,cmk,dop,engA,folE,folK,ftsZ,mpa,mtrB,pafA,pykA,ribA2
GO:0097159	organic cyclic compound binding	23	756	0.0389	Rv1496,Rv1711,Rv2148c,Rv2850c,ackA,acs,cmk,dop,engA,folE,folK,ftsZ,mpa,mtrA,mtrB,mutA,mutB,pafA,pykA,ribA2,rplA,rplJ,rplM
GO:1901363	heterocyclic compound binding	23	756	0.0389	Rv1496,Rv1711,Rv2148c,Rv2850c,ackA,acs,cmk,dop,engA,folE,folK,ftsZ,mpa,mtrA,mtrB,mutA,mutB,pafA,pykA,ribA2,rplA,rplJ,rplM
GO:0003824	catalytic activity	34	1310	0.0477	Rv1496,Rv1543,Rv1711,Rv2850c,Rv2851c,Rv3371,ackA,acs,chg2,cmk,dop,fadD21,folB,folE,folK,folP1,ftsZ,glmU,mpa,mtrB,mutA,mutB,pafA,panB,prcA,prcB,pta,pykA,ribA1,ribA2,ribC,ribG,ribH,yfiH

Table S4. Cellular Component enrichment in the PPI network of the up-regulated proteins of DR strains and other predicted functional partners.

#term ID	Description	Observed Gene Count	Background Gene Count	FDR	Matching Proteins
GO:0000502	proteasome complex	4	4	0.00028	bpa,mpa,prcA,prcB
GO:0005622	intracellular	28	781	0.0027	Rv1711,Rv2148c,ackA,bpa,cmk,folE,folP1,folP2,ftsZ,glmU,iniC,mpa,mtrA,mtrB,mutA,panB,prcA,prcB,pta,pykA,ribC,ribG,ribH,rplA,rplJ,rplL,rplM,sepF
GO:0044424	intracellular part	27	757	0.0033	Rv1711,ackA,bpa,cmk,folE,folP1,folP2,ftsZ,glmU,iniC,mpa,mtrA,mtrB,mutA,panB,prcA,prcB,pta,pykA,ribC,ribG,ribH,rplA,rplJ,rplL,rplM,sepF
GO:0044464	cell part	43	1541	0.0049	Rv1417,Rv1543,Rv1711,Rv2148c,Rv2272,Rv2273,Rv3371,ackA,acs,bpa,chg2,cmk,engA,fadD21,folE,folP1,folP2,ftsZ,glmU,iniA,iniC,lpqB,lpqW,mpa,mtrA,mtrB,mutA,mutB,pafA,panB,prcA,prcB,pta,pykA,ribC,ribG,ribH,rplA,rplJ,rplL,rplM,sepF,yfiH
GO:0005737	cytoplasm	25	729	0.0066	Rv1711,ackA,cmk,folE,folP1,folP2,ftsZ,glmU,iniC,mtrA,mtrB,mutA,panB,prcA,prcB,pta,pykA,ribC,ribG,ribH,rplA,rplJ,rplL,rplM,sepF
GO:0005839	proteasome core complex	2	2	0.0088	prcA,prcB
GO:0022624	proteasome accessory complex	2	2	0.0088	bpa,mpa
GO:0032991	protein-containing complex	9	184	0.0297	bpa,mpa,prcA,prcB,ribH,rplA,rplJ,rplL,rplM
GO:0005829	cytosol	15	416	0.0339	Rv1711,cmk,folP1,folP2,iniC,mtrB,mutA,pykA,ribC,ribG,ribH,rplA,rplJ,rplL,rplM
GO:0005886	plasma membrane	30	1091	0.0341	Rv1417,Rv1543,Rv2272,Rv2273,Rv3371,acs,bpa,chg2,engA,fadD21,ftsZ,iniA,iniC,lpqB,mpa,mtrA,mtrB,mutA,mutB,pafA,panB,prcA,prcB,pykA,ribG,rplA,rplJ,rplL,rplM,sepF

GO:1902494	catalytic complex	5	69	0.0341	bpa,mpa,prcA,prcB,ribH
GO:0022625	cytosolic large ribosomal subunit	3	26	0.0417	rplA,rplJ,rplM
GO:0005618	cell wall	17	529	0.0423	Rv1543,Rv3371,acs,bpa,chp2,engA,iniA,lpqB,mpa,muA,pafA,prcA,rplA,rplJ,rplL,rplM,yfiH

Table S5. Biological Process enrichment in the PPI network of the down-regulated proteins of DR strains and other predicted functional partners.

