***Supplementary Material***

## Tables

## Supplementary Tables

## Supplementary Table 1. Set of reactions of Keratan sulfate metabolism with up-regulation after tibolone treatment.

|  |  |  |  |
| --- | --- | --- | --- |
| ID | Subsystem | Formula reaction | Description  |
| G14T10g | Keratan sulfate synthesis | udpgal[g] + ksi\_pre14[g] -> h[g] + udp[g] + ksi\_pre15[g]  | beta-N-acetylglucosaminylglycopeptide beta-1,4-galactosyltransferase, Golgi |
| G14T15g | Keratan sulfate synthesis | udpgal[g] + ksi\_pre29[g] -> h[g] + udp[g] + ksi\_pre30[g]  | beta-N-acetylglucosaminylglycopeptide beta-1,4-galactosyltransferase, Golgi |
| G14T16g | Keratan sulfate synthesis | udpgal[g] + ksi\_pre32[g] -> h[g] + udp[g] + ksi\_pre33[g]  | beta-N-acetylglucosaminylglycopeptide beta-1,4-galactosyltransferase, Golgi |
| G14T17g | Keratan sulfate synthesis | udpgal[g] + ksi\_pre35[g] -> h[g] + udp[g] + ksi\_pre36[g]  | beta-N-acetylglucosaminylglycopeptide beta-1,4-galactosyltransferase, Golgi |
| G14T6g | Keratan sulfate synthesis | udpgal[g] + ksi\_pre2[g] -> h[g] + udp[g] + ksi\_pre3[g]  | beta-N-acetylglucosaminylglycopeptide beta-1,4-galactosyltransferase, Golgi |
| G14T7g | Keratan sulfate synthesis | udpgal[g] + ksi\_pre5[g] -> h[g] + udp[g] + ksi\_pre6[g]  | beta-N-acetylglucosaminylglycopeptide beta-1,4-galactosyltransferase, Golgi |
| G14T8g | Keratan sulfate synthesis | udpgal[g] + ksi\_pre8[g] -> h[g] + udp[g] + ksi\_pre9[g]  | beta-N-acetylglucosaminylglycopeptide beta-1,4-galactosyltransferase, Golgi |
| G14T9g | Keratan sulfate synthesis | udpgal[g] + ksi\_pre11[g] -> h[g] + udp[g] + ksi\_pre12[g]  | beta-N-acetylglucosaminylglycopeptide beta-1,4-galactosyltransferase, Golgi |
| S23T3g | Keratan sulfate synthesis | cmpacna[g] + l2fn2m2masn[g] -> h[g] + ksi\_pre1[g] + cmp[g]  | beta-galactoside alpha-2,3-sialyltransferase (complex N-glycan) |
| S6T13g | Keratan sulfate synthesis | ksi\_pre31[g] + paps[g] -> h[g] + ksi\_pre32[g] + pap[g]  | galactose/N-acetylglucosamine 6-O-sulfotransferase, Golgi apparatus |
| S6T14g | Keratan sulfate synthesis | ksi\_pre34[g] + paps[g] -> h[g] + ksi\_pre35[g] + pap[g]  | galactose/N-acetylglucosamine 6-O-sulfotransferase, Golgi apparatus |
| S6T15g | Keratan sulfate synthesis | ksi\_pre36[g] + paps[g] -> h[g] + pap[g] + ksi[g]  | galactose/N-acetylglucosamine 6-O-sulfotransferase, Golgi apparatus |
| S6T4g | Keratan sulfate synthesis | ksi\_pre4[g] + paps[g] -> h[g] + ksi\_pre5[g] + pap[g]  | galactose/N-acetylglucosamine 6-O-sulfotransferase, Golgi apparatus |
| S6T5g | Keratan sulfate synthesis | ksi\_pre7[g] + paps[g] -> h[g] + ksi\_pre8[g] + pap[g]  | galactose/N-acetylglucosamine 6-O-sulfotransferase, Golgi apparatus |
| S6T6g | Keratan sulfate synthesis | ksi\_pre10[g] + paps[g] -> h[g] + ksi\_pre11[g] + pap[g]  | galactose/N-acetylglucosamine 6-O-sulfotransferase, Golgi apparatus |
| S6T7g | Keratan sulfate synthesis | ksi\_pre13[g] + paps[g] -> h[g] + ksi\_pre14[g] + pap[g]  | galactose/N-acetylglucosamine 6-O-sulfotransferase, Golgi apparatus |
| S6T8g | Keratan sulfate synthesis | ksi\_pre16[g] + paps[g] -> h[g] + ksi\_pre17[g] + pap[g]  | galactose/N-acetylglucosamine 6-O-sulfotransferase, Golgi apparatus |

