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Supplemental Information

^{13}C-Flux Spectral Analysis of Host-Pathogen Metabolism Reveals a Mixed Diet for Intracellular *Mycobacterium tuberculosis*

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Inventory of Supplemental Information

(MTB), intracellular MTB, intracellular PEPCK KO and infected THP-1 macrophages cultivated with sodium [^{13}C] bicarbonate.

Table S4, Related to Figure 5. Experimental (GC-MS) mass distributions in the amino acid derivatives extracted from ΔPEPCK KO cultivated in [U^{13}-C$_6$] glucose RPMI and intracellular ΔPEPCK grown inside THP-1 macrophages which were pre-labelled with [U-^{13}C$_6$] glucose.

Table S5, Related to Experimental Procedures. Network reference model of the central metabolism of *Mycobacterium tuberculosis.*

Table S6, Related to Experimental Procedures. Experimental (GC-MS) and calculated mass distributions in the amino acid derivatives of *Mycobacterium tuberculosis* (MTB) residing in the macrophage environment (MAC) .

Table S5: Network reference model of the central metabolism of *Mycobacterium tuberculosis*

Reaction	Stoichiometry and C-atom transitions
GlcUptake(_0/_1)	GLC(#ABCDEF) → G6P(#ABCDEF)
GlycUptake(_0/_1)	GLYC_IN (#ABC) → GAP (#ABC)
OLACUptake(_0/_1)	OLAC (#AB) → ACE (#AB)
aceProd	ACE (#AB) ⇆ ACCOA (#AB)
AlaUptake	ALA_IN (#ABC) → ALA (#ABC)
AspUptake	ASP (#ABC) → ASP (#ABC)
CO2out	CO_2 (#A) → CO_{2ex} (#A)
GluUptake	GLU_IN (#ABCDE) → GLU (#ABCDE)
GlycUptake	GLYC (#ABC) → GAP (#ABC)
HisUptake	HIS_IN (#ABCDEF) → HIS (#ABCDEF)
IsoUptake	ISO_IN (#ABCDEF) → ISO (#ABCDEF)
LeuUptake	LEU_IN (#ABCDEF) → LEU (#ABCDEF)
LysUptake	LYS_IN (#ABCDEF) → LYS (#ABCDEF)
SerUptake	SER_IN (#ABC) → SER (#ABC)
ThrUptake	THR_IN (#ABCD) → THR (#ABCD)
TyrUptake	TYR_IN (#ABCDEFGHI) → TYR (#ABCDEFGHI)
ValUptake	VAL_IN (#ABCDE) → VAL (#ABCDE)
pgi	G6P (#ABCDEF) ↔ FBP (#ABCDEF)
fba	GAP (#CBA) + GAP (#DEF) ↔ FBP (#ABCDEF)
gapA	GAP (#ABC) ↔ PGA (#ABC)
pykeno	PGA (#ABC) ↔ PYRPEP (#ABC)
gnd	G6P (#ABCDEF) → P5P (#BCDEF) + CO_2 (#A)
tkt1	GAP (#CDE) + G6P (#ABabcd) ↔ P5P (#ABCDE) + E4P (#abcd)
tkt2	S7P (#ABabcde) + GAP (#CDE) ↔ P5P (#ABCDE) + P5P (#abcde)
tal	E4P (#defg) + G6P (#abcABC) ↔ GAP (#ABC) + S7P (#abcdefg)
pdh	PYRPEP (#ABC) → ACCOA (#BC) + CO_2 (#A)
cs	MALOAA (#ABCD) + ACCOA (#ab) ⇆ ICIT (#DCBbaA)
icdh	ICIT (#ABCDEF) ⇆ OXG (#ABCDE) + CO_2 (#F)
kor	OXG (#ABCDE) ⇆ SUCCOA (#BCDE) + CO_2 (#A)
scs	SUCCOA (#ABCD) ↔ SUC (#ABCD)
sdh	SUC (#ABCD) ↔ FUM (#ABCD)
fum(a/b)	FUM (#ABCD) ↔ MALOAA (0.5 #ABCD + 0.5 #DCBA)
icl	ICIT (#ABCDEF) ⇆ GLX (#AB) + SUC (#FCDE)
ms	GLX (#AB) + ACCOA (#ab) → MALOAA (#ABba)
pckmez	PYRPEP (#ABC) + CO_2 (#a) ↔ MALOAA (#ABCa)
alaProd	PYRPEP (#ABC) ⇆ ALA (#ABC)
kivProd	PYR (#ABC) + PYR (#abc) → KIV (#ABCbc) + CO_2 (#a)
valProd	KIV (#ABCDE) ⇆ VAL (#ABCDE)
leuProd	KIV (#ABCDE) + ACCOA (#ab) ⇆ LEU (#BCDEab) + CO_2 (#A)
serProd	GAP (#ABC) ⇆ SER (#ABC)
gl1	SER (#ABC) ⇆ GLY (#AB) + MTHF (#C)
hisProd	P5P (#ABCDE) +MTHF(#F) ⇆ HIS (#FEDCBA)
gl2	GLY (#AB) ⇆ MTHF (#B) + CO2(#A)
aspProd	MALOAA (#ABCD) ⇆ ASP (#ABCD)

