**Supplementary Table 3. Parameters in the model of tumor cell metabolism.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Description** | **Value** | **Unit** | **Remarks** |
|  Metabolic Model |
| Vcyt | volume cytosolic H2O per total intracellular H2O | 0.9 | liter/liter intracellular H2O | references (in parentheses):(*1*)  |
| Vmat | volume mitochondrial H2O per total intracellular H2O | 0.1 | liter/liter intracellular H2O | (*1*) |
| Vext | volume extracellular H2O per total intracellular H2O |  | liter/liter intracellular H2O | depends on experimental conditions |
|  Head section glycolysis |
| KATP,head | Michaelis constant, Km, of head section glycolysis for ATP  | 1000 | µmol/liter | (*2-4*) |
| Kglucose,head | Km of head for glucose | 51.1 (10.8) | µmol/liter | (\*) optimized (interquartile range: IQR); compare with (*2-4*) |
| Vmax,head | maximal forward rate of enzyme, Vmax | 394.3 (13.5) | µM/s | (\*) optimized value (IQR) |
|  Tail section glycolysis |
| KFBP,tail | Km for FBP | 0.24 (1.06) | µmol/liter | (\*) optimized (IQR); compare (*2-4*) |
| KNAD,tail | Km for NAD | 33.5 (36.2) | µmol/liter | (\*) optimized (IQR); compare (*2-4*) |
| KADP,tail | Km for ADP | 220.4 (128.7) | µmol/liter | (\*) optimized (IQR); compare (*2-4*) |
| Ki,NADH,tail | inhibitory constant for NADH | 2.77 (6.6) | µmol/liter | (\*) optimized (IQR); compare (*2-4*) |
| Vmax,tail | Vmax of tail section | 1708 (438) | µM/s | (\*) optimized (IQR) |
|  Mitochondrial ATP synthesis - oxidative phosphorylation |
| KADP,mit | Km for ADP | 22.1 (41.8) | µmol/liter | (\*) optimized (IQR); compare (*5-9*) |
| KPi,mit | Km for Pi | 800 | µmol/liter | (*5-9*) |
| KO2,mit | Km for O2 | 0.26 | µmol/liter | (*10*) |
| Vsynmax | maximal rate of mitochondrial ATP synthesis | 306.8 (14.7) | µM/s | (\*) optimized (IQR) |
|  Lactate dehydrogenase reaction |
| Kpyr,ldh | K­m for pyruvate | 335 | µmol/liter | (*3*) |
| KNADH,ldh | Km for NADH | 2 | µmol/liter | (*3*) |
| Klac,ldh | Km for lactate | 17000 | µmol/liter | (*3*) |
| KNAD,ldh | Km­ for NAD | 849 | µmol/liter | (*3*) |
| Keq,ldh | equilibrium constant for the lactate dehydrogenase reaction | 16198 | dimensionless | (*3*) |
| Vmax,ldh,for | maximal rate lactate dehydrogenase reaction: forward from pyruvate to lactate | 4939 | µM/s | (*11, 12*) |
|  ATP hydrolysis for cellular processes (except phosphorylation of glucose) |
| khyd,AdN | reduction of glycolysis per unit decrease in sum of ATP and ADP concentrations | 0.166 (0.030) | s-1 | (\*) optimized (IQR);in vitro (Fig. 2) and tissue (Figs. 3, 4, S1-S3)S=Supplementary Figure |
| Vmax,hyd | ATP hydrolysis under basal conditions | 199.0 (3.8) | µM/s | (\*) optimized (IQR); simulation Fig. 2, Figs. 3, 4, S1-S3. |
| ATP hydrolysis at low adenine nucleotide levels, Eq. 6 (for tissue simulations) |
| AdNcutoff | AdN cutoff value; boundary between Eqs. 5 and 6 | 3189 | µM | simulations Figs. 3, 4 and S3 |
| khyd,AdN,low | linear part Eq. 6 | 0.0098704 | 1/s | simulations Figs. 3, 4 and S1-S3 |
| Cpower | coefficient power law | 9.73 10-47 |  | simulations Figs. 3, 4 and S1-S3 |
| γ | power coefficient in Eq. 6 | 13.58 |  | simulations Figs. 3, 4 and S1-S3 |
|  ADP breakdown and synthesis |
| kbreakdown,ADP | rate constant for breakdown of ADP | 0.000224 (8.3 10-5) | µM-1.s-1 | (\*) optimized (IQR) |
| ksynthesis,ADP | rate constant for synthesis of ADP | 0.001261 (0.00028) | s-1 | (\*) optimized (IQR) |
|  Storage carbon metabolites from glycolytic intermediates |
| kstore | rate constant for storage of carbon metabolites | 0.005202 (0.00043) | s-1 | (\*) optimized (IQR) |
