Analysis in Antitumor Mechanism with mTOR Using Apriori Algorithm

Hyun Kwon, Yerin Oh, and Taeseon Yoon
Hankuk Academy of Foreign Studies/Natural Science, Yong-in, Republic of KOREA
Email: bs02703@gmail.com; Brave1000@naver.com; tsyoon@hafs.hs.kr

***Abstract*—Nowadays, mTOR is expected to be an evidence to find out the origin of cancer and is being considered as a method of new medical technology. As mTOR has many roles, we speculated this is because of its components. Thus, we concatenated computer algorithm to discover mTOR. We used Apriori Algorithm which is an algorithm for frequent item set mining and association rule learning over transactional databases. For this, we divided sections into four, especially 7, 9, 13, 17 windows. According to the windows, we could analyze that leucine was the most dominant component and alanine and glutamic acid comes after with a low percentage. Leucine revitalizes mTOR much more actively, and that is the reason why leucine has the highest ratio of it. Additionally, glutamic acid and alanine interacts with each other to activate metabolism for making a cycle.**

***Index Terms*—apriori, mTOR, antitumor mechanism, leucine, glutamic acid, alanine**

I. Introduction

Day by day, human technology is improving a lot. One of the mainstreams, many people is dealing with cancer and it could be the one most efficient way to help people enjoy their life more healthy if there is a certain way to conquer cancer perfectly. Starting from here, we thought, ifthe present medical science cannot exterminate cancer completely, presuming a location of the outbreak of one's cancer would be another new solution for the treatment. A number of studies proved that the mammalian target of rapamycin; mTOR, can be used to find out a spot of cancer. We tried to find the method for finding it, and we reached at the computer program, Apropri algorithm. Using this algorithm, we were able to find the spot of mTOR, by analyzing the patterns of leucine, alanine, and glutamic acid.

As the importance of the computer technology is improving, we wanted to combine the two major subjectsto make an advancement of human technology. This new combined subject can give us advantages of making procedures more practical and accurate.

II. Relative Research

MTOR (the HUGO-approved official symbol = MTOR; HGNC ID; HGNC:3942) also known as mammalian target of rapamycin, mTOR, or FK506-binding protein 12-rapamycin-associated protein 1 (FRAP1), is a seine and threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription.It belongs to the phosphatidylinositol 3-kinase-related kinase protein family and it can be classified in mTORC1, mTORC2. It works in regulating rejection of transplantation. [1] Also it is an immunosuppressant that blocks vessel restenosis and has potential anticancer applications. [2]

A. Mammalian Target of Rapamycin Complex 1

MTORC1 has five components: mTOR, which is the catalytic subunit of the complex, regulatory-associated protein of mTOR, mammalian lethal with Sec13 protein 8 (mLST8, also known as GβL),proline-rich AKT substrate 40 kDa (PRAS40), and DEP-domain-containing mTOR-interacting protein (Deptor). The exact function of the majormTOR-interacting proteins in mTORC1 still remains elusive. Also it has been proposed thatmTOR interacts with the raptor by regulating assembly of the complex and by recruiting substrates for mTOR and GβL proteins 1, 2 and 3 to form a complex that is the target of rapaycin.Here we can demonstrate that mTOR is also part of a distinct complex defined by the novel protein rictor (rapamycin-insentive companion of mTOR). [2] On the other hand, the role of mLST8 in mTORC1 is also unclear, as deletion of this protein does not affect mTORC1 activity in vivo. Upon activation, mTORC1 directly phosphorylates PRAS40 and Deptor, which reduces their physical interaction with mTORC1 and further activates mTORC1 signaling. [3]

B. Deptor

Similar to its role in mTORC1, it comprises six different proteins: mTOR; rapamycin-insensitive companion of mTOR (Rictor), mammalian stress-activated protein kinase interacting protein(mSIN1), protein observed with Rictor-1(Protor-1), mLST8, and Deptor. [4] Deptor is an mTOR-interacting protein whose expression is negatively regulated by both mTORC1 and mTORC2. Loss of Deptor activates S6K1, promotes cell growth and survival, and activates mTORC1 and mTORC2 kinase activities. Deptor overexpression suppresses S6K1 but, by relieving feedback inhibition from mTORC1 to PI3K signaling, activates Akt. [5] So far, Deptor is the only characterized endogenous inhibitor of mTORC2. We decide ingredients of organizing mTOR helps to find a reason how it can control cell growth. [4]

Manuscript received June 10, 2014; revised February 10, 2015.