#term ID	Description	Observed Gene Count	Background Gene Count	FDR	Matching Proteins
GO:0044419	interspecies interaction between organisms	31	301	6.22E-09	PE13,PE35,PE5,PPE18,PPE68,ahpC,ahpE,ctpV,dlaT,eccCb1,eccD1,espA,espB,espC,espJ,espL,esxA,esxB,esxH,esxL,fbpB,groEL2,hbhA,hspX,katG,lppX,mpt83,mycP1,sodA,sodC,tpx
GO:0009405	pathogenesis	22	160	2.66E-08	PE13,PE35,PE5,PPE18,PPE68,ctpV,dlaT,eccCb1,espA,espB,espC,espJ,esxA,esxB,esxH,esxL,hbhA,katG,lppX,mycP1,sodA,tpx
GO:0098869	cellular oxidant detoxification	9	17	5.62E-07	ahpC,ahpD,ahpE,dlaT,katG,sodA,sodC,tpx,trxB2
GO:0006189	'de novo' IMP biosynthetic process	8	12	7.48E-07	purE,purF,purH,purK,purL,purM,purN,purQ
GO:0009306	protein secretion	8	14	1.09E-06	eccCb1,espA,espB,espC,esxA,esxB,tatA,tatB
GO:0046040	IMP metabolic process	8	15	1.37E-06	purE,purF,purH,purK,purL,purM,purN,purQ
GO:0020012	evasion or tolerance of host immune response	9	25	2.47E-06	ahpC,ahpE,eccCb1,eccD1,espC,katG,sodA,sodC,tpx
GO:0044413	avoidance of host defenses	10	35	2.47E-06	ahpC,ahpE,eccCb1,eccD1,espC,espL,katG,sodA,sodC,tpx
GO:0071806	protein transmembrane transport	8	17	2.47E-06	eccCb1,espA,espB,espC,esxA,esxB,tatB,tatC
GO:0015031	protein transport	9	29	3.69E-06	eccCb1,espA,espB,espC,esxA,esxB,tatA,tatB,tatC
GO:0033036	macromolecule localization	10	41	4.19E-06	eccCb1,espA,espB,espC,esxA,esxB,lppX,tatA,tatB,tatC
GO:0052572	response to host immune response	14	96	4.23E-06	ahpC,ahpE,eccCb1,eccD1,espC,espL,esxA,fbpB,hspX,katG,mpt83,sodA,sodC,tpx
GO:0042592	homeostatic process	10	43	5.26E-06	ahpC,ahpD,ahpE,dlaT,eccA3,mctB,mymT,sodC,tpx,trxB2
GO:0070887	cellular response to chemical stimulus	10	43	5.26E-06	ahpC,ahpD,ahpE,dlaT,hspX,katG,sodA,sodC,tpx,trxB2
GO:0051701	interaction with host	15	119	7.06E-06	ahpC,ahpE,eccCb1,eccD1,espC,espL,esxA,fbpB,hbhA,hspX,katG,mpt83,sodA,sodC,tpx
GO:0044315	protein secretion by the type VII secretion system	6	9	9.46E-06	eccCb1,espA,espB,espC,esxA,esxB
GO:0009605	response to external stimulus	16	144	1.24E-05	ahpC,ahpE,eccA3,eccCb1,eccD1,espC,espL,esxA,fbpB,hspX,katG,mpt64,mpt83,sodA,sodC,tpx
GO:0042221	response to chemical	16	153	2.37E-05	ahpC,ahpD,ahpE,csoR,ctpV,dlaT,fbpB,hspX,inhA,katG,mymT,rpoB,sodA,sodC,tpx,trxB2
GO:0045454	cell redox homeostasis	7	21	3.33E-05	ahpC,ahpD,ahpE,dlaT,sodC,tpx,trxB2
GO:0071702	organic substance transport	10	56	3.33E-05	eccCb1,espA,espB,espC,esxA,esxB,lppX,tatA,tatB,tatC
GO:0009168	purine ribonucleoside monophosphate biosynthetic process	9	45	4.54E-05	dlaT,purE,purF,purH,purK,purL,purM,purN,purQ
GO:0044403	symbiont process	17	187	5.68E-05	ahpC,ahpE,eccCb1,eccD1,espC,espL,esxA,fbpB,groEL2,hbhA,hspX,katG,lppX,mpt83,sodA,sodC,tpx
GO:0019725	cellular homeostasis	8	39	0.00013	ahpC,ahpD,ahpE,dlaT,eccA3,sodC,tpx,trxB2
GO:0009167	purine ribonucleoside monophosphate metabolic process	9	54	0.00016	dlaT,purE,purF,purH,purK,purL,purM,purN,purQ

