EU-funded researchers are advancing a novel form of cancer therapy described as a ‘magic bullet’ against certain types of tumours. Their work promises to lead to more personalised and effective treatments for breast, ovarian and other forms of cancer over the coming years.

The research, conducted in the DDResponse project, builds on the relatively recent discovery that the suppression through medicine of a cell's ability to repair itself could be used to selectively kill some types of cancerous cells. DDResponse is using this discovery to investigate highly targeted treatments with fewer side effects than chemotherapy or radiotherapy.

“During the course of the project, we have seen how this approach has gone from being a promising idea to proving its effectiveness in a clinical environment. It’s a major step toward more personalised cancer treatment,” explains project manager Dik van Gent at Erasmus University Medical Center in the Netherlands.

Environmental, chemical and metabolic factors regularly damage the DNA strands of every cell in the human body, which are repaired by sophisticated mechanisms collectively known as the DNA damage response (DDR).

In healthy cells, multiple mechanisms can be used to repair damage, but in some types of cancer cells the DNA damage response is deficient due to genetic mutations. These deficiencies can be exploited to selectively destroy the cancer cells while leaving healthy cells unaffected – a process known as synthetic lethality.

**Broadening the targets for synthetic lethality**

In DDResponse, the researchers studied the effects of inhibiting the PARP enzymes that repair single-strand DNA breaks on hereditary ovarian and breast cancer cells lacking the genes BRCA1 or BRCA2. Mutations of these two tumour-suppressor genes account for up to 10% of all breast cancers and approximately 30% of ovarian cancers.
Olaparib, a PARP-inhibiting drug developed by DDResponse project partner AstraZeneca, has recently been approved for use against ovarian cancer in patients with BRCA1/2 mutations and is in phase III clinical trials for hereditary breast cancer.

Building on that work, the DDResponse team studied how other genetic alterations in cancer cells may influence the activity of the DNA damage response with the aim of discovering more therapeutic uses for synthetic lethality.

“PARP inhibitors are being used clinically against a very selective sub-set of cancer cells at present, but we have found indications that they could be effective against a much broader spectrum of cancers, including some that are not hereditary in origin,” Van Gent says.

Working with the two largest cancer hospitals in Denmark and the Netherlands, the DDResponse researchers established in-vitro cultures of primary breast and ovarian cancer cells to characterise their DNA damage response mechanisms, enabling the development of a list of genetic markers that could reliably predict the outcome of PARP-inhibition treatment.

In turn, they also developed an analytical test to screen patients with cancers who could be eligible for treatment with PARP inhibitors in order to ensure the most effective choice of therapy. And they studied the toxicity of PARP inhibitor treatment used alone or in combination with other chemotherapeutic drugs.

“Trials to date have shown that PARP inhibition has far fewer side effects than other forms of therapy, while being equally or more effective in patients with specific cancer types,” Van Gent explains. “Much more research needs to be carried out, but it is certainly possible that in 5 to 10 years, more types of cancer will be able to be treated in this way.”

The DDResponse partners, who plan to continue their research collaboration, have made important advances towards that goal.

See also:
CORDIS [3]

Project:
The DNA damage response and breast cancer
Project Acronym:
DDRESPONSE
Project website:

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Links