doi: 10.12720/jomb.5.1.72-75

C. Amino Acids

From the studies on the mechanism of mTOR activation by amino acids, the possibility was considered that amino acids may be activating some of the cell signaling elements upstream from mTOR in the insulin/growth factor signaling pathway such as PI 3-kinase and serine/threonine protein kinase, protein kinase B (AKT). A change in the conformation state of AKT is thought to uncover phosphorylation sites that are subsequently phosphorylated by one or more constitutively active protein kinase. Phosphorylation of AKT on its activation loop at Ser 473 is required for activation. Whether AKT can directly phosphorylate mTOR is a matter of controversy, although phosphorylation of mTOR is associated with insulin stimulation of the kinase. However, in contrast to the situation with insulin and growth factors, amino acids do not stimulate PI 3-kinase or AKT activity in any tissue where this has been examined. Thus amino acids activate mTOR signaling by an AKT-independent mechanism. [6]

III. Experiment

We had an experiment about mTORC1 and got a result, using apriori algorithm. We went forward with the experiment by dividing it into four cases; 7window, 9window, 13window, and 17window. We got different measurements of each case and overall we could come to the conclusion that acid I-Leucine has the highest frequency and responds to almost all of mTOR factors. As a special case, we could found the a-Alanine which can be manufactured in the body from pyruvate and be branched chain amino acids such as valine, leucine, and isoleucine; 38 in amino 5 of 7window and 23 in amino 7, 22 in amino 9 of 13window. Also, we had 28 e-Glutamics in amino 8 of 9window.

A. Apriori Algorithm

We use apriori algorithm to find out which protein most consists of mTOR. Apriori is an algorithm for frequent item set mining and association rule learning over transactional databases. So, we use this A.I., especially apriori algorithm, to find out component of mTOR to find out why leucine figures out a lot, and how leucine effects on mTOR.

B. Leucine

As there has been found leucine the most in mTOR sequence, leucine has a big role in it. Most of the effects of amino acids on mTOR signaling are abolished by lowering the concentration of leucine, or mimicked by adding leucine and, to a lesser extent, the other branched-chained amino acids. At 4X concentrations, leucine was the only amino acid capable of stimulating rapamycin-sensitive 4E-BP1 phosphorylation in adipocytes. At much higher concentrations, other amino acids structurally related to leucine were able to stimulate 4E-BP1 phosphorylation. [6]

C. Alanine

Alanine can be easily formed and thus has close links to metabolic pathways such as glycolysis, gluconeogenesis, and the citric acid cycle. It also arises together with lactate and generates glucose from protein via the alanine cycle. Alanine plays a key role in glucose–alanine cycle between tissues and liver. In muscle and other tissues that degrade amino acids for fuel, amino groups are collected in the form of glutamate by transamination. Glutamate can then transfer its amino group through the action of alanine aminotransferase to pyruvate, a product of muscle glycolysis, forming alanine and α-ketoglutarate.

D. E-glutamic

Glutamate also plays an important role in the body's disposal of excess or waste nitrogen. Glutamate undergoes deamination, an oxidative reaction catalyzed by glutamate dehydrogenase. Ammonia (as ammonium) is then excreted predominantly as urea, synthesized in the liver. Transamination can, thus, be linked to deamination, effectively allowing nitrogen from the amine groups of amino acids to be removed, via glutamate as an intermediate, and finally excreted from the body in the form of urea.

IV. Result

During the whole experiment, we can figure out that only leucine is detected in mTOR. For this, we expected that only leucine takes charge for mTOR's role. This is because mTOR intensively distributes on muscle cells and leucine enforces muscle cells. However, we can get this data only from 17window. In 7 and 13window, we could find the fine distribution alanine. For this, alanine also reacts on mTOR. After analyzing 9window, glutamic acid also figured out. These two amino acids help to guess that Alanine plays a key role in glucose–alanine cycle between tissues and liver, so glutamic acid and alanine interacts each other to make glucose-alanine cycle.

