Supplementary material for

Lactobacillus rhamnosus colonisation antagonizes *Candida albicans* by forcing metabolic adaptations that compromise pathogenicity

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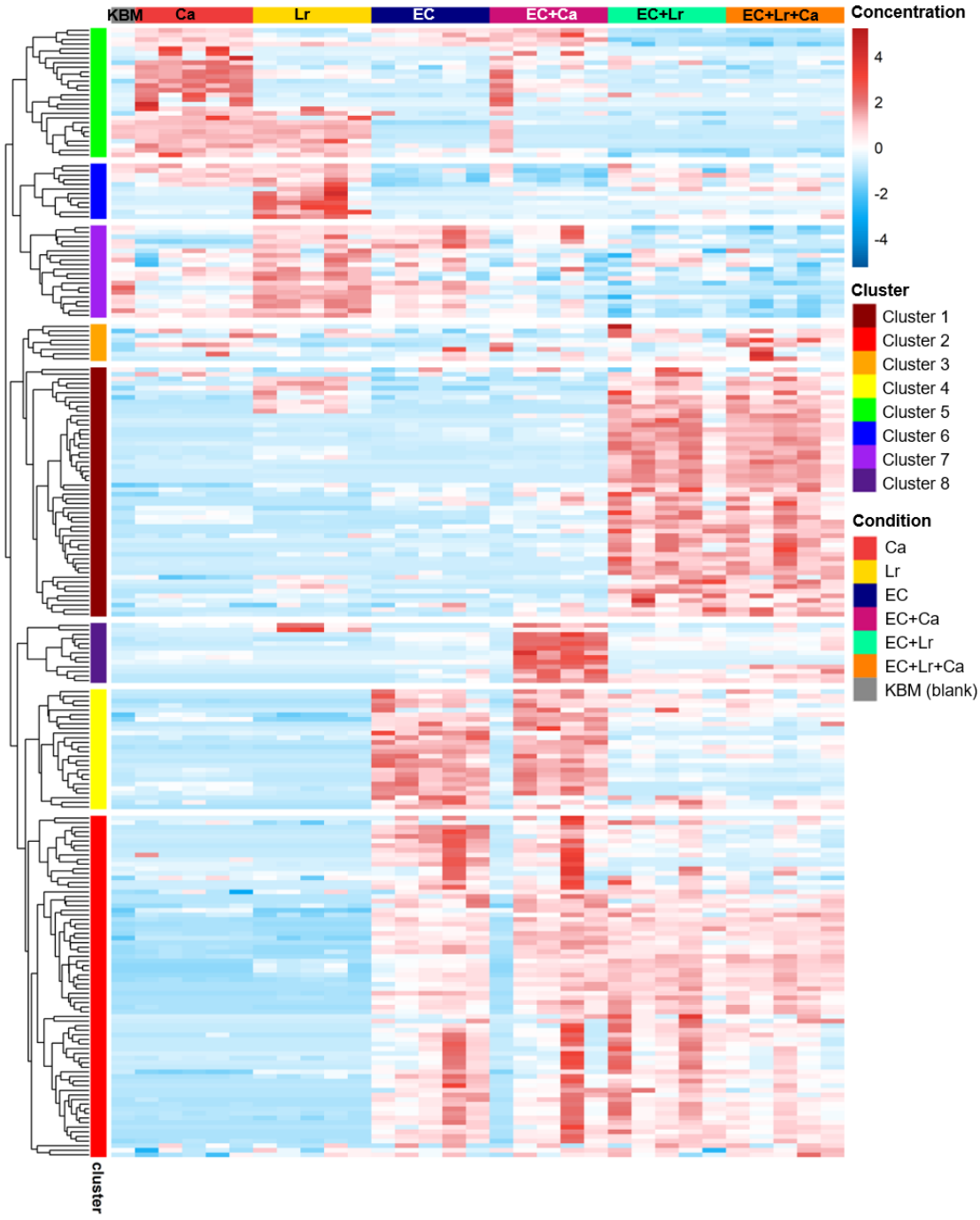
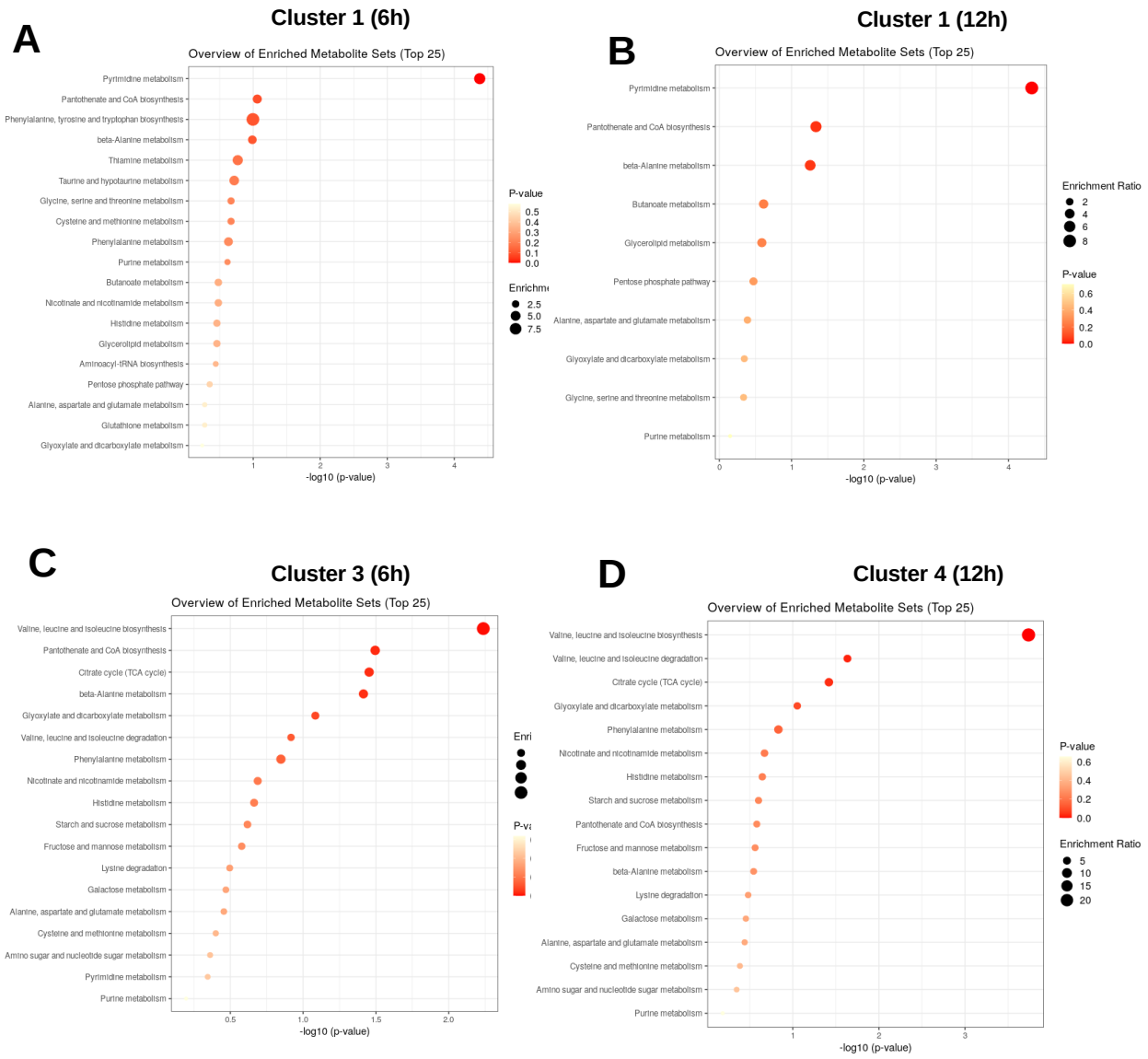