|  Parameters algebraic equations |
| NADtot | total nicotinamide adenine dinucleotide content | 200 | µM | (*13, 14*) |
| ratioP/O2 | ratio of ATP synthesized per O2 consumed | 5.6 | dimensionless | (*15-17*) |
| RPGI/FBP | ratio of total phosphorylated glycolytic intermediates content to fructose 1,6-bisphosphate content | 1.243 (0.047) | dimensionless | (\*) optimized (IQR);total phosphorylated glycolytic intermediates varying with fixed ratio to FBP; other stores of metabolites increase in time (Eq. 9) and are not proportional to FBP. Cf. (*13, 16, 18-24*)  |
|  Inhibition of head section of glycolysis |
| kf | second order forward rate constant for inhibition by glycolytic intermediates | 1.01∙10-5­ (7.5 10-7) | µM-1s-1 | (\*) optimized (IQR) |
| kb | backward rate constant for disinhibition of head section | 0.00315 (0.00034) | s-1 | (\*) optimized (IQR) |
|  |
| Transport equations of tissue model |
|  Geometric parameters |
| Lcyl | length of cylindrical shell per unit volume of intracellular H2O |  | cm / liter | calculated from tissue radius, intracellular water content and interstitial space |
| r­inner | inner radius of cylindrical shell |  | cm |  |
| router | outer radius of cylindrical shell |  | cm |  |
| Vperivascular | volume of blood vessel and immediately adjacent tissue per volume of intracellular H2O  | 0.04 | liter / liter | (*25*) |
| rperivascular | radius of the perivascular space  | 9.5 | µm | (*26*); compatible with Vperivascular |
| volume fraction cells | volume consisting of cells as fraction of total tissue volume | 0.50 | liter / liter | tumor tissue(*27, 28*) |
| Cell types |
| fcell type 1 | fraction of total cell volume that consists of cells with full tumor glycolytic capacity |  |  |  |
| fcell type 2 | fraction of total cell volume that consists of cells with reduced glycolytic capacity |  |  |  |
| Diffusion coefficients |
| DO2 | diffusion coefficient of oxygen | 1.75∙10-5 | cm2 s-1 | (*26, 29, 30*) |
| Dglc | diffusion coefficient of glucose | 0.5∙10-5 | cm2 s-1 | (*26, 30, 31*) |
| Dlac | diffusion coefficient of lactate | 0.9∙10-5 | cm2 s-1 | (*26, 32*) |
| Dpyr | diffusion coefficient of pyruvate | 0.9∙10-5 | cm2 s-1 | (*26, 32*) |
| Blood flow and concentrations |
| Fblood | blood flow per liter intracellular H2O | 0.0044 | liter blood / liter intracellular H2O / s | (*25*) |
| c­a,glucose | arterial glucose concentration | 9858 | µmol/L | for implanted tumor experiments in rats (*33*) |
| ca,lactate | arterial lactate concentration | 3108 | µmol/L | (*33*) |
| ca,pyruvate | arterial pyruvate concentration | 144 | µmol/L | (*33*) |
| ca,O2 | arterial unbound oxygen concentration | 120.8 | µmol/L | (*33*) |
| Oxygen dissociation curve blood |
| csat,HbO2 | concentration of oxygen carried by saturated hemoglobin | 7350 | µM | (*33*) |
| nHill | Hill coefficient | 2.6 | dimensionless | (*34*) |
| c50,O2 | O2 concentration at which hemoglobin is 50% saturated with O2 | 52 (arterial)60 (venous) | µM | hemoglobin half saturation value rat blood(*34*):p50 = 39.3 mmHg at pH = 7.34 (arterial) (*33*); p50 = 45.5 mmHg at pH = 7.24 (venous) ;O2 solubility = 1.33 µM/mmHg (*35*) |
| (\*) these parameters are optimized on data from experiment 1-3, see description in Supplementary Material: Calibrating the computational model with experimental data. Interquartile range (IQR) determined by replicated Markov chain Monte Carlo is given for each optimized parameter. |

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