GO:0050896	response to stimulus	25	401	0.00016	ahpC,ahpD,ahpE,csoR,ctpV,dlaT,eccA3,eccCb1,eccD1,espC,espL,esxA,fbpB,groEL2,hspX,inhA,katG,mpt64,mpt83,mymT,rpoB,sodA,sodC,tpx,trxB2
GO:0052059	evasion or tolerance by symbiont of host-produced reactive oxygen species	4	4	0.00019	ahpC,katG,sodA,sodC
GO:0072593	reactive oxygen species metabolic process	4	5	0.00032	katG,sodA,sodC,trxB2
GO:0009152	purine ribonucleotide biosynthetic process	9	63	0.0004	dlaT,purE,purF,purH,purK,purL,purM,purN,purQ
GO:0065008	regulation of biological quality	11	97	0.0004	Rv3057c,ahpC,ahpD,ahpE,dlaT,eccA3,mctB,mymT,sodC,tpx,trxB2
GO:0010035	response to inorganic substance	8	49	0.00045	csoR,ctpV,hspX,katG,mymT,sodA,sodC,trxB2
GO:0052060	evasion or tolerance by symbiont of host-produced nitric oxide	4	6	0.00048	ahpC,ahpE,sodC,tpx
GO:0006810	transport	13	158	0.0014	ctpV,eccA3,eccCb1,espA,espB,espC,esxA,esxB,lppX,mctB,tatA,tatB,tatC
GO:0019430	removal of superoxide radicals	3	3	0.0017	sodA,sodC,trxB2
GO:0040007	growth	27	541	0.0019	PPE4,Rv0525,aroF,dlaT,eccA3,eccB3,eccC3,eccCb1,eccD1,eccD3,eccE3,fbpB,groEL2,hisD,hspX,kasA,lppX,purE,purF,purH,purL,purQ,rpoB,tatA,tatB,tatC,trxB2
GO:0034614	cellular response to reactive oxygen species	4	11	0.0022	katG,sodA,sodC,trxB2
GO:0009150	purine ribonucleotide metabolic process	9	85	0.0024	dlaT,purE,purF,purH,purK,purL,purM,purN,purQ
GO:0051716	cellular response to stimulus	12	167	0.0063	ahpC,ahpD,ahpE,dlaT,eccA3,hspX,katG,mpt64,sodA,sodC,tpx,trxB2
GO:0051409	response to nitrosative stress	4	16	0.0064	ahpC,ahpE,hspX,tpx
GO:0055085	transmembrane transport	10	123	0.0068	ctpV,eccCb1,espA,espB,espC,esxA,esxB,mctB,tatB,tatC
GO:0046688	response to copper ion	3	7	0.0076	csoR,ctpV,mymT
GO:0010038	response to metal ion	4	19	0.0103	csoR,ctpV,hspX,mymT
GO:0006979	response to oxidative stress	6	50	0.0107	ahpD,katG,sodA,sodC,tpx,trxB2
GO:0043953	protein transport by the Tat complex	2	2	0.0169	tatB,tatC
GO:0055070	copper ion homeostasis	2	2	0.0169	mctB,mymT
GO:0006950	response to stress	12	197	0.0206	ahpC,ahpD,ahpE,eccA3,groEL2,hspX,katG,mpt64,sodA,sodC,tpx,trxB2
GO:0065007	biological regulation	19	398	0.0224	Rv3057c,ahpC,ahpD,ahpE,csoR,dlaT,eccA3,espL,fbpB,groEL2,hbhA,hspX,katG,mctB,mycP1,mymT,sodC,tpx,trxB2
GO:0042783	active evasion of host immune response	3	14	0.0349	eccCb1,eccD1,espC
GO:0055076	transition metal ion homeostasis	3	16	0.0463	eccA3,mctB,mymT

Table S6. Molecular Function enrichment in the PPI network of the down-regulated proteins of DR strains and other predicted functional partners.