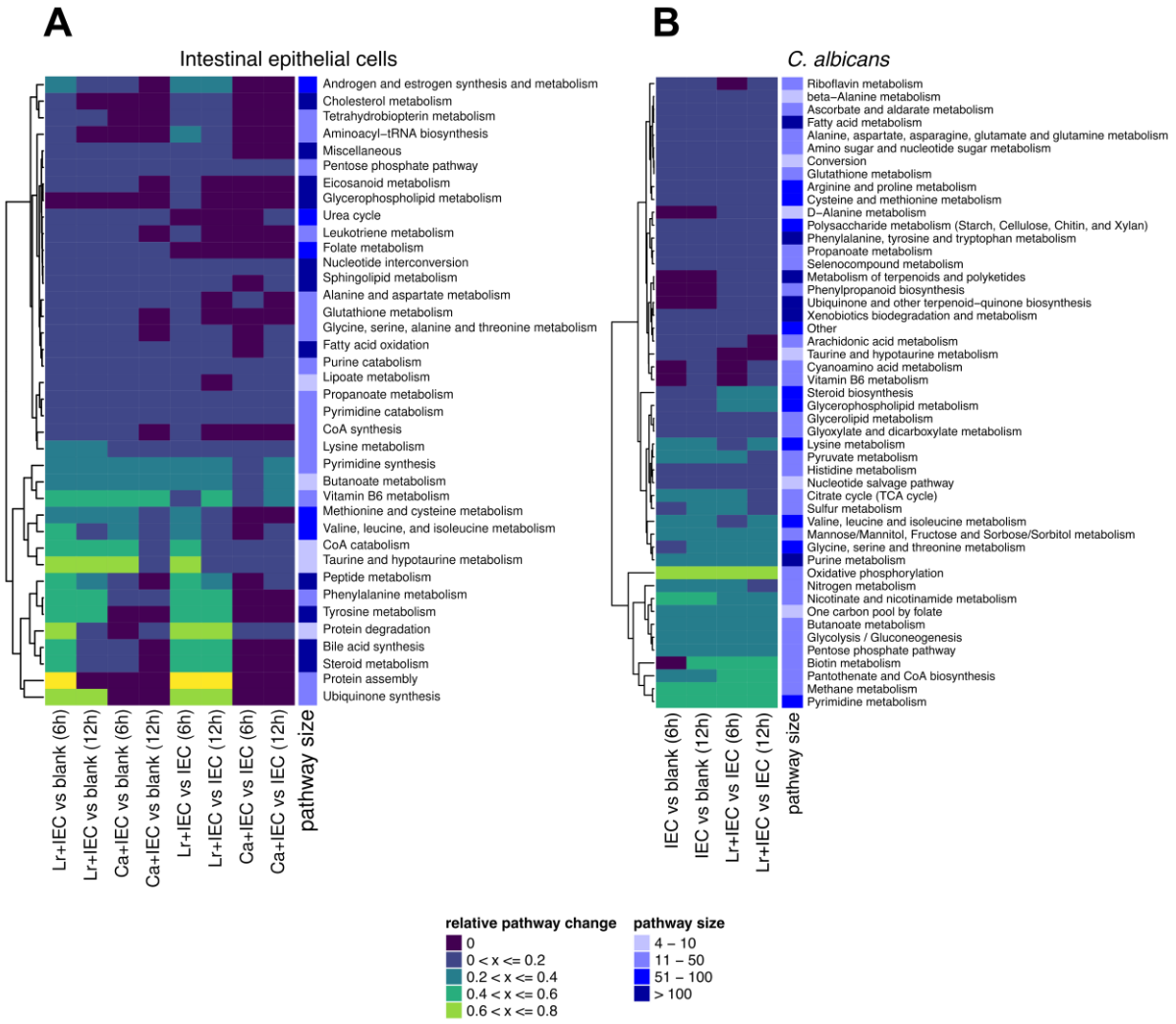
Supplementary Fig. 1: Untargeted metabolomics of *in vitro* intestinal epithelial *L. rhamnosus* colonization and *C. albicans* infection

Hierarchical clustering of the presence and absence of metabolites in the *in vitro* model at 12 hours post infection (hpi).



Supplementary Fig. 2: Enriched metabolic pathways

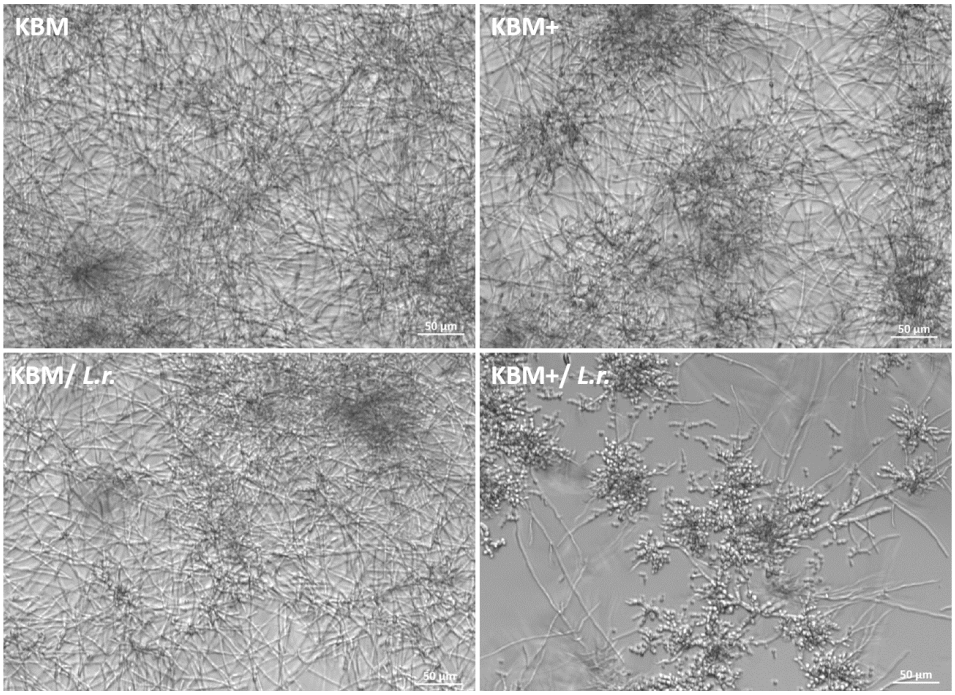
Overview of the top 25 enriched metabolic sets in the supernatants analysed by a hypergeometric test in the clusters of (A) metabolites produced by IECs and *L. rhamnosus* in synergy at 6h and (B) 12h; and (C) produced by IECs and consumed by *L. rhamnosus* at 6h and (D) 12h. Dot size represents enrichment ratio obtained with overrepresentation analysis and colour of the dots represents *p*-value (FDR-correction applied, FDR ≤ 0.1 was considered).



