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Rapamycin- A Future versatile drug

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Abstract

Rapamycin was isolated as anti-fungal drug but it has many wide range of applications. Many experiments have been conducted to know about the mechanism of rapamycin and its activity on tumour cells. The mTOR pathway is crucial because it regulates the protein synthesis, lipid metabolisms etc. In this, we discuss about the structure, mechanism of pathway, applications of the drug,in different fields and the isolation of its identical characters in recent research experiments. Along with rapamycin certain drugs are used like cyclosporine, tacrolimus. Tacrolimus and rapamycin has a similar binding site i.e IL-2 hence it is replaced by rapamycin.

Keywords: Rapamycin, mTOR pathway, identical characters.

Introduction

Suren Sehgal was first person to isolate rapamycin from bacteria named ***Streptomyces hygroscopicus*** **,** later Ayerst studied that it contain antifungal activity but, later studies stated that it also have immunosuppression and anti-proliferative properties, it also inhibits the antibodies formation. Due to immunosuppression property it was majorly considered for prevention of organ rejection after transplantation. Many experiments on rapamycinwere conducted by Ayerst and Sehgal but was not successful. For some years rapamycin drug was lost, i.e experiments on it were halted. After 6 years isolation of CC1-779- an analogue of rapamycinwhich was identified as a drug against tumour cells. [1]

Structure of Rapamycin:

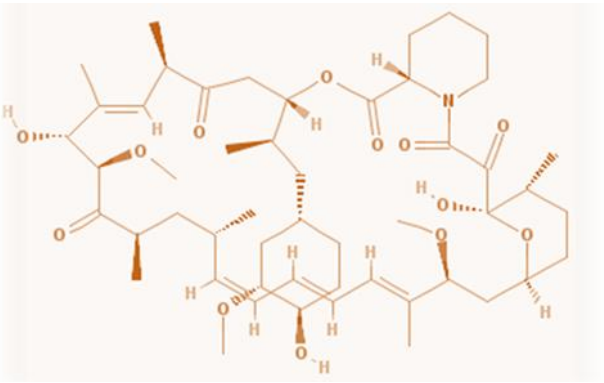

Fig: 1Structure of Rapamycin

The chemical formula for rapamycin is C51H79NO13 shown in fig:1. It is a macrocyclic lactone compound produced naturally from bacteria. [2]

Activation of MTOR pathway:

Cellular pathways are of two different types intracellular and extracellular. This pathway occurs in intracellular region. In every pathways the two main components required are signaling molecule and the receptor molecule. Here in this pathway the signaling molecule is growth factors such as epidermal growth factors (EPG),fibroblast growth factor insulin growth factor (IGF) etc.

STEP-1:

The growth factor binds to the thyrosine kinase sub untis. As soon as it binds autophosphorylation occurs in between the subunits and it activates PI3Kinase protien.

STEP-2:

This PI3kinase (phosphoinositide 3 kinase)later on activates the PDK1 protein (phosphoinositide dependent kinase).

STEP-3:

The protein PDK1 activates AKT (a serine/threonine complex) molecule which plays a crucial role in activation of mTOR (mammalian target of rapamycin) pathway.

STEP-4:

Activated AKT molecule activates mTOR molecule. It doesnot do it directly, it is mediated by some other molecules such as TSC1(and TSC2, Rheb proteins.

TSC1 (and TSC2 proteins blocks the Rheb protein which is a crucial molecule to activate mTOR. Thus AKT blocks the action of TSC1, TSC2 molecules and initiates the Rheb molecule.

Protein named Rheb activates mTOR (mammalian target of rapamycin) shown in figure:2. This is upstream pathway[21]