thrProd	ASP (#ABCD) ⇆ THR (#ABCD)
metProd	ASP (#ABCD) → MET (#ABCD)
lysProd(1/2)	PYRPEP (#ABC) + ASP (#ABCD) ⇆ LYS (0.5 #BCabcd + 0.5 #ABCbcd) + CO_2 (0.5 #A + 0.5 #a)
isoProd	THR (#ABCD) + PYRPEP (#abc) ⇆ ISO (#ABCDbc) + CO_2 (#a)
gluProd	OXG (#ABCDE) ⇆ GLU (#ABCDE)
proProd	GLU (#ABCDE) → PRO (#ABCDE)
ornProd	GLU (#ABCDE) → ORN (#ABCDE)
pheProd1	E4P (#ABCD) + PYRPEP (#abc) → CHO (#bcABCDa)
pheProd2	CHO (#ABCDEFG) + PYRPEP (#abc) → PHE (#abcABCDEF) + CO_2 (#G)
tyrProd	CHO (#ABCDEFG) + PYRPEP (#abc) ⇆ TYR (#abcABCDEF) + CO_2 (#G)
Bio	0.046 ALA+ 0.009 LEU+ 0.006 SER + 0.012 GLY + 0.012 LYS +0.005 ISO + 0.017 HIS + 0.026 ASP+ 0.007 THR+ 0.002 MET +0.007 PRO + 0.018 GLU + 0.002 TYR + 0.003 PHE + 0.026 VAL + 0.018 G6P + 0.041 F6P (taken from G6P pool) + 0.065 P5P + 0.001 GAP + 0.005 PGA + 0.015 PEP (taken from PYRPEP pool) + 0.015 PYR (taken from PYRPEP pool) + 0.589 ACCOA + 0.022 MALOAA + 0.015 OXG [all in mmol g_{DW}^{-1}] → 1 BIO [in g_{DW}]

Legend:
⇆: net fluxes possible in both directions, zero exchange flux
→: net flux in specified direction, zero exchange flux
↔: net flux possible in both directions, exchange flux present

Model assumptions and simplifications:
Linear reaction sequences without carbon cleavage were condensed for simplification. Metabolite pools F6P and G6P are lumped to one pool (G6P), as the interconverting phosphoglucose isomerase reaction has usually a high exchange rate. Pyruvate and PEP, malate and oxaloacetate were lumped to one pool PYRPEP and MALOAA, respectively. Irreversibility assumptions are due to thermodynamic considerations and indicated by directed arrows.