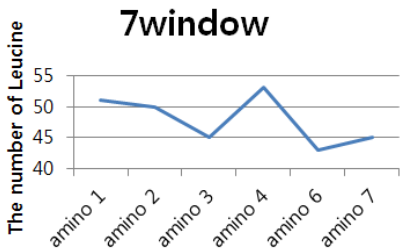

Figure 1. 7window experiment

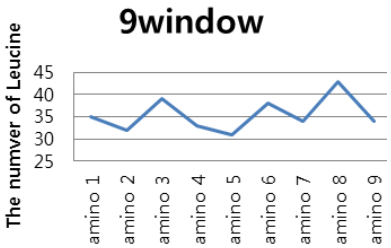

Figure 2. 9window experiment

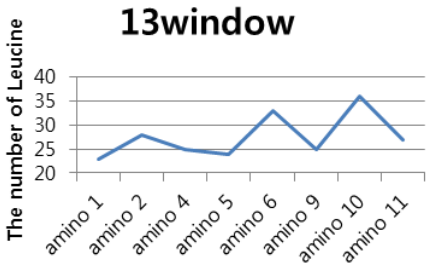

Figure 3. 13window experiment

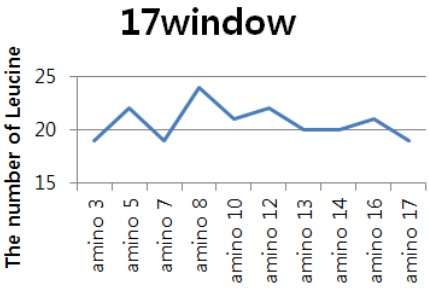

Figure 4. 17window experiment

From the previous studies we could have found how leucine, alanine, and glutamic acids which came out of our experiment, works in the mammalian cycle. In adipocytes and some other cell types, leucine appears to be the main regulatory amino acid. Potential role for mTOR in adipocytes that were previously posited include hypertrophic growth, leptin secretion, protein synthesis and adipose tissue morphogenesis. [7] We have established its work especially from pancreatic that leucine-induced insulin secretion by β-cells involves increased mitochondrial metabolism by oxidative decarboxylation and allosteric activation of glutamate dehydrogenase (GDH). [7] Studies using various leucine analogs also confirmed the close association of mitochondrial metabolism and the ability of leucine analogs to activate $P70^{s6k}$. These findings indicate that leucine at physiological concentrations stimulates $P70^{s6k}$ phosphorylation via the mTOR pathway, in part, by serving both as a mitochondrial fuel and an allosteric activator of GDH. [8] Furthermore, certain amino acids, notably the essential amino acids, not only serve as precursors for protein synthesis, but also have important regulatory roles in the initiation phase of mRNA translation. The glucose-alanine cycle enables pyruvate and glutamate to be removed from the muscle and find their way to the liver. Glucose is regenerated from pyruvate and the returned to muscle: the energetic burden of gluconeogenesis is thus imposed on the liver instead of the muscle. All available ATP in muscle is devoted to muscle contraction. A key process in amino acid degradation is transamination, in which the amino group of an amino acid is transferred to α-ketoacid, typically catalyzed by a transaminase. Transamination of α-ketoglutarate gives glutamate. The resulting α-ketoacid product is often a useful one as well, which can contribute as fuel or as a substrate for further metabolism processes.

V. Conclusion

A. Result

We divided mTOR into genetic sections and discover the sequence of them. Each has different amino acids and we found that almost every section, it has leucine. So the above graphs are showing only about for the amount of leucine. From Fig. 1, the highest amount of leucine rates at 53. Also, the noticeable rate from Fig. 2 is 43, Fig. 3 is 36, and Fig. 4 is 24. It shows that almost every part of mTOR, they are consisting of leucine the most. However, we could also find alanine and glutamine, actually it was very slight size compared to leucine. We found alanine from 7 window 38, 13 window 23 and 22, and glutamine from 9 window 28. Therefore, we can conclude that mTOR is mostly composed of leucine, alanine and glutamine acid.

B. Expectation

Based on the results, mTOR can work mostly in tissues and liver because of leucine. Also they can work through the cycle in mTOR and help the human cellular metabolism.

MTOR can be used in many ways such as medical field or cosmetic field. This needs, however, much basic information about mTOR to apply in many fields and we are expecting that relationship between mTOR and protein will help to apply much easier. Following studies we willing to do is to focus more on the rate of alanine and glutamine. We wonder what influence cab they can effect on mTOR and how can we define that cycle for another role.

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Hyun Kwon was born in 1998. She is currently a student in science major of Hankuk Academy of Foreign Studies, Korea. She is deeply interested in Biochemistry and medical science. She has been studying pattern analysis and computer programming and its application to Chemistry and Biology.

Yerin Oh was born in 1997. She is currently a second grade student in Science Major of Hankuk Academy of Foreign Studies, Korea. She is mostly interested in Engineering and Biology.

Taeseon Yoon was born in 1972. He is currently a teacher in Science Major of Hankuk Academy of Foreign Studies, Korea. He is mostly interested in Engineering and Biology. He has been studying pattern analysis and computer programming and its application to Chemistry and Biology.