Starving cancer cells

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Inhibitors of mTOR have emerged as a novel class of anti-cancer drugs, with at least three pharmaceutical companies developing their own candidate. New evidence suggests that mTOR inhibitors work by fooling cancer cells into thinking that they are starving.

The novel compounds are all derivatives of rapamycin, a fungicide that was isolated in 1975 from *Streptomyces hygroscopicus*, a bacterium discovered in a soil sample from Easter Island in the South Pacific. Rapamycin is best known for its immunosuppressive properties. The compound was licensed by Wyeth (Madison, NJ, USA) in 1999 in the USA and in Europe in 2000 as Rapamune®, approved for the prevention of transplant rejection in renal transplant patients.

Rapamycin also has well known anti-proliferative properties; indeed, immunosuppression by rapamycin is based on its anti-proliferative activity against T-cells. However, for many years, pharmaceutical companies were reluctant to explore its potential as an anti-tumour agent, partly because its mechanism of action was not known at the time and because there were concerns that cancer patients would become immunosuppressed. Some 20 years later, this has all changed.

Mechanism of action

In 1994, scientists discovered mTOR (mammalian Target of Rapamycin, also known as FRAP or RAFT1). mTOR is a large protein of 290 kDa with many functional domains. Many issues surrounding the function of mTOR are still a mystery, but it seems clear that mTOR is part of the phosphatidylinositol-3-kinase (PI3K) signaling pathway, thus playing a crucial role in translation, cell growth and division (reviewed in [1]; see Fig. 1). Inhibition of mTOR leaves cells arrested in the G1 phase of the cell cycle.

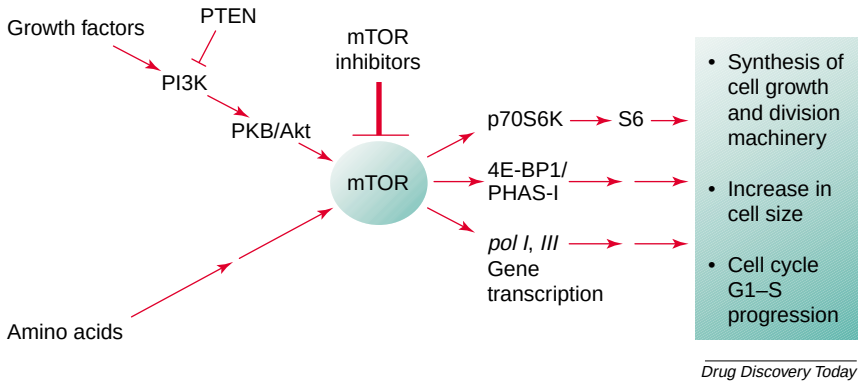

Figure 1. Inhibition of mTOR interferes with a key signal transduction pathway that is altered in many types of cancer. The nutrient-stimulated pathway regulates protein synthesis, cell cycle progression and proliferation. Abbreviations: P3IK, phosphatidylinositol-3-kinase; PKB/Akt, protein kinase B; mTOR, mammalian Target of Rapamycin; p70S6k, ribosomal protein S6 kinase; 4E-BP1, eukaryotic initiation factor 4E (eIF-4E) binding protein 1 (also known as PHAS-I); pol I, polymerase I; pol III, polymerase III; PTEN, phosphatase and tensin homolog deleted on chromosome ten. Figure kindly provided by Tim Clackson, ARIAD Pharmaceuticals, Cambridge, MA, USA.

The interesting thing about rapamycin derivatives is not only that they target a crucial signaling pathway, but that this pathway is actually deregulated in many types of cancer, rendering cells more susceptible to the effects of the drugs. For example, cells that lack the tumour suppressor gene PTEN – which is defective in many types of cancer, including prostate, uterine, ovarian and pancreatic cancer as well as melanoma, leukemia and glioma – are hypersensitive to the inhibition of mTOR [2]. According to Peter Houghton, an mTOR expert at St Jude Children's Research Hospital (Memphis, TN, USA), there is also evidence that if tumour cells lack p53, their response to mTOR inhibition is death through apoptosis. 'This indicates that rapamycin derivatives could have tumour-selective activity,' says Houghton.

He adds, 'Certain transforming events in tumours seem to cause tumour cells to be more sensitive than normal cells, and hopefully we can exploit that ultimately when we genotype or phenotype patients in terms of their tumours.' At some point, clinicians might be able to determine before treatment whether a specific tumour is more sensitive to rapamycin derivatives, perhaps in combination with an inhibitor of another pathway. 'Single agents are going to have some activity, but when you start to combine different signaling agents, that is where they will have remarkable activity,' concludes Houghton.