#term ID	Description	Observed Gene Count	Background Gene Count	FDR	Matching Proteins
GO:0016209	antioxidant activity	9	17	8.88E-07	ahpC,ahpD,ahpE,dlaT,katG,sodA,sodC,tpx,trxB2
GO:0004601	peroxidase activity	5	9	0.0013	ahpC,ahpD,ahpE,katG,tpx
GO:0051920	peroxiredoxin activity	4	6	0.003	ahpC,ahpD,ahpE,tpx

GO:0016667	oxidoreductase activity, acting on a sulfur group of donors	5	19	0.0075	ahpC,ahpD,dlaT,tpx,trxB2
GO:0051287	NAD binding	6	30	0.0075	aroF,hisD,inhA,katG,mmsA,mmsB
GO:0015036	disulfide oxidoreductase activity	4	12	0.0134	ahpD,dlaT,tpx,trxB2
GO:0016668	oxidoreductase activity, acting on a sulfur group of donors, NAD(P) as acceptor	3	8	0.0492	ahpC,dlaT,trxB2

Table S7. Cellular Component enrichment in the PPI network of the down-regulated proteins of DR strains and other predicted functional partners.

#term ID	Description	Observed Gene Count	Background Gene Count	FDR	Matching Proteins
GO:0005576	extracellular region	30	287	1.77E-09	PE13,PE35,PE5,PPE18,PPE68,cfp21,eccB3,espA,espB,espC,espJ,esxA,esxB,esxH,esxK,esxL,esxN,esxR,fbpB,groEL2,hspX,katG,lppX,mpt63,mpt64,mpt70,mpt83,sodA,sodC,tpx
GO:0030312	external encapsulating structure	37	532	1.44E-07	PE13,PPE18,PPE68,Rv0968,ahpC,cfp21,ctpV,dlaT,eccA3,eccB3,eccC3,eccCb1,eccD1,eccD3,eccE3,espC,espL,esxA,esxB,esxL,fbpB,groEL2,hbhA,hisD,hspX,inhA,kasA,katG,lppX,mctB,mpt63,mpt64,mpt83,rpoB,sodC,sseA,tpx
GO:0005618	cell wall	36	529	3.04E-07	PE13,PPE18,PPE68,Rv0968,ahpC,cfp21,ctpV,dlaT,eccA3,eccB3,eccC3,eccCb1,eccD1,eccD3,eccE3,espC,espL,esxA,esxB,esxL,fbpB,groEL2,hbhA,hisD,hspX,inhA,kasA,katG,lppX,mpt63,mpt64,mpt83,rpoB,sodC,sseA,tpx
GO:0044464	cell part	66	1541	6.00E-07	PE13,PE35,PE5,PPE18,PPE36,PPE4,PPE68,Rv0525,Rv0968,Rv0970,Rv2204c,Rv3057c,ahpC,ahpD,ahpE,aroF,cfp21,csoR,ctpV,dlaT,eccA3,eccB3,eccC3,eccCb1,eccD1,eccD3,eccE3,espA,espC,espK,espL,esxA,esxB,esxL,esxN,fbpB,groEL2,hbhA,hisD,hspX,inhA,kasA,katG,lppX,mctB,mmsA,mpt63,mpt64,mpt70,mpt83,mycP1,purH,purK,purL,purM,purQ,rpmB1,rpoB,sodA,sodC,sseA,tatA,tatB,tatC,tpx,trxB2
GO:0071944	cell periphery	55	1224	5.72E-06	PE13,PPE18,PPE36,PPE4,PPE68,Rv0525,Rv0968,Rv0970,Rv2204c,ahpC,ahpD,cfp21,csoR,ctpV,dlaT,eccA3,eccB3,eccC3,eccCb1,eccD1,eccD3,eccE3,espA,espC,espK,espL,esxA,esxB,esxL,esxN,fbpB,groEL2,hbhA,hisD,hspX,inhA,kasA,katG,lppX,mctB,mpt63,mpt64,mpt83,mycP1,purH,purK,purQ,rpoB,sodA,sodC,sseA,tatA,tatB,tatC,tpx
GO:0005615	extracellular space	5	8	0.0001	espA,mpt63,mpt70,mpt83,sodC
GO:0005886	plasma membrane	46	1091	0.00043	PPE36,PPE4,PPE68,Rv0525,Rv0968,Rv0970,Rv2204c,ahpC,ahpD,csoR,ctpV,dlaT,eccA3,eccB3,eccC3,eccCb1,eccD1,eccD3,eccE3,espA,espK,espL,esxA,esxB,esxL,esxN,fbpB,groEL2,hbhA,hspX,inhA,kasA,katG,lppX,mpt83,mycP1,purH,purK,purQ,rpoB,sodA,sodC,sseA,tatA,tatB,tatC
GO:0009986	cell surface	7	34	0.00043	PE35,PE5,PPE18,PPE68,hbhA,lppX,mycP1
GO:0016020	membrane	47	1122	0.00043	PPE36,PPE4,PPE68,Rv0525,Rv0968,Rv0970,Rv2204c,ahpC,ahpD,csoR,ctpV,dlaT,eccA3,eccB3,eccC3,eccCb1,eccD1,eccD3,eccE3,espA,espK,espL,esxA,esxB,esxL,esxN,fbpB,groEL2,hbhA,hspX,inhA,kasA,katG,lppX,mctB,mpt83,mycP1,purH,purK,purQ,rpoB,sodA,sodC,sseA,tatA,tatB,tatC
GO:0005829	cytosol	24	416	0.00062	Rv2204c,Rv3057c,ahpC,ahpD,ahpE,aroF,dlaT,eccA3,espK,groEL2,hbhA,hisD,hspX,kasA,katG,purK,purM,rpmB1,rpoB,sodA,sseA,tatC,tpx,trxB2
GO:0044444	cytoplasmic part	25	483	0.0021	Rv2204c,Rv3057c,ahpC,ahpD,ahpE,aroF,dlaT,eccA3,espK,groEL2,hbhA,hisD,hspX,kasA,katG,mm