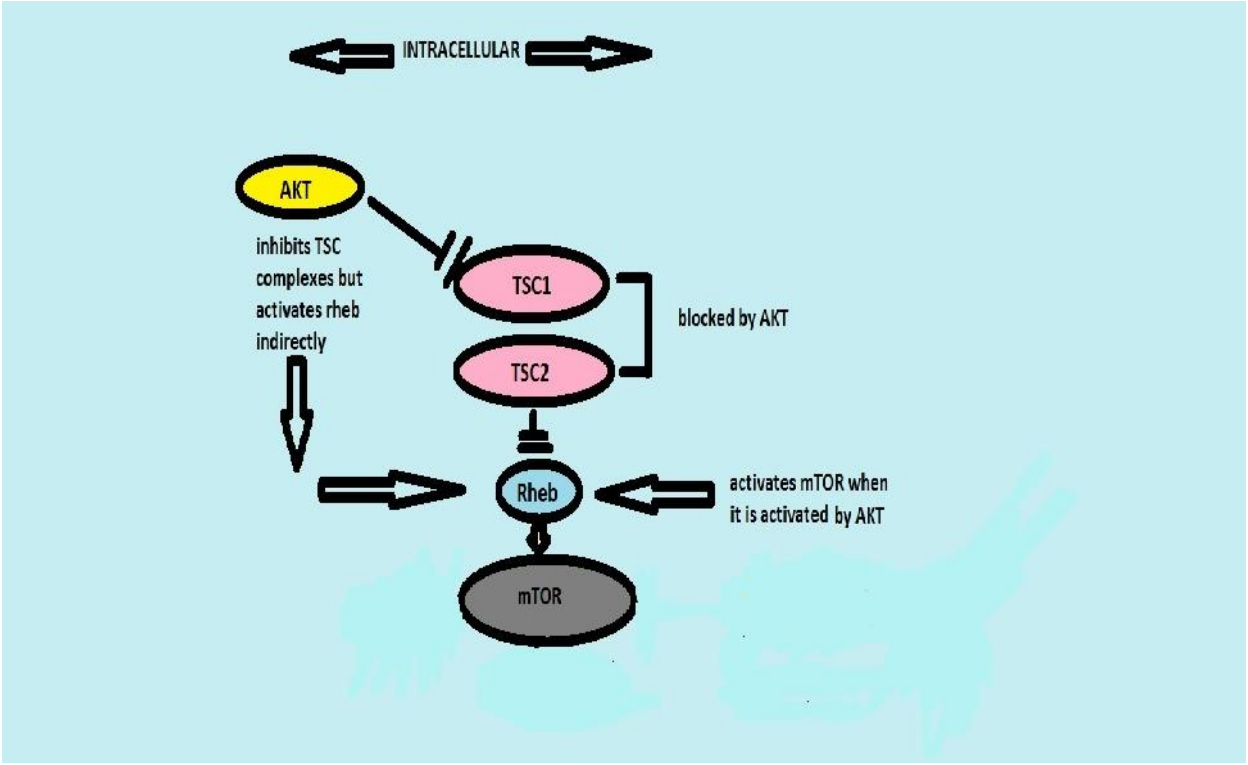

Fig:2 Mammalian target of rapamycin activation

Mechanism of mTOR Pathway:

As AKT activates mTOR, it regulates two pathways mTORC1 and mTORC2. mTORC1 consists of mTOR, raptor, deptor, mLST8 and PRAS40 subunits.mTORC2 consists of mTOR, protor, deptor, rictor and mLST8 subunits. As mTORC2 consists of rapamycin insensitive component. mTORC1 activates p70S6kinase protein and 4EBP1proteins[21]. The p70S6kinase induces protein sysnthesis. Whereas 4EBP1 protein inhibits the synthesis of protein. S6K proteinfurther produces S6 which regulates the protein synthesis.[22] On other side protein named 4EBP1 blocks the process of protein synthesis.Mtor also regulates the lipid synthesis and mitochondrial biogenesis.[1]

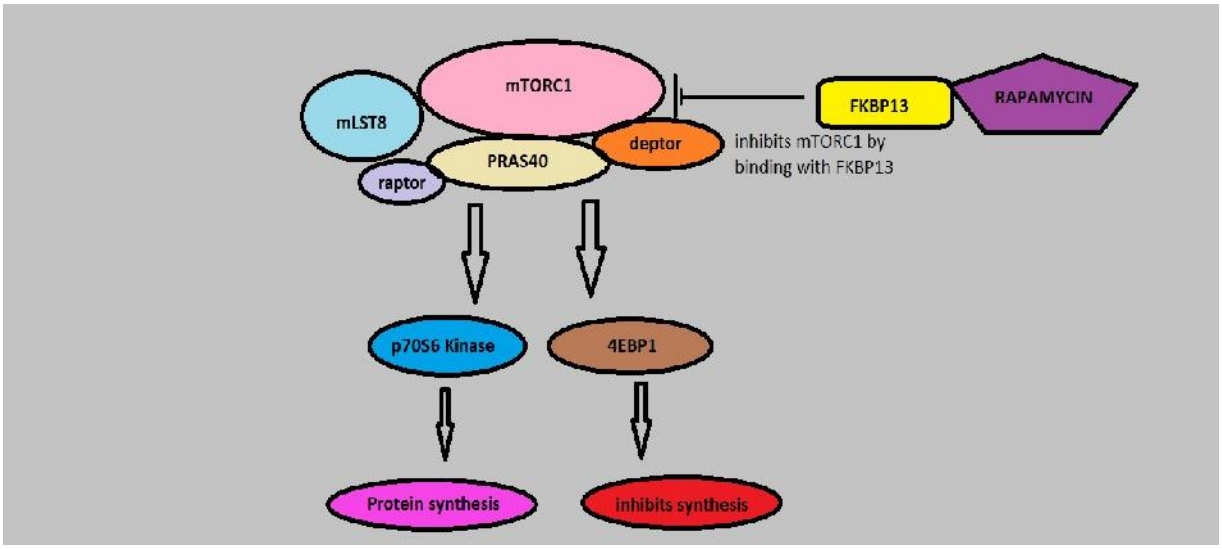

Fig:3 Mammalian target of rapamycin pathway

Rapamycin blocks the process of MTOR :

