Dynamic Modelling and Simulation of the Hypoxia-Inducible Factor 1α (HIF-1α) SUMOylation in Response to Hypoxia

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Abstract— **Hypoxia, low oxygen level in tissues, is encountered in both physiological processes and pathological situations, such as ischemia and cancer. Recent experimental data have shown that protein post-translational modifications (PTMs), in particular SUMOylation, play crucial roles in cellular response to hypoxia. In this study, we develop a mathematical model of SUMOylation-dependent synergism of hypoxia response to gain a better understanding of how HIF interacts with SUMO proteins to sense oxygen and respond to hypoxia. The primary result shows the effect of oxygen concentration on SUMO conjugation level.**

Clinical Relevance— **This result has implications for cancer treatment by using model prediction to drug treatment under varying degrees of hypoxia.**

I. INTRODUCTION

Post-translational modifications (PTMs) are critical events in cellular signaling that allow regulation and fine-tuning of protein function [1]. Recent experimental work suggested that SUMOylation as one PTM type is a key determinant of cell fate in response to these extreme stresses, including hypoxia stress [2]. Given the importance the HIFs in cellular response to hypoxia, there has been some progress in the mathematical modelling of HIF regulatory network [3]. However, there is no study regarding mathematical modelling of HIF network associated with its SUMOylation process in literature. This study aims to develop a mathematical model of SUMOylation-dependent synergism of hypoxia response to gain a better understanding of how HIF1α interacts with SUMO proteins to sense oxygen and respond to hypoxia.
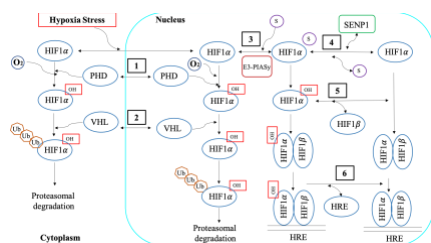
II. METHODS

Figure 1. Biological mechanism of the cell response to hypoxia

The biological mechanism of the cell response to hypoxia is shown in Figure 1, based on which the ordinary differential equations (ODEs) model is developed, where the mass action

kinetics are assumed for the majority of the rate laws and the Michaelis-Menten kinetics are used to describe the rate of enzymatic reactions involved. This model integrates our current understanding of the interaction between the known HIFα pathway components associated with SUMOylation process.

III. RESULTS

The simulation time was set as 24 hours. The simulated levels of SUMO conjugation ($HIF1\alpha_s$), which the oxygen tension decreased from 0.1 to 0.01, 0.005 and 0.001 are shown in Figure 2. It shows that the SUMOylation process in the cells is activated to cope with the hypoxia stress. Under hypoxic conditions, the level of $HIF1\alpha_s$ increased at the beginning, and then kept in a stable state afterwards.
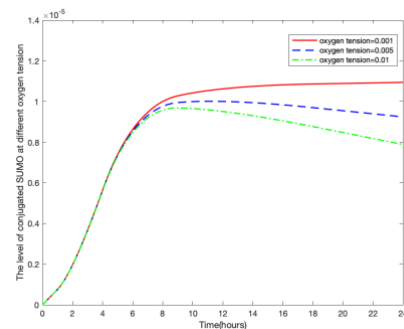

Figure 2. Simulation of SUMO conjugation ($HIF1\alpha_s$) level while oxygen tension from 10% to 1%, 0.5% and 0.1%

IV. DISCUSSION & CONCLUSION

The preliminary results have shown our findings are consistent with the previous experimental observations qualitatively through comparing SUMO conjugation level under different oxygen tension.

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