					sA,purK,purM,rpmB1,rpoB,sodA,sseA,tatC,tpx,trxB2
GO:0031975	envelope	5	32	0.0108	PE5,groEL2,mctB,mpt70,mpt83
GO:0030313	cell envelope	4	19	0.0114	groEL2,mctB,mpt70,mpt83
GO:0005737	cytoplasm	30	729	0.0158	Rv2204c,Rv3057c,ahpC,ahpD,ahpE,aroF,csoR,dlaT,eccA3,eccCb1,espK,esxA,groEL2,hbhA,hisD,hs pX,kasA,katG,mmsA,purK,purL,purM,purQ,rpmB1,rpoB,sodA,sseA,tatC,tpx,trxB2
GO:0044165	host cell endoplasmic reticulum	2	2	0.0169	esxA,esxB
GO:0044228	host cell surface	2	3	0.0248	esxA,esxB
GO:0042597	periplasmic space	3	15	0.035	mpt70,mpt83,sodA

Table S8. Biological Process enrichment in the PPI network of the specific expressed proteins of DR strains and other predicted functional partners.

#term ID	Description	Observed Gene Count	Background Gene Count	FDR	Matching Proteins
GO:0009108	coenzyme biosynthetic process	11	88	1.99E-05	moaA1,moaA2,moaC1,moaC3,moeB2,nadA,nadB,nadC,nadD,nadE,pfkB
GO:0009435	NAD biosynthetic process	5	7	4.57E-05	nadA,nadB,nadC,nadD,nadE
GO:0019674	NAD metabolic process	5	9	5.65E-05	nadA,nadB,nadC,nadD,nadE
GO:0019359	nicotinamide nucleotide biosynthetic process	6	22	9.42E-05	nadA,nadB,nadC,nadD,nadE,pfkB
GO:0006777	Mo-molybdopterin cofactor biosynthetic process	5	13	0.00012	moaA1,moaA2,moaC1,moaC3,moeB2
GO:0019720	Mo-molybdopterin cofactor metabolic process	5	13	0.00012	moaA1,moaA2,moaC1,moaC3,moeB2
GO:0046496	nicotinamide nucleotide metabolic process	6	30	0.00017	nadA,nadB,nadC,nadD,nadE,pfkB
GO:0090407	organophosphate biosynthetic process	11	159	0.00027	moaA1,moaA2,moaC1,moaC3,moeB2,nadA,nadB,nadC,nadD,nadE,pfkB
GO:0019637	organophosphate metabolic process	11	205	0.0022	moaA1,moaA2,moaC1,moaC3,moeB2,nadA,nadB,nadC,nadD,nadE,pfkB
GO:0006531	aspartate metabolic process	2	2	0.0158	nadA,nadD
GO:0006796	phosphate-containing compound metabolic process	11	269	0.0158	moaA1,moaA2,moaC1,moaC3,moeB2,nadA,nadB,nadC,nadD,nadE,pfkB
GO:0034628	'de novo' NAD biosynthetic process from aspartate	2	2	0.0158	nadA,nadD
GO:0046874	quinolinate metabolic process	2	2	0.0158	nadA,nadC
GO:0018130	heterocycle biosynthetic process	12	355	0.0376	mce2R,moaA1,moaA2,moaC1,moaC3,moeB2,nadA,nadB,nadC,nadD,nadE,pfkB
GO:1901566	organonitrogen compound biosynthetic process	13	401	0.0376	cysO,moaA1,moaA2,moaC1,moaC3,moeB1,moeB2,nadA,nadB,nadC,nadD,nadE,pfkB

