The Correction Term of A Three-Pool Kinetic Model for In Vitro Anaerobic Glycolysis Under MRI

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INTRODUCTION

In Oncology, the Warburg effect is a form of modified cellular metabolism based on aerobic fermentation found in cancer cells, which tend to favor anaerobic glycolysis rather than the oxidative phosphorylation pathway which is the preference of most other cells in the body. The activity of anaerobic glycolysis reaction may be detected in-vitro or in-vivo by ^{13}C MRS of hyperpolarized (HP) substrates. The HP signal of ^{13}C substrates can be boosted by the technique called Dynamic Nuclear Polarization in the commercial polarizer.

AIM

The dynamic signals from HP substrates and products have been fitted to a number of mathematical models to determine metabolic reaction rates [1]. However, the acquisition time period in HP ^{13}C experiment may not reach the steady-state status between HP ^{13}C pyruvate and cells. Here, we have introduced a correction term, the metabolic reaction rate in anaerobic glycolysis as a function of time, into the traditional model to verify the feasibility.

METHOD

- **Model:** use three compartment bidirectional model to fit the conversion rates of pyruvate to lactate, and lactate to pyruvate in the intracellular region. Figure 1 and Equations have explained this model in detail.
- **Hyperpolarization:** the HP ^{13}C signal was generated by a commercial polarizer, GE SPINLab.
- **In-Vitro experiment**, THP1 cells (6x10^7) were in 9 ml medium. The HP ^{13}C pyruvate, 1 ml, was poured into this medium. One group of these cells were exposed by radiation (15 Gy). The other group of these cell were not exposed by radiation. Two sets of in-vitro experiments were conducted.
- **Data acquisition:** HP ^{13}C signal was acquired by the generic pulse-and-acquire MRS at GE 3T with MNS research package.
- **Data post-processing:** the raw data was reconstructed, apadization, phase correction, and background subtraction by GE Sage software. T_1 values of ^{13}C Pyruvate also needed to be calculated by the least square fit before we input ^{13}C pyruvate and lactate data into our model.

RESULTS

1. Adding the correction term in our model has fitted the ^{13}C lactate in cell experiments is comparable to the traditional model without the correction term in Fig. 2(b).
2. In Figure 2(a), pyruvate data among experiment, our model and traditional model were overlapped. The scale comparison between Fig. 2 (a) and Fig. 2(b) in the y-axis (signal) reflected small amount of HP Lac. conversion to HP Pyr. Thus, the correction term of our model in ^{13}C pyruvate did not reveal the large difference compared to the traditional model.
3. Table 1 showed the chemical reaction rate between radiation and non-radiation groups. The value in the radiation group was lower than that in the non-radiation group. This result reflected that lactate production after radiation was less.
4. The uncertaintv of fitted results in Table 1 was about 30%.

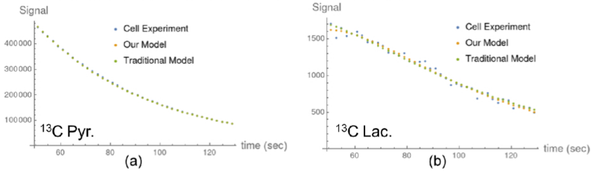

Fig. 2 This THP1 cell data was irradiated by ^{137}Cs. Dynamic data comparison between our model, traditional model and cell experiment. (a) The dynamic data, blue dot, represents the extracellular and intracellular signal of ^{13}C pyruvate in the cell experiment. The orange dot represents our model. The green dot represents traditional model. (b) The dynamic data points represents the intracellular signal of ^{13}C Lactate in the cell experiment (blue), our model (orange), and traditional model (green).

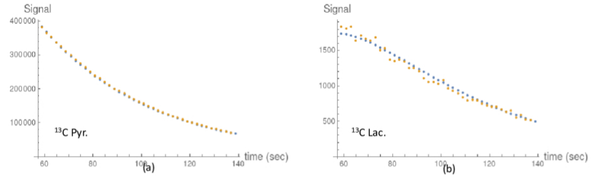

Fig. 3 This THP1 cell data was not irradiated by X-ray. Dynamic data comparison between our model, and cell experiment. (a) The dynamic data, orange dot, includes the extracellular and intracellular signal of ^{13}C pyruvate in the cell experiment. The blue dot represents our model. (b) The dynamic data points represents the intracellular signal of ^{13}C Lactate in the cell experiment (orange), and our model (blue).