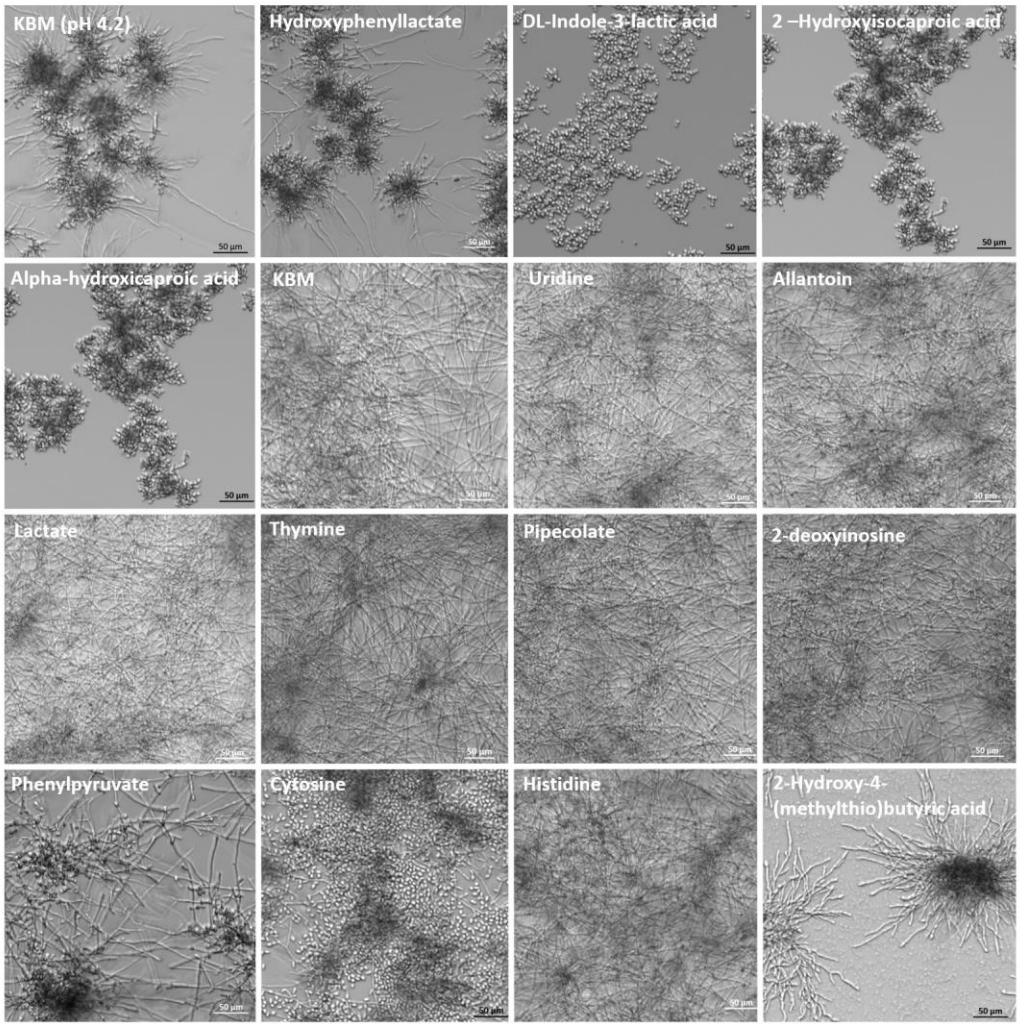
Supplementary Fig. 3: Pathway flux activity of IECs and *C. albicans*

Simulation of pathway activity levels in IECs (A) and in *C. albicans* (B) compared between different setups as indicated. Relative pathway change was determined by identifying the number of pathway-specific reactions for which feasible flux ranges differ according to flux variability analysis.