Table S9. Cellular Component enrichment in the PPI network of the specific expressed proteins of DR strains and other predicted functional partners.

#term ID	Description	Observed Gene Count	Background Gene Count	FDR	Matching Proteins
GO:0019008	molybdopterin synthase complex	2	2	0.0237	moaA1,moaA2

Table S10. Biological Process enrichment in the PPI network of the unexpressed proteins of DR strains and other predicted functional partners.

#term ID	Description	Observed Gene Count	Background Gene Count	FDR	Matching Proteins
GO:0071770	DIM/DIP cell wall layer assembly	11	19	0.00024	Rv2953,Rv2959c,drdB,fadD26,papA5,pks1,ppsA,ppsB,ppsC,ppsD,ppsE
GO:0018958	phenol-containing compound metabolic process	8	14	0.0052	ideR,mbtB,mbtG,mbtI,ppsA,ppsB,ppsC,ppsD
GO:0034660	ncRNA metabolic process	16	68	0.0052	dtd,fmt,gltS,ksgA,pheT,rimM,rlmN,rnc,rsmE,rsmI,trmB,trmD,trlI,trpS,truA,ybeY
GO:0071766	Actinobacterium-type cell wall biogenesis	13	49	0.0057	Rv2953,Rv2959c,drdB,fadD23,fadD26,mmpL3,papA5,pks1,ppsA,ppsB,ppsC,ppsD,ppsE
GO:0034470	ncRNA processing	12	43	0.006	fmt,ksgA,rimM,rlmN,rnc,rsmE,rsmI,trmB,trmD,trlI,truA,ybeY
GO:0001510	RNA methylation	7	14	0.0104	ksgA,rlmN,rsmE,rsmI,trmB,trmD,trlI
GO:0044085	cellular component biogenesis	22	139	0.0104	Rv1433,Rv2953,Rv2959c,drdB,engA,fadD23,fadD26,ksgA,mmpL3,papA5,pks1,ppsA,ppsB,ppsC,ppsD,ppsE,rimM,rlmN,rnc,rsmE,rsmI,ybeY
GO:0009451	RNA modification	9	30	0.019	fmt,ksgA,rlmN,rsmE,rsmI,trmB,trmD,trlI,truA
GO:0006364	rRNA processing	7	21	0.0194	ksgA,rimM,rlmN,rnc,rsmE,rsmI,ybeY
GO:0006399	tRNA metabolic process	11	47	0.0194	dtd,fmt,gltS,pheT,rlmN,rnc,trlI,trpS,truA
GO:0006633	fatty acid biosynthetic process	13	64	0.0194	fadD23,fadD26,mbtB,pks1,pks2,pks4,pks5,ppsA,ppsB,ppsC,ppsD,ppsE,ufaA1
GO:0008610	lipid biosynthetic process	22	155	0.0194	Rv2953,Rv2957,Rv2958c,Rv2959c,Rv2962c,drdB,fadD23,fadD26,mbtB,mmpL8,papA1,papA5,pks1,pks2,pks4,pks5,ppsA,ppsB,ppsC,ppsD,ppsE,ufaA1
GO:0009273	peptidoglycan-based cell wall biogenesis	14	74	0.0194	Rv1433,Rv2953,Rv2959c,drdB,fadD23,fadD26,mmpL3,papA5,pks1,ppsA,ppsB,ppsC,ppsD,ppsE
GO:0030488	tRNA methylation	4	4	0.0194	rlmN,trlI,trmB,trlI
GO:0032259	methylation	13	65	0.0194	Rv0145,Rv0146,Rv0560c,Rv1405c,Rv2959c,ksgA,rlmN,rsmE,rsmI,trlI,truA
GO:0042844	glycol metabolic process	5	7	0.0194	fadD26,ppsA,ppsB,ppsC,ppsD
GO:0044550	secondary metabolite biosynthetic process	6	14	0.0194	cysD,cysN,ideR,mbtB,mbtG,mbtI
GO:0046189	phenol-containing compound biosynthetic process	5	7	0.0194	mbtI,ppsA,ppsB,ppsC,ppsD
GO:0071554	cell wall organization or biogenesis	16	95	0.0194	Rv1433,Rv2953,Rv2959c,drdB,fadD23,fadD26,mmpL3,mmpL8,papA5,pks1,ppsA,ppsB,ppsC,ppsD,ppsE,ufaA1
GO:0071840	cellular component organization or biogenesis	24	182	0.0194	Rv1433,Rv2953,Rv2959c,drdB,engA,fadD23,fadD26,ksgA,mmpL3,mmpL8,papA5,pks1,ppsA,ppsB,ppsC,ppsD,ppsE,rimM,rlmN,rnc,rsmE,rsmI,ufoA1,ybeY
GO:0072330	monocarboxylic acid biosynthetic process	16	92	0.0194	bioD,dlaT,fadD23,fadD26,mbtB,mbtI,pks1,pks2,pks4,pks5,ppsA,ppsB,ppsC,ppsD,ppsE,ufoA1
GO:0097040	phthiocerol biosynthetic process	5	7	0.0194	fadD26,ppsA,ppsB,ppsC,ppsD
GO:1901264	carbohydrate derivative transport	4	4	0.0194	drdB,drdB,mmpL3
GO:0006400	tRNA modification	6	17	0.0321	fmt,rlmN,trlI,truA
GO:0097041	phenolic phthiocerol biosynthetic process	4	6	0.0321	ppsA,ppsB,ppsC,ppsD
GO:0008033	tRNA processing	7	25	0.0341	fmt,rlmN,rnc,trlI,truA
GO:0042254	ribosome biogenesis	8	33	0.0346	engA,ksgA,rimM,rlmN,rnc,rsmE,rsmI,ybeY
GO:0010106	cellular response to iron ion starvation	5	12	0.0355	Rv0560c,irtA,mbtB,mbtI,pks2