Clinical development of rapamycin derivatives

Following the resurgence of interest in mTOR inhibitors as cancer therapies, several pharmaceutical companies have now got rapamycin derivatives in the pipeline (Fig. 2). Key to the recent success of these compounds as anti-tumour

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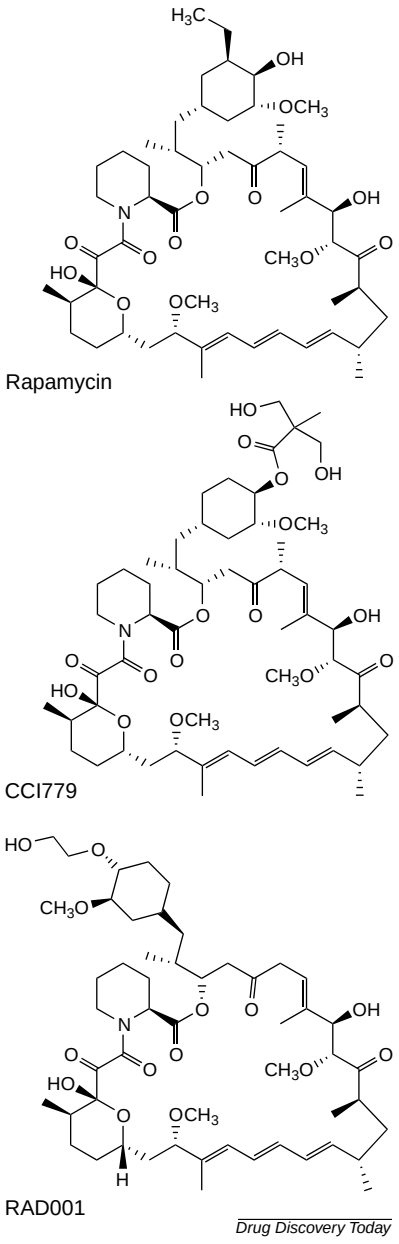

Figure 2. Structures of rapamycin and two rapamycin derivatives currently in clinical trials.

agents has been the realization that undue immunosuppression can be avoided by dosing intermittently.

CCI779

Wyeth's compound CCI779 (cell-cycle inhibitor 779) is a rapamycin ester analog. Phase I trials demonstrated that the compound is well tolerated, with only mild side effects such as acneiform rash and mild thrombocytopenia [3,4]. At present, CCI779 is in Phase II trials in patients with breast cancer and is going into Phase III trials for first-line renal cell carcinoma, a disease that is often refractory to treatment. In March 2002, Wyeth announced that CCI779 has been designated for the fast-track development program by the FDA for the treatment of renal cell carcinoma following the failure of interleukin-2 therapy for this disease. The compound is administered intravenously once a week; it is also being investigated for oral formulation. New data will be presented at the upcoming American Society of Clinical Oncology (ASCO) 2002 conference (Orlando, Florida).

RAD001

RAD001 (Novartis, Basel, Switzerland) is a hydroxyethyl ether derivative of rapamycin, formulated for oral administration. The compound has almost completed Phase III clinical trials in the USA for transplantation therapy. At the *93rd Annual American Association for Cancer Research (AACR) Meeting* (6–10 April 2002, San Francisco, CA, USA), Novartis presented results showing that daily administration of RAD001 at doses ranging from 2.5–10.0 mg kg^{-1} day^{-1} prevented tumour growth in 12 out of 14 mouse xenograft and all (1/1) rat syngeneic models of human cancer, including pancreatic, colon and lung cancer; in two of these models, treatment resulted in tumour regression [5]. The first clinical trial, a Phase Ib study, began in February 2002.

AP23573

AP23573 (ARIAD Pharmaceuticals, Cambridge, MA, USA) was developed using structure-based drug design. The company's Vice President for Gene Therapy and Genomics, Tim Clackson, reported at the *93rd Annual AACR Meeting* that nude mice bearing glioblastoma xenografts showed a 46% reduction in mean tumour volume after treatment with AP23573 for five days compared with tumour growth of 150% in control mice [6]. The compound, developed for oral or intravenous administration, is targeted to enter clinical trials later this year.

Clackson adds, 'One thing we emphasized at the meeting is our view that mTOR inhibitors really work by fooling tumour cells into thinking that they are starving.' It is the emerging view in the field that mTOR is an integrator of information on growth factors and nutrients outside the cell [7]. 'All these signals feed into mTOR as a central processor of information,' explains Clackson.

Clackson says they are now doing a series of experiments to look at the effects of AP23573 on the size of cells and on their transcriptional profile, searching for hallmarks of the starvation response. 'Cells actually get bigger when mTOR is turned on, and that is obviously a prerequisite for their division,' says Clackson. Inhibition of mTOR shuts all of that down, and it is striking that mTOR inhibition by our compound really mimics the natural starvation response of cells.'

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