Method: Model Description

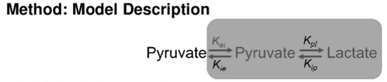

Fig. 1 Schematic of pyruvate uptake and metabolism. Illustration of parameters that need to be included in three compartment bidirectional modeling pyruvate delivery and conversion. These include K_{ei} ,the rate of transfer from extracellular space (e) to intracellular space (i), K_{ip}, the conversion rate from pyruvate to lactate in the intracellular space, K_{ip}, the conversion rate from lactate to pyruvate in the intracellular space. "P_{EXT}" extracellular pyruvate. "P_{INT}" intracellular pyruvate. "L_{INT}" intracellular lactate.

In this three-pool bidirectional model, we consider that $P_{EXT}(t)$ is the substrate outside the cellular membrane, $P_{INT}(t)$ is the same substrate inside the cellular membrane, and $L_{INT}(t)$ is the product in the cytoplasm. Figure 1 is the schematic diagram of a bidirectional three-pool model. Eqs. (1)-(3), were described for a Three-Pool kinetic model. $K_{pl}(t)$, and $K_{lp}(t)$ are correction terms in our model. $K_{pl,f}$ and $K_{lp,f}$ are the constant conversion rates, which have been used in the past literature [1,2]. T_{delay} reflects the degree of reaction rate.

$$P'_{EXT}(t) = K_{ie}P_{INT}(t) - K_{ei}P_{EXT}(t) - \rho_{P,EXT}P_{EXT}(t) \quad ----------(1)$$

$$P'_{INT}(t) = K_{ei}(t)P_{EXT}(t) - K_{ie}P_{INT}(t) + K_{lp}(t)L_{INT}(t) - K_{pl}(t)P_{INT}(t) - \rho_{P,INT}P_{INT}(t) \quad (2)$$

$$L'_{INT}(t) = K_{pl}(t)P_{INT}(t) - K_{lp}(t)L_{INT}(t) - \rho_{L,INT}L_{INT}(t) \quad ---------(3)$$

$$K_{pl}(t) = K_{pl,f}\left(1 - e^{-t/T_{delay}}\right) \qquad K_{lp}(t) = K_{lp,f}\left(1 - e^{-t/T_{delay}}\right)$$

We assume that the effective relaxivity, $\rho_{P,EXT}$, $\rho_{P,INT}$, and $\rho_{L,INT}$ are the same to simplify this model. Time, t, was initiated at the moment of HP pyruvate mixture with the cells.

	K_{pl} (x10^{-3}) S^{-1}	K_{lp} (x10^{-3}) S^{-1}
Radiation	0.55(1-e$^{-t/36.7}$)	36.3(1-e$^{-t/36.7}$)
Non-Radiation	0.33(1-e$^{-t/4.31}$)	15.9(1-e$^{-t/4.31}$)

Table 1 The conversion rates and correction term were fitted by our model. The cells has two groups. One was imaged after irradiated by ^{137}Cs. The other was imaged directly without radiation. The signal in the radiation group corresponded to Fig. 2. The signal in the non-radiation group corresponded to Fig. 3.

CONCLUSIONS

The correction term in our three-pool model has fitted the experimental ^{13}C Lactate data the same as the traditional model. However, only one set of data may not draw a conclusion for the correction term in our model. The further validation and the uncertainty of K_{pl}, K_{lp}, and T_{delay} of other datasets and comparison between our model and the traditional model are still needed.

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REFERENCES

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1. Day, S. E., Kettunen, M. I., Gallagher, F. A., Hu, D. E., Lerche, M., Wolber, J., et al. (2007).Detecting tumor response to treatment using hyperpolarized 13C magnetic resonanceimaging and spectroscopy. Nature Medicine, 13(11), 1382–1387. http://dx.doi.org/10.1038/nm1650.
2. Daniels, C.J., M.A. McLean, R.F. Schulte, F.J. Robb, A.B. Gill, N. McGlashan, M.J. Graves, M. Schwaiger, D.J. Lomas, K.M. Brindle, and F.A. Gallagher, A comparison of quantitative methods for clinical imaging with hyperpolarized 13C-pyruvate. NMR in Biomedicine, 2016. 29(4): p. 387-399.

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