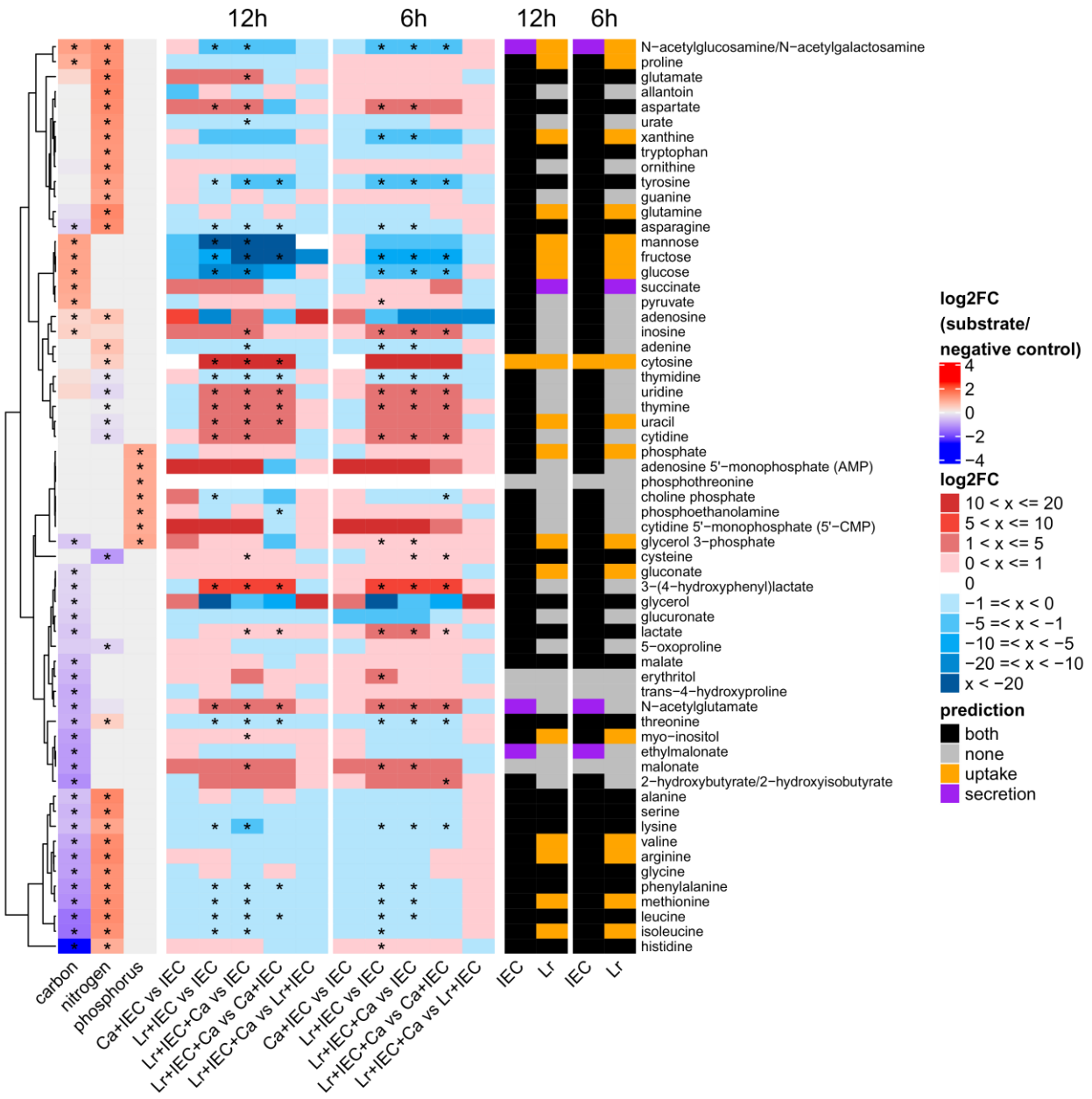
A


KBM
KBM+
KBM/ L.r.
KBM+/ L.r.

B

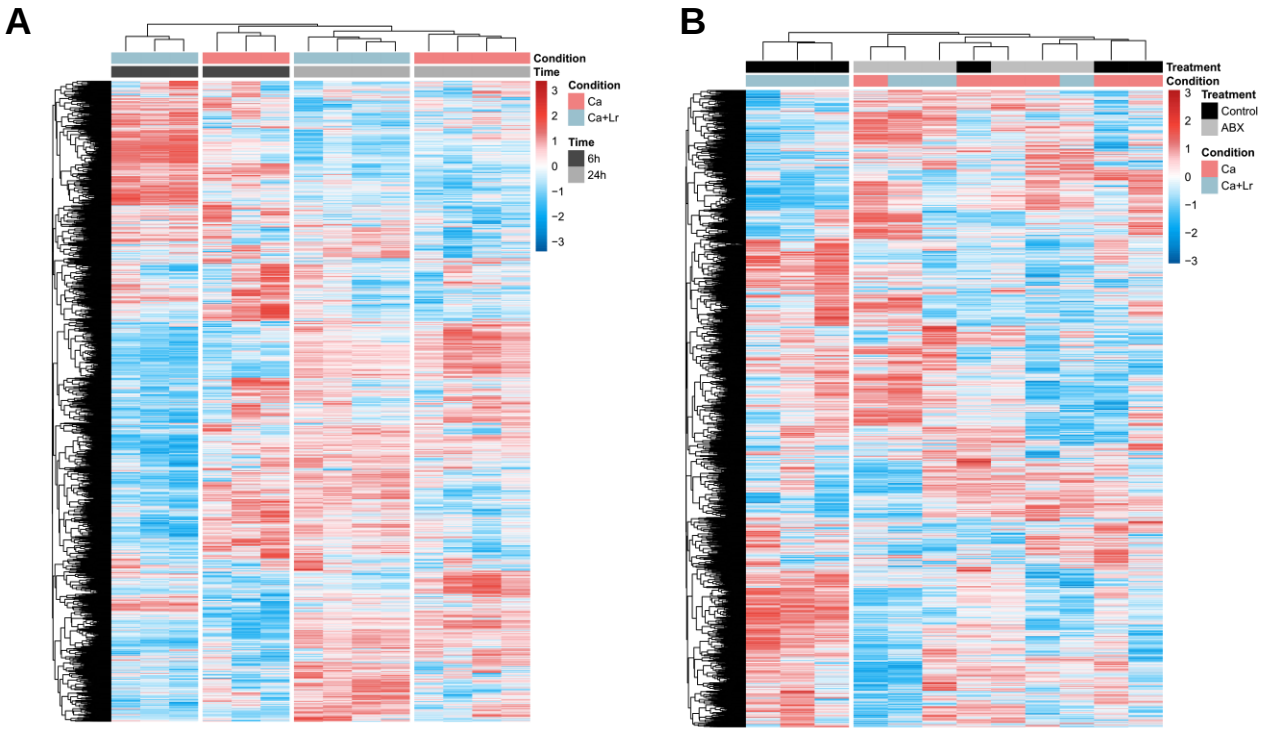

KBM (pH 4.2)
Hydroxyphenyllactate
DL-Indole-3-lactic acid
2 –Hydroxyisocaproic acid
Alpha-hydroxicaproic acid
KBM
Uridine
Allantoin
Lactate
Thymine
Pipecolate
2-deoxyinosine
Phenylpyruvate
Cytosine
Histidine
2-Hydroxy-4-(methylthio)butyric acid

Supplementary Fig. 4: Impact of *L. rhamnosus*-colonization derived metabolites on *C. albicans*
(A) Representative images of *C. albicans* morphology changes grown in *L. rhamnosus*-conditioned or unconditioned media, after 20 h at 37°C with 5% CO_2 (n=3 biological replicates). (B) Representative images of *C. albicans* morphology grown in presence of all the metabolites tested, at neutral or acidic pH, after 20 h at 37°C with 5% CO_2 (n=2 biological replicates).



Supplementary Fig. 5: *L. rhamnosus* colonization creates an unfavourable metabolic environment for *C. albicans*

Phenotypic microarray growth experiments for wild-type *C. albicans* on a carbon, nitrogen or phosphorous source (left). Metabolome data measured at 6 and 12 h as well as metabolic modelling predictions (right) are indicated for the whole panel of metabolites. For metabolic modelling, media was adapted from metabolome data derived from IECs spent media or blank. Uptake or secretion was determined by identifying feasible flux ranges for metabolite-specific exchange reactions alongside optimization for biomass. ANOVA (two-sided) was performed for phenotypic microarrays, Wilcoxon test (two-sided) for metabolomics, with FDR correction (* = $p_{adj} \leq 0.05$).



Supplementary Fig. 6: Changes in *C. albicans* gene expression upon infection of *L. rhamnosus* colonized IECs

(A) Hierarchical clustering based on Euclidean distance of *C. albicans* gene expression at 6 and 24 h during *in vitro* infection of IECs in the presence and absence of *L. rhamnosus* colonization. Data summarized from n=3 and n=4 independent experiments at 6 and 24 hpi respectively. (B) Hierarchical clustering based on Euclidean distance of *C. albicans* gene expression during *in vitro* infection of IECs in the presence and absence of *L. rhamnosus* colonization and in the presence and absence of antibiotics. Data summarized from n=3 at 24 hpi.