GO:0009712	catechol-containing compound metabolic process	4	7	0.0407	ideR,mbtB,mbtG,mbtI
GO:0019540	siderophore biosynthetic process from catechol	4	7	0.0407	ideR,mbtB,mbtG,mbtI
GO:0042891	antibiotic transport	4	7	0.0407	Rv1634,drrA,drrB,drrC
GO:1901617	organic hydroxy compound biosynthetic process	7	28	0.0453	fadD26,mbtI,ppsA,ppsB,ppsC,ppsD,snoP
GO:0043215	daunorubicin transport	3	3	0.0455	drrA,drrB,drrC
GO:1900753	doxorubicin transport	3	3	0.0455	drrA,drrB,drrC
GO:0010467	gene expression	29	274	0.0468	fmt,gltS,ideR,ksgA,lepA,mmpR5,mtrA,pheT,prfA,rimM,rlmN,rnc,rplS,rplU,rpmA,rpsP,rsbW,rsmE,rsmI,sigH,sigL,sigL,sigM,trmB,trmD,trlI,trlS,truA,ybeY

Table S11. Cellular Component enrichment in the PPI network of the unexpressed proteins of DR strains and other predicted functional partners.

#term ID	Description	Observed Gene Count	Background Gene Count	FDR	Matching Proteins
GO:0032991	protein-containing complex	26	184	0.0085	accD5,atpH,carA,cysD,cysN,dlaT,drrB,drrC,mbtI,obg,pheT,pks4,ppsA,ppsB,ppsC,ppsD,ppsE,rimM,rplS,rplU,rpmA,rpsP,snoP,tmB,trlI,xseB
GO:0034081	polyketide synthase complex	6	10	0.0085	pks4,ppsA,ppsB,ppsC,ppsD,ppsE
GO:1902494	catalytic complex	13	69	0.0145	accD5,carA,cysD,cysN,dlaT,drrB,drrC,mbtI,pheT,snoP,tmB,trlI,xseB