## Supplementary Table 2. Set of critical reactions of PA model that have a critical and divergent role in the healthy and tibolone models.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Reaction | PA\_model | Healthy model | Tibolone model | Subsystem |
| 3DSPHR | Critical | Critical | Critical | Sphingolipid metabolism |
| ADSL1 | Critical | Critical | Critical | Nucleotide interconversion |
| ADSL2 | Critical | Critical | Critical | Purine synthesis |
| ADSS | Critical | Critical | Critical | Nucleotide interconversion |
| AGPAT1 | Critical | Critical | Critical | Triacylglycerol synthesis |
| AICART | Critical | Critical | Critical | Purine synthesis |
| AIRCr | Critical | Critical | Critical | Purine synthesis |
| C3STDH1Pr | Critical | Critical | Critical | Cholesterol metabolism |
| C3STKR2r | Critical | Critical | Critical | Cholesterol metabolism |
| C4STMO1r | Critical | Critical | Critical | Cholesterol metabolism |
| CDIPTr | Critical | Critical | Critical | Glycerophospholipid metabolism |
| CEPTE | Critical | Critical | Critical | Glycerophospholipid metabolism |
| CHOLK | Critical | Critical | Critical | Glycerophospholipid metabolism |
| CLS\_hs | Critical | Critical | Critical | Glycerophospholipid metabolism |
| CO2ter | Critical | Critical | Critical | Transport, endoplasmic reticular |
| COAtm | Critical | Intermittent | Critical | Transport, mitochondrial |
| DAGK\_hs | Critical | Critical | Critical | Glycerophospholipid metabolism |
| DATPtn | Critical | Critical | Critical | Transport, nuclear |
| DCTPtn | Critical | Critical | Intermittent | Transport, nuclear |
| DESAT18\_10 | Critical | Critical | Critical | Fatty acid synthesis |
| DGTPtn | Critical | Intermittent | Intermittent | Transport, nuclear |
| DHCR72r | Critical | Critical | Critical | Cholesterol metabolism |
| DHCRD1 | Critical | Critical | Critical | Sphingolipid metabolism |
| DSAT | Critical | Critical | Critical | Sphingolipid metabolism |
| ECOAH1m | Critical | Critical | Critical | Tryptophan metabolism |
| EX\_Rtotal(e) | Critical | Critical | Critical | Exchange/demand reaction |
| EX\_Rtotal2(e) | Critical | Critical | Critical | Exchange/demand reaction |
| EX\_chol(e) | Critical | Critical | Critical | Exchange/demand reaction |
| EX\_cys\_L(e) | Critical | Intermittent | Critical | Exchange/demand reaction |
| EX\_glu\_L(e) | Critical | Intermittent | Intermittent | Exchange/demand reaction |
| EX\_ile\_L(e) | Critical | Critical | Critical | Exchange/demand reaction |
| EX\_inost(e) | Critical | Critical | Critical | Exchange/demand reaction |
| EX\_leu\_L(e) | Critical | Critical | Critical | Exchange/demand reaction |
| EX\_lnlnca(e) | Critical | Critical | Critical | Exchange/demand reaction |
| EX\_lys\_L(e) | Critical | Critical | Critical | Exchange/demand reaction |
| EX\_met\_L(e) | Critical | Critical | Critical | Exchange/demand reaction |
| EX\_phe\_L(e) | Critical | Critical | Critical | Exchange/demand reaction |
| EX\_pi(e) | Critical | Critical | Critical | Exchange/demand reaction |
| EX\_pro\_L(e) | Critical | Intermittent | Redundant | Exchange/demand reaction |
| EX\_thr\_L(e) | Critical | Critical | Critical | Exchange/demand reaction |
| EX\_trp\_L(e) | Critical | Critical | Critical | Exchange/demand reaction |
| EX\_tyr\_L(e) | Critical | Critical | Critical | Exchange/demand reaction |
| EX\_val\_L(e) | Critical | Critical | Critical | Exchange/demand reaction |
| FACOAL1832 | Critical | Critical | Critical | Fatty acid oxidation |
| FACOAL184 | Critical | Critical | Critical | Fatty acid oxidation |
| FAOXC180x | Critical | Critical | Critical | Fatty acid oxidation |
| FORt2m | Critical | Intermittent | Critical | Transport, mitochondrial |
| FORtr | Critical | Critical | Critical | Transport, endoplasmic reticular |
| FTHFLm | Critical | Intermittent | Critical | Folate metabolism |
| GAPD | Critical | Intermittent | Intermittent | Glycolysis/gluconeogenesis |
| GARFT | Critical | Critical | Critical | Purine synthesis |
| GHMT2r | Critical | Intermittent | Intermittent | Glycine, serine, alanine, and threonine metabolism |
| GLNS | Critical | Critical | Critical | Glutamate metabolism |
| GLUPRT | Critical | Critical | Critical | Purine synthesis |
| GNMT | Critical | Critical | Critical | Glycine, serine, alanine, and threonine metabolism |
| GPAM\_hs | Critical | Critical | Critical | Triacylglycerol synthesis |
| H2Otp | Critical | Intermittent | Intermittent | Transport, peroxisomal |
| HACD1m | Critical | Critical | Critical | Tryptophan metabolism |
| HMGCOASim | Critical | Intermittent | Critical | Cholesterol metabolism |