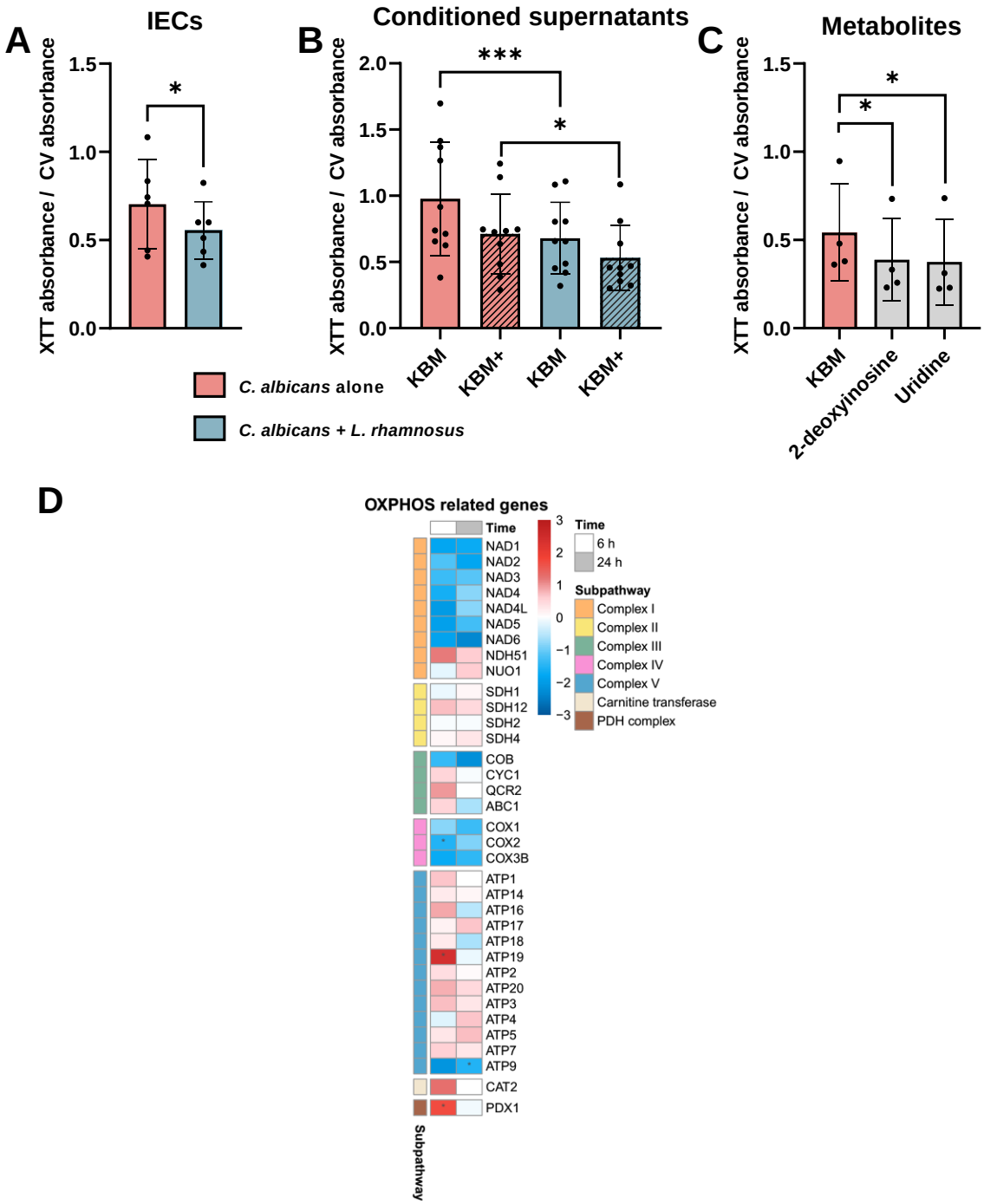
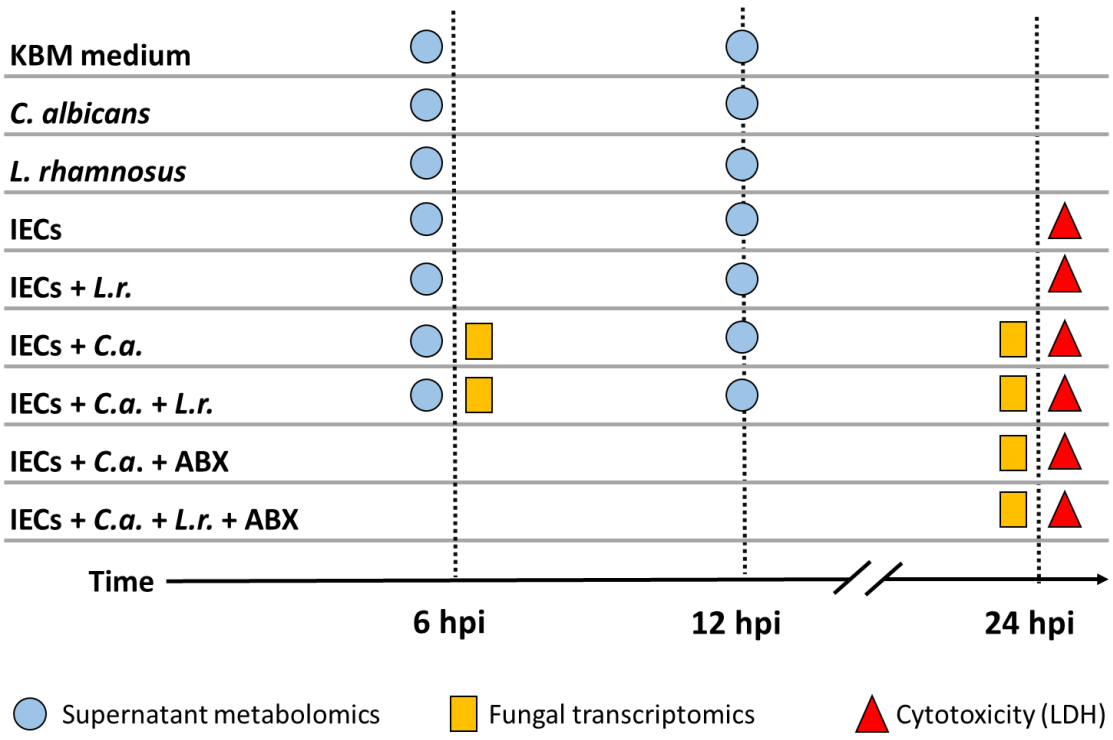


Fig. S7 *L. rhamnosus* modulates activity of *C. albicans* mitochondrial dehydrogenases

