Medical research

Low dose of cancer drug improves overgrowth syndrome: lessons for cancer therapy?

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Abnormal activity of the enzyme PI3K can drive cancer development and growth. PI3K inhibitors are available and a low dose of such inhibitors causes a dramatic improvement in patients who have non-cancerous overgrowth caused by PI3K mutations.

Those investigating rare genetic conditions perennially hope that the discovery of disease-causing mutations will lead swiftly to tailored therapy. Sadly this is not often the case because genetic defects usually impair body functions or structures in ways that are difficult or impossible to treat using available medicines. Writing in *Nature*, Canaud *et al*.[1] now suggest a rare exception to this rule. They study severe non-cancerous overgrowth syndromes caused by mutations in the kinase enzyme called PI3K, and show beneficial effects of a PI3K inhibitor drug that was initially developed for cancer treatment. Their results move a potentially transformative therapy for these conditions a step closer.

Human development from a single fertilized egg to an adult body of around 37 trillion cells[2] while maintaining symmetrical paired body parts is an astonishing feat that requires lifelong coordination of cellular division, survival and death. Growth-factor proteins can aid cellular coordination by acting through cell-surface receptors to stimulate intracellular signalling networks. The latter often include PI3K, which is essential for normal regulation of growth and development by the insulin and insulin-like growth factor hormones.

Cancer requires flagrant breaching of the rules of good cellular citizenship needed in a multicellular organism: cancer cells acquire genetic abnormalities that subvert the checks and balances that normally constrain cell growth and migration. Mutations that activate PI3K signalling, most commonly in the gene *PIK3CA*, which encodes a catalytic subunit of PI3K, are among the commonest mutations that drive solid cancers[3]**.** PI3K signalling can also be activated by mutations that inactivate the enzyme PTEN that normally keeps PI3K activity in check. Such links between overactive PI3K signalling and cancer motivated researchers to develop PI3K inhibitors. However, the clinical impact of these drugs to treat cancer has been less impressive than hoped, because of high-dosage-associated toxicities and because, even if activated PI3K is inhibited by drugs, other proteins can compensate and provide alternative cancer-promoting pathways[4].

In 2012, it was reported that certain human *PIK3CA* mutations that had previously been linked to cancer cause rare, non-cancerous forms of human overgrowth[5-7]. A hallmark of these types of overgrowth is abnormally increased growth affecting the body patchily and asymmetrically**.** This is because the causal *PIK3CA* mutations occur after the start of embryonic development and in only some cells[5, 6, 8], leading to a “mosaic” pattern of cellular overgrowth. The severity of the overgrowth varies widely from person to person, ranging from an isolated skin growth to a complex multisystem disorder called CLOVES syndrome[5], which features severe and often widespread overgrowth that contains an abundance of fat cells and abnormal blood vessels. As *PIK3CA* mutations are a common

feature of many overgrowth syndromes, the term PROS (for *PIK3CA*-related overgrowth spectrum)[8] is used as a unifying description of such cases.

PROS has not been linked to an increase in the risk of formation of the solid cancers in which *PIK3CA* mutations are most prevalent. It is at present not clear why PROS does not give rise to cancer, but *PIK3CA* mutation in PROS is usually seen in cell types of a different embryonic origin to those that develop cancer with *PIK3CA* mutations. However, severe forms of PROS can be debilitating or life-threatening. Vascular problems or organ dysfunction can occur due to the compression caused by overgrown tissue. Current treatments aim to reduce excess tissue by surgery or by physical blockade of enlarged blood, and other treatment options are urgently needed. The availability of targeted inhibitors for *PIK3CA* that had already been tested for use in clinical cancer treatment, gave reason for hope of a possible new therapy for PROS. Yet questions come to mind about prolonged exposure to these drugs. Would this cause side effects, would cells adapt to blunt the effect of treatment, as occurs in cancer[4]? Established overgrowth in PROS may moreover not be amenable to reversal by therapy.

Canaud *et al.*[1] take a major step towards addressing these questions. Previous attempts to model PROS in mice engineered to express disease-causing *Pik3ca* mutations at natural expression levels produced excess growth in only some of the expected tissues[9]. Canaud and colleagues generated another type of PROS model mouse strain that was engineered to be born expressing high levels of an artificially-activated form of *Pik3ca*, the mouse version of human *PIK3CA*. The authors found that these animals developed problems similar to the human condition including overgrowth of adipose, muscle and vascular tissue and premature death caused by vascular complications. When the authors treated their PROS model mice with a low dose of the PI3K inhibitor called alpelisib, they documented an impressive, rapid and substantial decrease in the animals' overgrown tissue, preventing premature death.

Most crucially, Canaud *et al.* then assessed the effect of low-dose alpelisib treatment in 19 people with PROS, who had severe or life-threatening complications. They initially used the lowest dose (100 mg/day) that had been tested in clinical trials in cancer, or a dose that was never tested in cancer (50 mg/day) but that was available as a pill, to give to children daily. Dramatic anatomical and functional improvements occurred in all patients across many different types of affected organs, with benefits noted within days of starting therapy. The study was not randomized, blinded or placebo controlled, however, these initial results are sufficiently striking to suggest this outcome is very likely clinically important. Alpelisib resistance was not observed, and the drug was remarkably well tolerated. A predicted side effect of PI3K inhibition is high blood glucose caused by interference with insulin's PI3K-mediated metabolic effects, however, blood glucose elevation only occurred in three people and the elevation was modest. In children, the drug did not have a significant effect on normal growth, which suggests that overgrown tissue can be targeted without harmfully blocking PI3K-dependent childhood growth. More systematic clinical studies are now needed, and ethics committees will have to assess whether it is now ethical to include a placebo in such studies for severely affected patients.

The study of PI3K inhibition to treat PROS might also offer something back to the design of cancer therapies. The aim of PI3K-inhibitor treatment in PROS would be to suppress pathological levels of PI3K signalling while minimizing side-effects during long-term, and probably lifelong, therapy. By

contrast, the conventional cancer therapy approach is to identify differences between healthy and cancerous cells, and to hit the cancer-specific characteristics as hard as possible to induce cancer cell death. In cancer clinical trials, PI3K inhibitors are usually studied at the maximum dose tolerated, yet whether this makes sense is unclear, given that the low-level activity of mutated *PIK3CA* is probably similar to the low-level activity of the enzyme in PROS. Might a low dose of inhibitor be beneficial in cancer through abolishing the 'extra' PI3K activity provided by the *PIK3CA* mutation, while not completely wiping out all PI3K signalling as would be the case with a high dose of the inhibitor? This strategy could be tested, for example, in cancer prevention, especially for types of cancer in which PI3K activation or PTEN inactivation is an early event[10, 11] or in PTEN hamartoma tumour syndrome (PHTS) patients who carry a mutation in PTEN in all the cells of their body and are cancer-prone[12]. Low-dose PI3K inhibition might also be an option after other current cancer therapies such as chemotherapy or surgery, to slow cancer evolution and adaptation to selective pressures[13]. Long-term, low-dose PI3K inhibition might even offer other benefits— it increases the metabolic health of obese mice and monkeys[14] and sustained blockade of PI3K pathway can slow ageing in animal models[15]. Perhaps the time has come to target abnormal signalling in cancer with a lighter touch, which could allow combination therapies to be used that are currently precluded for reasons of toxicity. After all, there is no need to use a hammer to kill a fly, and this principle may also apply to cancer treatment.

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