Controlling the birth of neurons through the critical mTOR pathway

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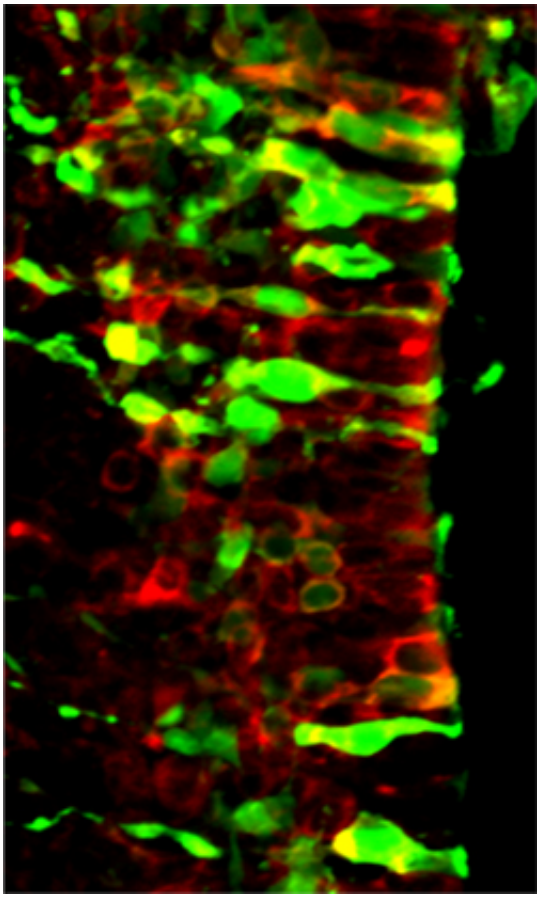

Birth of new neurons. Credit: Yale School of Medicine

(Medical Xpress)—The native peoples of Easter Island are known locally as the Rapa Nui. In the 1970s, a potent antifungal was discovered in a bacterium that lives in the soil there. Researchers named the

molecule, rapamycin, after the island and its people. Since that time, rapamycin has gone on to have an illustrious career, proving itself as a potent immunosuppressant in organ transplantation, in cardiology, and in the treatment of several kinds of cancer. An important target molecule regulated by rapamycin was later discovered in yeast, and was descriptively named TOR, for "target of rapamycin." The mammalian version of TOR, mTOR, has emerged as a central regulator of the state of cell, and gates the levels of many proteins through its actions at the level of their translation.

A group of researchers from the Yale School of Medicine has recently uncovered a critical function for a larger complex of proteins, known collectively as mTORC, in the role of neural stem cell differentiation. In their paper, just published in *Cell Reports*, they propose a new pathway for mTORC1 action that would be both an ideal target for preventing or rescuing many kinds of abnormal brain development in newborns, and for controlling the life cycle of tumors.

In a nutshell, the researchers found that mTORC, which acts as a phosphatidylinositol 3-kinase-related-kinase, represses the activity of a key repressor of translation, known as 4EBP. Basically what this means, is that mTORC action leads to the specific translation of proteins which drive neural stem cells to become neurons. The identification of 4EBP as the intermediary in this pathway could be therapeutically important. It provides another potential target for drugs to act with greater specificity than say, straight rapamycin. While we are not trying to act as both internal medicine doctor and pharmaceutical drug discoverer here, we should note the action of rapamycin is known to have different effects on different parts of the mTORC complex itself. In addition to rapamycin, a host of other drugs have been shown to act as mTOR inhibitors—and at least in culture, a few of them are as familiar as caffeine.

Those of us who do not make a living by directly studying this pathway might have one small criticism reading this interesting paper. As we just mentioned, many of these protein complexes have different components with different names. Just as mTORC is actually split into two units, with the names mTORC1 and 2, likewise 4E-BP is associated by the authors in various places to contain both 4E-BP1 and 2. The problem is when they describe complex experimental manipulations, and the result of those manipulations, some of them pertain just to 4EB-P1, and others just to 4EB-P2. That makes it difficult to determine, at least here on the outside, what exactly is the function of the manipulation when it is called out as just plain old 4E-BP.

We understand that much of the cell interior, and the protein associations taking place there, are in a constant state of flux. That makes it difficult to step right away to assigning a pathway to a therapeutic success, and vice-versa. In looking at the vast literature on mTOR, it is hard to say what functions the pathway is not involved in. One explanation for the magnitude and diversity of mTOR effects, is that it appears that it is necessary for one of the most basic needs of the cell—the maintenance of mitochondrial oxidation. In skeletal muscle for example, rapamycin reduces expression of mitochondrial transcriptional regulators like PGC-1alpha and Estrogen-related receptor alpha. Inhibitors of mTOR have also seen extensive action in trials for the treatment of breast cancer.

A broader theme on that last point, is that drugs in breast cancer treatment, like for example tamoxifen, have been show to operate mitochondrial estrogen receptor-beta. In a recent post about dendritic spines and memory, a commenter pointed to the essential role of estrogen in authorizing changes in the brain, presumably structural, that are critical not just for memory but also processing and perception. One the other hand, if this action is not structural, and can erase or restore these powers like a selective anesthetic, than how else might they operate

except by defunding neurons of something very dear, like energy?

At the risk of getting too far afield from mTOR, we want to conclude be saying that in assigning detailed molecular action to a drug or other molecular agent in a cell, we may just be capturing the middle ground. There may also be descriptive power in appeal to particular features of just the molecule itself, like for example, how it moves in a membrane. At the other end of the spectrum, the action of the drug could be described at the level of behavior of cell organelle; how it moves, increases or replicates. As researchers are increasingly able to just sit back and watch cells under the action of a drug, the focus on the molecular path and partner may start to take backseat to tale of richer effects.

More information: mTORC1 Targets the Translational Repressor 4E-BP2, but Not S6 Kinase 1/2, to Regulate Neural Stem Cell Self-Renewal In Vivo,*Cell Reports*, dx.doi.org/10.1016/j.celrep.2013.09.017