(A) Mitochondrial activity, represented as conversion of XTT by mitochondrial dehydrogenases (XTT absorbance) normalized with biomass (crystal violet (CV) absorbance, of *C. albicans* incubated in supernatants of *L. rhamnosus*-colonized or uncolonized IECS (1h, 37°C, 5% CO_2) (n=6, * = *p* 0.0350), or (B) in *L. rhamnosus*-conditioned or unconditioned KBM or KBM+ medium independently of host cells (1h, 37°C, 5% CO_2) (n=10, *** = *p* 0.0007 for KBM and * = *p* 0.0170 for KBM+), or (C) in presence or absence of 50 mM uridine (* = *p* 0.0470)or 2-deoxyinosine (* = *p* 0.0278) (24h, 37°C, 5% CO_2) (n=4). Bars represent the mean and error bars show standard

deviation (SD), dots represent the mean of technical replicates of the individual experiments, data were compared for significance using a paired t-test (two-tailed), * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$. Source data are provided as a Source Data file. (D) Heatmap showing the transcriptional regulation of *C. albicans* OXPHOS genes as a result of *L. rhamnosus* colonization prior to infection at 6 and 24 hpi. Legend colour represents the Log_2 fold change of the regulation in presence *vs.* absence of *L. rhamnosus*. The asterisks (*) represent significance, based on the criteria of a Log_2 fold change of > 1 or < -1 and a moderated t-test Bonferroni corrected *p*-value of < 0.05. Data summarized from n=3 and n=4 independent experiments at 6 and 24 hpi respectively.



Supplementary Fig. 8: Study design

Overview of the samples, taken at different time points for transcriptional, metabolic, and cytotoxicity analysis in the *in vitro* model, in the presence of intestinal epithelial cells (IECs), *L. rhamnosus* (*L.r.*), *C. albicans* (*C.a.*) and antibiotics (ABX).

Supplementary Table 1: Metabolites of the clusters 1-8 shown in Fig. 2B (6 hpi).

Cluster 1 "Secreted by *L. rhamnosus* colonized IECs"
(N(1) + N(8))-acetylspermidine
1-carboxyethyltyrosine
1-palmitoyl-2-linoleoyl-GPC (16:0/18:2)
2'-deoxycytidine
2'-deoxyinosine
2-hydroxy-3-methylvalerate
2-hydroxy-4-(methylthio)butanoic acid
2-hydroxybutyrate/2-hydroxyisobutyrate
2-hydroxyglutarate
2R,3R-dihydroxybutyrate
3-(4-hydroxyphenyl)lactate
3-formylindole
3-hydroxyoctanoate
3-indoleglyoxylic acid
4-methylthio-2-oxobutanoate
5-methyluridine (ribothymidine)
allantoin
alpha-hydroxyisocaproate
alpha-hydroxyisovalerate
benzoate
cysteine
cytidine
cytosine
dihydroorotate
glycerate
glycerophosphoglycerol
histidine
hypoxanthine
imidazole lactate
indolelactate
lactate
N-acetylglutamate
N-acetylproline
N-acetylthreonine
N-acetyltryptophan
N-acetyltyrosine
N-carbamoylaspartate
N-formylmethionine
nicotinamide riboside
nicotinate ribonucleoside
orotate
phenyllactate (PLA)
phenylpyruvate
phosphate
pipecolate
p-toluic acid
sedoheptulose
thioproline
thymine
trimethylamine N-oxide
uracil
uridine

Cluster 2 "Secreted by IECs"
1-carboxyethylisoleucine
1-carboxyethylleucine
1-carboxyethylphenylalanine
1-carboxyethylvaline
1-methylnicotinamide
1-palmitoyl-2-oleoyl-GPC (16:0/18:1)
1-stearoyl-2-oleoyl-GPC (18:0/18:1)
2'-deoxycytidine
2'-deoxyuridine
2'-O-methylcytidine
3-hydroxy-3-methylglutarate
3-hydroxybutyrate (BHBA)

Cluster 2 "Secreted by IECs" Continued
3-hydroxyisobutyrate
4-acetamidobutanoate
4-imidazoleacetate
7-methylguanine
alanine
Allantoin
alpha-ketoglutarate
4-guanidinobutanoate
arabonate/xylonate
argininosuccinate
Benzoate
beta-alanine
Betaine
cholesterol
choline phosphate
creatine
creatinine
cystathionine
dimethylarginine (SDMA + ADMA)
erythritol
erythronate
ethylmalonate
fumarate
gamma-glutamyl-alpha-lysine
gamma-glutamylthreonine
glucuronate
glycerol 3-phosphate
glycerophosphoethanolamine
glycerophosphoglycerol
glycerophosphoinositol
glycerophosphorylcholine (GPC)
glycerophosphoserine
glycine
guanine
gulonate
homoarginine
hypotaurine
hypoxanthine
kynurenine
Lactate
malate
mannitol/sorbitol
methionine sulfone
N1-methyladenosine
N1-methylinosine
N6,N6,N6-trimethyllysine
N-acetylalanine
N-acetyl-isoputreanine
N-acetylleucine
N-acetylneuraminate
nicotinamide ribonucleotide (NMN)
nicotinamide riboside
N-monomethylarginine
ornithine
palmitoyl sphingomyelin (d18:1/16:0)
pantothenate
p-cresol sulfate
phenol red
phenol sulfate
phenylacetylglycine
proline
pseudouridine
pyridoxal
pyridoxamine
pyridoxate
pyridoxine (Vitamin B6)
ribonate

Cluster 2 "Secreted by IECs" Continued
succinate
sulfate
taurine
thiamin (Vitamin B1)
threonate
trans-4-hydroxyproline
Urate

Cluster 3 "Secreted by IECs consumed by *L. rhamnosus*"
1-ribosyl-imidazoleacetate
2'-O-methyluridine
3-methyl-2-oxobutyrate
3-ureidopropionate
4-methyl-2-oxopentanoate
5-methylthioadenosine (MTA)
acetylcarnitine (C2)
aconitate [cis or trans]
carnitine
carnosine
citrate
cysteinylglycine disulfide
deoxycarnitine
fructose
gamma-glutamylalanine
gamma-glutamylglutamine
gamma-glutamylhistidine
gamma-glutamylisoleucine
gamma-glutamylleucine
gamma-glutamylmethionine
gamma-glutamylserine
Hippurate
Isocitrate
N-acetylglucosamine/N-acetylgalactosamine
N-acetylmethionine
nicotinamide
S-1-pyrroline-5-carboxylate
Xanthine

Cluster 4 "Consumed by IECs"
2'-deoxyadenosine
3-sulfo-L-alanine
Adenosine
alpha-lipoate
Arginine
Aspartate
cysteine s-sulfate
cysteine sulfinic acid
Cystine
Gluconate
Glutamate
Glutamine
Inosine
Isoleucine
Leucine
mannonate
methionine
methionine sulfoxide
N-acetylarginine
N-acetylglutamine
phenylalanylhydroxyproline
phosphoethanolamine
phosphothreonine
Serine
Valine

