A Model for β-cell's death during ER stress

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The main causes and developing processes for the type II diabetes is still largely unknown. Yet obvious loss of β-cell in islet has been observed when diabetes happened. Both ER stress and apoptosis induced by it play important roles in β-cell loss. To answer how such apoptosis come into being, we have built a mathematical model to describe the molecule network from ER stress to cell death. Such model finds a way to illustrate the underline principle of single β-cell decision making facing with different inner environment.

***Keywords* — β-cell, Apoptosis, ER stress, Type II Diabetes.**

I. Introduction

The number of people living with, and dying from, diabetes across the world is shocking [1]. There are two major forms of diabetes, type I and type II. The latter type accounts for almost 90% of all cases of diabetes in adults worldwide [1]. As a chronic disease, the main causes and developing processes for the type II diabetes are of great complexity. Nevertheless obvious loss of β-cells in islets has been observed when diabetes happened [2]. It's has also been observed that at the early stage of diabetes, the number of β-cell in each islet suffers a large amount of decrease as well as the number of islets in pancreas [2]. Thus, deciphering how β-cells lost during the happening of diabetes is not only of great interest in science but also potentially important in clinic.

The β-cell in islets play a role in secreting insulin, a hormone regulates storage of glycogen in the liver and accelerates oxidation of sugar in cells. The β-cell is under a great 'pressure' when the blood glucose is high and it has to secret a great load of insulin. A part of such pressure comes from the ER stress. ER stress raise from the situation that a cell translates too much protein at a time. This unfolded protein has to be folded and processed accurately and efficiently in endoplasmic reticulum (ER) [3]. As a 'bottleneck', usually there will be considerable unfolded protein accumulating inside endoplasmic reticulum which makes a chain of reactions to release such bottleneck. This situation is the so called ER stress and the following reactions are unfolded protein response (UPR).

UPR has been extensively studied by many groups [3][4]. However, the role UPR play in the β-cell's death remains unknown. It is known that UPR can activate cell apoptosis [5]. But at what extend UPR will cause apoptosis almost surely is still a problem. The 'extend' here refers to the time, intensity and even the action pattern of ER stress. We aim to answer the problem above thoroughly.

II. Summary of Results

We have established an ODE model to simulate the process from the upstream ER-stress sensor to the whole downstream UPR system, including some proapoptosis gene such as CHOP. The input of this model is the amount of unfolded protein's mRNA. This model includes two main feedback to repress the unfolded protein accumulating in endoplasmic reticulum and one of its feedback, will simultaneously induced CHOP. We simulated the ODE model, compared it with the experimental data came from our collaborators. It shows that our model fits their data qualitatively. And we furthered our research on this model into analytical part. Especially on what kind of input situation will the final expression level of CHOP lead the cell to apoptosis. Some improvement has been made on this part of job, and we'll complete it in the future.

It has been found that ER stress induced apoptosis is not only type of cell death [6]. This means that the model has to update, including more relative pathway.

III. Conclusion

We have established a feasible ODE model to describe the whole process from different kind of unfolded protein input to the final CHOP expression level. And we have made some analytical job on this model in order to give an explanation of this process and answer the question of why β-cell choose to die.

IV. References

[1] Scully T. Diabetes in numbers[J]. Nature, 2012, 485(7398): S2-S3.
[2] Rhodes C J. Type 2 Diabetes-a Matter of ß-Cell Life and Death?[J]. Science, 2005, 307(5708): 380-384
[3] Erguler K, Pieri M, Deltas C. A mathematical model of the unfolded protein stress response reveals the decision mechanism for recovery, adaptation and apoptosis[J]. BMC systems biology, 2013, 7(1): 16.
[4] Diedrichs D R. A mathematical model of the unfolded protein response to stress in the endoplasmic reticulum of mammalian cells[J]. 2012.
[5] Walter P, Ron D. The unfolded protein response: from stress pathway to homeostatic regulation[J]. Science, 2011, 334(6059): 1081-1086.
[6] Mathis, Diane, Luis Vence, and Christophe Benoist. "β-Cell death during progression to diabetes." Nature 414.6865 (2001): 792-798.

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