| HMGCOAtm | Critical | Intermittent | Critical | Transport, mitochondrial |
| Htr | Critical | Intermittent | Critical | Transport, endoplasmic reticular |
| IMPC | Critical | Critical | Critical | Purine synthesis |
| IPDPtx | Critical | Critical | Critical | Transport, peroxisomal |
| LNLNCAt | Critical | Critical | Critical | Transport, extracellular |
| LNSTLSr | Critical | Critical | Critical | Cholesterol metabolism |
| LSTO2r | Critical | Critical | Critical | Cholesterol metabolism |
| OROTGLUt | Critical | Intermittent | Redundant | Transport, extracellular |
| PETHCT | Critical | Critical | Critical | Glycerophospholipid metabolism |
| PGK | Critical | Intermittent | Intermittent | Glycolysis/gluconeogenesis |
| PGPPT | Critical | Critical | Critical | Glycerophospholipid metabolism |
| PGPP\_hs | Critical | Critical | Critical | Glycerophospholipid metabolism |
| PRAGSr | Critical | Critical | Critical | Purine synthesis |
| PRASCS | Critical | Critical | Critical | Purine synthesis |
| PRFGS | Critical | Critical | Critical | Purine synthesis |
| PRPPS | Critical | Critical | Critical | Pentose phosphate pathway |
| RE3273C | Critical | Critical | Critical | Phosphatidylinositol phosphate metabolism |
| RTOTAL2FATPc | Critical | Critical | Critical | Transport, extracellular |
| SARCStm | Critical | Critical | Critical | Transport, mitochondrial |
| SARDHm | Critical | Critical | Critical | Urea cycle |
| SERPT | Critical | Critical | Critical | Sphingolipid metabolism |
| SMS | Critical | Critical | Critical | Sphingolipid metabolism |
| SQLEr | Critical | Critical | Critical | Cholesterol metabolism |
| STCOAtx | Critical | Critical | Critical | Transport, peroxisomal |
| biomass\_reaction | Critical | Critical | Critical | Exchange/demand reaction |
| r0276 | Critical | Intermittent | Critical | Purine catabolism |
| r0287 | Critical | Critical | Critical | Fatty acid oxidation |
| r0480 | Critical | Critical | Critical | Glycerophospholipid metabolism |
| r0488 | Critical | Critical | Critical | Cholesterol metabolism |
| r0633 | Critical | Critical | Critical | Fatty acid oxidation |
| r0666 | Critical | Critical | Critical | Purine synthesis |
| r0730 | Critical | Critical | Critical | Fatty acid oxidation |
| r0731 | Critical | Critical | Critical | Fatty acid oxidation |
| r0732 | Critical | Critical | Critical | Fatty acid oxidation |
| r0733 | Critical | Critical | Critical | Fatty acid oxidation |
| r0734 | Critical | Critical | Critical | Fatty acid oxidation |
| r0735 | Critical | Redundant | Critical | Fatty acid oxidation |
| r0780 | Critical | Critical | Critical | Cholesterol metabolism |
| r0781 | Critical | Critical | Critical | Cholesterol metabolism |
| r0788 | Critical | Critical | Critical | Sphingolipid metabolism |
| r0789 | Critical | Critical | Critical | Sphingolipid metabolism |
| r0791 | Critical | Critical | Critical | Fatty acid oxidation |
| r0839 | Critical | Intermittent | Redundant | Transport, extracellular |
| r1254 | Critical | Critical | Critical | Fatty acid oxidation |
| r1380 | Critical | Critical | Intermittent | Cholesterol metabolism |
| r1381 | Critical | Critical | Intermittent | Cholesterol metabolism |

# Figures

# Supplementary Figures

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**Supplementary Figure 1.** Summary of pathways associated with biochemical reactions that presented high flow variability compared to tibolone. Percentage of activation, inactivation and decrease or increase of the flow value was calculated compared scenarios. (A) Reactions activated by tibolone treatment. (B) Reactions that are inactivated by treatment with tibolone. (C) Reactions that decrease metabolic flow from treatment with tibolone. (D) Reactions that increase metabolic flow from tibolone treatment.

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**Supplementary Figure 2.** Venn diagram showing the number of reactions associated in each model with redundant, intermittent, and critical reactions, and their intersections.

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**Supplementary Figure 3.** Control of glycolysis and its association with central reactions of different metabolic subsystems. (A) Flux coupling graph for the GAPD reaction, from a healthy cell. Total and directional coupling relationships are observed, in addition to reactions with competitive or inhibitory coupling. (B) Flux coupling graph of the critical GAPD reaction in the lipotoxic model. Mostly inhibitory or competitive interactions are observed with reactions associated with other subsystems, related to the central metabolism of the cell, generating a critical regulation of cellular metabolism.