Cluster 5 "Secreted by *C. albicans*"
2,3-dihydroxyisovalerate
4-hydroxyphenylpyruvate
folate
glutarate (C5-DC)
glycerol
kynurenate

Cluster 6 "Inconclusive"
2-oxoarginine
3-hydroxybutyroylglycine
5-oxoproline
adenosine 5'-monophosphate (AMP)
biotin
choline
cytidine 5'-monophosphate (5'-CMP)
myo-inositol
N-acetylasparagine
N-acetylaspartate (NAA)
N-acetylhistidine
pyroglutamine
tryptophan

cluster 7 "Consumed by *L. rhamnosus* colonized IECs"
adenine
arabitol/xylitol
asparagine
cysteine-glutathione disulfide
fructosyllysine
gamma-glutamylvaline
Glucose
Lysine
phenylalanine
Ribitol
riboflavin (Vitamin B2)
threonine
thymidine
Tyrosine

Cluster 8 "Secreted by *L. rhamnosus* alone"
alpha-ketoglutaramate
argininate
diacetylspermidine
glutamine conjugate of C6H10O2 (2)
malonate
methylsuccinate
mevalonate
mevalonolactone
N-acetylleucine
N-acetylisoleucine
N-acetylphenylalanine
N-acetylputrescine
N-acetylserine
pyruvate

Supplementary Table 2: Metabolites of the clusters 1-8 shown in Fig. S1 (12 hpi).

Cluster 1 "Secreted by *L. rhamnosus* colonized IECs"
(N(1) + N(8))-acetylspermidine
1-carboxyethyltyrosine
2'-deoxyinosine
2-hydroxy-3-methylvalerate
2-hydroxy-4-(methylthio)butanoic acid
2-hydroxybutyrate/2-hydroxyisobutyrate
2-hydroxyglutarate
2R,3R-dihydroxybutyrate
3-(4-hydroxyphenyl)lactate
3-formylindole
3-hydroxyoctanoate
3-indoleglyoxylic acid
3-ureidopropionate
5-methyluridine (ribothymidine)
alpha-hydroxyisocaproate
alpha-hydroxyisovalerate
cytidine
cytosine
dihydroorotate
glycerate
indolelactate
mevalonate
mevalonolactone
N-acetylglutamate
N-acetylthreonine
N-acetyltryptophan
N-acetyltyrosine
N-carbamoylaspartate
nicotinate ribonucleoside
phenyllactate (PLA)
pipecolate
sedoheptulose
thymine
uracil
uridine

Cluster 2 "Secreted by IECs"
1-carboxyethylisoleucine
1-carboxyethylleucine
1-carboxyethylphenylalanine
1-carboxyethylvaline
1-methylnicotinamide
1-palmitoyl-2-oleoyl-GPC (16:0/18:1)
1-stearoyl-2-oleoyl-GPC (18:0/18:1)
2'-deoxycytidine
2'-deoxyuridine
2'-O-methylcytidine
3-hydroxy-3-methylglutarate
3-hydroxybutyrate (BHBA)
3-hydroxyisobutyrate
4-imidazoleacetate
7-methylguanine
Alanine
Allantoin
alpha-ketoglutarate
arabonate/xylonate
argininosuccinate
Benzoate
beta-alanine
betaine

Cluster 2 "Secreted by IECs" continued
cholesterol
choline phosphate
creatine
creatinine
cystathionine
dimethylarginine (SDMA + ADMA)
erythritol
erythronate
ethylmalonate
fumarate
gamma-glutamylthreonine
glucuronate
glycerol 3-phosphate
glycerophosphoethanolamine
Glycerophosphoglycerol
Glycerophosphoinositol
glycerophosphorylcholine (GPC)
Glycerophosphoserine
Gulonate
Homoarginine
Hypotaurine
Hypoxanthine
Lactate
malate
mannitol/sorbitol
methionine sulfone
N1-methyladenosine
N1-methylinosine
N6,N6,N6-trimethyllysine
N-acetylalanine
N-acetyl-isoputreanine
N-acetylleucine
N-acetylneuraminate
nicotinamide riboside
N-monomethylarginine
ornithine
Palmitoyl sphingomyelin (d18:1/16:0)
pantothenate
p-cresol sulfate
phenol sulfate
pseudouridine
pyridoxal
pyridoxamine
pyridoxate
ribonate
Sulfate
taurine
trans-4-hydroxyproline
Urate

Cluster 3 "Inconclusive"
1-palmitoyl-2-linoleoyl-GPC (16:0/18:2)
3-hydroxybutyroylglycine
benzoate
cholesterol
imidazole lactate
methylsuccinate
N-acetylaspartate (NAA)
N-acetylproline

Cluster 4 "Secreted by IECs and consumed by *L. rhamnosus*"
1-ribosyl-imidazoleacetate
3-methyl-2-oxobutyrate
3-methyl-2-oxovalerate
4-methyl-2-oxopentanoate
5-methylthioadenosine (MTA)
acetylcarnitine (C2)
aconitate [cis or trans]
carnitine
carnosine
citrate
deoxycarnitine
fructose
gamma-glutamylalanine
gamma-glutamylglutamine
gamma-glutamylhistidine
gamma-glutamylisoleucine
gamma-glutamylleucine
gamma-glutamylmethionine
gamma-glutamylserine
gamma-glutamylvaline
hippurate
isocitrate
N-acetylglucosamine/N-acetylgalactosamine
N-acetylmethionine
nicotinamide
S-1-pyrroline-5-carboxylate
xanthine

Cluster 5 "Secreted by *C. albicans*"
2,3-dihydroxyisovalerate
2'-deoxyadenosine
3-sulfo-L-alanine
4-methylthio-2-oxobutanoate
adenosine
alpha-lipoate
arabitol/xylitol
aspartate
benzoate
cysteine s-sulfate
glycerol
imidazole lactate
kynurenate
N-acetylleucine
N-acetylputrescine
phenylalanylhydroxyproline
ribitol

Cluster 6 "Secreted by *L. rhamnosus* alone"
adenosine
argininate
diacetylspermidine
gluconate
glutamine conjugate of C6H10O2 (2)
Inosine
malonate
N-acetylisoleucine
N-acetylphenylalanine
N-acetylserine
phosphothreonine

cluster 7 "Consumed by *L. rhamnosus* colonized IECs"
adenine
arginine
asparagine
biotin
cystine
fructosyllysine
glucose
glutamine
HEPES
isoleucine
leucine
lysine
mannitol/sorbitol
mannose
methionine
phenylalanine
serine
Threonine
tryptophan
valine

Cluster 8 "Secreted by *C. albicans* infected IECs"
cysteine-glutathione disulfide
indoleacetate
isovalerate (i5:0)
nicotinamide ribonucleotide (NMN)