Rapamycin binds to the protein FKBP12 of mTORC1 and blocks the further production of S6k and 4EBP1 [1] . Due to the inhibition of mTORC1 pathway there is a major chance for occurance of autophagy. [6]

Application of rapamycin as a drug:

- Based on many laboratory results NCI proved that rapamycin have a nature of inhibiting different types of tumour cells in man like colon 26, B16 43melanocarcinma,[3] lymphangioleiomyomatosis (tumour in lungs), angiomyolipomas (tumour in kidney) [6] etc.
- Experimentally the increased angiogenic factors like VEGF can increase the activation of mTOR hence the angiogensis is promoted was proved. As rapamycin inhibits mTOR the anggenic factors are inhibited,the process is stoped.Recent research showed that the combination of sirolimus and tacrolimus drugs showed a positive result on angiofibromas.[5]
- A number of pharmological experiments on inhibition of mTORC1 shows that this mechanism gives neuroprotection and fight against dieseases like Alzheimer's disease, Parkinson's disease, Huntington's disease and so on.[6]
- Ehninger and his team have done experiments on more than 150 traits of mice and found that it increased the lifespan of mice but doesn't effect aging in it. They concluded that many traits of mice are effected by cancer as rapamycin is a relevent inhibitor for cancer cells it increased the lifespan but did not effect any aging protein. [7]
- Rapamycin was recently experimented on children suffering from Hutchinson-gilford progeria syndrome (HGPS). This disease accelerates the aging in children i.e a 12years child turns to old age this is due to the accumilation of progerin in the cell.[8] children treated with rapamycin got rid from this accumilation and turned healthyi.e it decreases the production of insoluble progerin and clears the cell.[9] This is also one of the achievement of the drug.
- After several trails on mice,rats both U.S and global groups for the first time clinicaly gave rapa to pateints with organ transplant with 2 or 5mg dose. Both doses decreased the organ rejection. But when compared to 2mg dose 5mg gave less results of organ rejection in american study.[10]

- Experiment of rapamycin to the mice with cerebral malaria exposed positive result i.e it increased the survival inhibited the breakdown of blood barrier in brain.[14]
- Rapamycin also restores the normal behaviour of mice which is suffering with synaptic purning.[15]
- Rapamycin limits the growth of aneurysms by preserving median elastic and smooth muscles in rapamycin group. [18]
- OLZ (olanzapine) increased the concentration of amino acids in hepatic cells which alter the metabolism through mTOR pathway. This increased mTOR in hepatic cells.[19]
- Recent experiment also showed the anti-lymphangiogenic property of rapamycin which affords us many further medical advantages in treatment of malignant tumours. [20]

Based on the nature of rapamycin numerous experiments were conducted but at last FDA certified rapamune only for inhibition of organ rejection nature. Still researches are going on to find its benefits as an anti-cancer, anti-aging drug and so on.

Contrasting results of rapamycin:

1] Insensitive activity of rapamycin on yeast TORC1 :

Recent research on yeast with rapamycin exhibited a major confusion in the functioning of rapamycin in mammals and also in yeast.

When yeast is treated with rapamycin the result expected was to terminate the budding process in yeast but the result was contrast to their estimation. Researchers found that it partially inactivated the TORC1 protein in yeast. Either it inactivates totally or partially this was clearly not known. [11]

2] Diabetic symptoms due to intake of rapamycin:

Recent experiment in Dana-Farber cancer institute scientists observed that the intake of rapamycin caused diabetic symptoms in animals but the animal with absence of YY1 protein doesn't show any diabetic symptom. The mechanism is still unkown by researches. [12]

Scientist named Lamming conducted experiment on mice to know the contradictory nature of rapamycin. When the level of rictor was reduced in mTORC2 he found that the mice produced high level of sugar in liver and increased intolerance state was found. Rapamycin intake doesn't worsen the state of mice. In the same way when he destituted raptor from mTORC1 the sugar level was normal intake of rapamycin doesn't extend the life of mice. Experiment was succesful but many contraversial questions were elevated like mice were genetically similar and this effect was more common in old mice but he experimented in young mice.[13]

Analouges of rapamycin :

Tacrolimus and cyclosporin together are given to patients with kidney transplantation but most of the people require further treatment along with these drugs. Hence the introduction of rapamycin which is analouge to tacrolimus treats well against organ rejection and decreases the toxicity of cyclosporin. [16]

Due exposure of cells with rapamycin for a long time there is a chance of binding of rapamycin to free mTOR molecule by which activation of AKT also gets inhibited which in turn inhibit both mTOR complexes. Recent experiment regarding this mechanism was succesful.[17]

Conclusion

Due to the lack of clarity in the mechanism of rapamycin it is hard to come over with a single use of this drug. Although it has been approved as inhibitor of organ rejection drug it also have further identical properties which may lead to a new era in cancer treatment. Further researches must be done regarding the supression or inhibition of rapamycin on particular protein.

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