Supplementary Table 3: Abbreviations used in Fig.6

Abbreviation	Full name
Reactions	
ACO	Aconitate Hydratase
AKGDH	alpha-Ketoglutarate Dehydrogenase
ALPL	2-Acetolactate Pyruvate-Lyase
CAR2	Ornithine Aminotransferase
ccoN	Cytochrome c Oxidase
CS	Citrate Synthase
DLD	D-lactate Dehydrogenase
ENO	Enolase
FBA	Fructose-Bisphosphate Aldolase
fbcH	Ubiquinol-Cytochrome c Reductase
FBP	Fructose-1,6-Bisphosphatase
FUM	Fumarate Hydratase
G6PD	Glucose-6-phosphate 1-Dehydrogenase
GAPDH	Glyceraldehyde 3-Phosphate Dehydrogenase
GPI	Glucose-6-Phosphate Isomerase
HK	Hexokinase
HPPR	Hydroxyphenylpyruvate Reductase
IDH	Isocitrate Dehydrogenase
ISL	Isocitrate Lyase
LDH	L-Lactate Dehydrogenase
MDH	Malate Dehydrogenase
MS	Malate Synthase
nuoA	NADH-Quinone Oxidoreductase
PCK	Phosphoenolpyruvate Carboxykinase
PDH	Pyruvate Dehydrogenase
PFK	6-Phosphofructokinase
PGAM	Phosphoglycerate Mutase
PGD	6-Phosphogluconate Dehydrogenase
PGK	Phosphoglycerate Kinase
PGL	6-Phosphogluconolactonase
PGM	Phosphoglucomutase
PK	Pyruvate Kinase
PMA	Plasma Membrane ATPase
PRO1	gamma-glutamyl kinase
PRO2	gamma-glutamyl phosphate reductase
RPE	Ribulose-Phosphate 3-Epimerase
RPI	Ribose 5-Phosphate Isomerase
SDH	Succinate Dehydrogenase
SUCD	Succinyl-CoA Synthetase
TAL	Transaldolase
TK	Transketolase
TPI	Triosephosphate Isomerase
Metabolites	
2PG	2-Phospho-D-glycerate
34HPLAC*	3,4-Dihydroxyphenylpyruvate (mapped to Phenylpyruvate measurements)
34HPPYR*	3,4-Dihydroxyphenyllactate (mapped to Phenyllactate measurements)
3PG	3-Phospho-D-glycerate
ACAC	Acetoacetate

ACCOA	Acetyl-CoA
ADP	Adenosine 5'-diphosphate
ALA	Alanine
ALAC	2-Acetolactate
AMP	Adenosine 5'-monophosphate
ATP	Adenosine 5'-triphosphate
BPG	D-Glycerate 1,3-diphosphate
DHAP	Dihydroxyacetone phosphate
F6P	beta-D-Fructose 6-phosphate
FDP	beta-D-Fructose 1,6-bisphosphate
Ficyt c	Ferricytochrome c
Focyt c	Ferrocytochrome c
G1P	alpha-D-Glucose 1-phosphate
G3P	D-Glycerate 3-phosphate
G6P	alpha-D-Glucose 6-phosphate
GLC	Glucose
GLU	Glutamate
H20	Water
H+	Hydrogen
ILE	Isoleucine
LAC	Lactate
LEU	Leucin
LYS	Lysine
MET	Methionine
NADH	Nicotinamide adenine dinucleotide (reduced)
NAD+	Nicotinamide adenine dinucleotide
O2	Oxygen
ORN	Ornithine
PEP	Phosphoenolpyruvate
PHE	Phenylalanine
PLAC	Phenyllactate
PPYR	Phenylpyruvate
PRCOA	Propanoyl-CoA
PRPP	5-Phosphoribosyl diphosphate
PUT*	Putrescine (mapped to N-acetylputrescine)
PYR	Pyruvate
St	Sulfate
SUCC	Succinate
THR	Threonine
TRP	Tryptophan
TYR	Tyrosine
VAL	Valine

Supplementary Table 4: Overview of screened deletion mutants for damage potential

Damage phenotype of deletion mutants from the Noble collection (Noble *et al.* 2010 *Nat Genetics*) corresponding to differentially regulated genes during infection of *L. rhamnosus* colonized IECs. Mutant phenotype is classified as hypovirulent or hypervirulent when the damage caused to IECs was significantly lower or higher than the wild type, respectively, and non-significant (ns) when it was not.

KO gene	Mutant phenotype	*P* value	KO gene	Mutant phenotype	*P* value
ace2	Hypovirulent	0,004	orf19.5565	ns	0,9998
ahr1	Hypovirulent	<0,0001	orf19.6874	ns	0,9807
aox1	ns	0,9984	orf19.7328	Hypervirulent	0,0838
aro80	ns	0,3589	orf19.7370	ns	0,9008
asm3	ns	0,9993	orf19.7516	ns	0,9996
cfl2	ns	0,9993	orf19.7554	ns	0,9832
cht2	ns	0,9913	pdk2	Hypervirulent	0,054
cip1	ns	0,9818	pex4	ns	0,9989
cyb5	ns	0,9364	pga13	ns	0,999
fcr1	ns	0,5483	pga45	ns	0,9912
gal4	ns	0,9987	pga7	ns	0,9842
gis2	ns	0,9917	pra1	ns	0,8833
het1	ns	0,4653	prk1	ns	0,9997
hgt6	ns	0,9985	prn2	ns	0,9999
hyr1	Hypervirulent	<0,0001	prn4	ns	0,904
kre5	Hypovirulent	0,0003	ptp3	Hypovirulent	<0,0001
mal2	ns	0,9991	pwp1	ns	0,3467
mec3	ns	0,9996	rbe1	Hypervirulent	0,0242
mid1	ns	>0,9999	rbt4	ns	0,9817
nik1	ns	0,9983	rgs2	Hypervirulent	0,0511
opt4	ns	0,9997	rim13	ns	0,9985
opt7	Hypervirulent	0,0572	sef1	ns	0,9608
orf19.1314	ns	0,8752	snq2	ns	0,9981
orf19.173	ns	0,999	sod6	ns	0,9999
orf19.215	ns	0,9995	swi4	ns	0,9661
orf19.3156	ns	0,9995	tye7	ns	0,9997
orf19.3395	ns	>0,9999	uga32	ns	0,9991
orf19.3720	ns	0,9815	vid27	ns	0,9994
orf19.3982	ns	>0,9999	wor2	ns	0,9991
orf19.4014	ns	0,9982	ycp4	ns	0,6831
orf19.4292	Hypovirulent	<0,0001	yhb1	ns	0,923
orf19.4445	ns	0,9993	ypt7	Hypervirulent	0,0766
orf19.4459	Hypervirulent	0,0009	ywp1	ns	0,9996
orf19.449	ns	0,9993	zcf27	Hypervirulent	<0,0001
orf19.4843	ns	0,624			