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Exploiting the DNA damage response for personalized tumor treatment

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Abstract

One of the hallmarks of cancer is genetic instability, which has been studied extensively in cell lines, primary cells and animal models. Various types of genetic instability are associated with a reduced capacity to carry out efficient repair of DNA damage, inflicted by environmental mutagens or endogenous causes, such as reactive oxygen species generated by normal metabolism. These investigations not only highlighted the dangers of repair deficiencies, but they also provided a starting point for personalized medicine. Defects in specific DNA repair pathways can be used as the Achilles' Heel of the tumor. An important concept is synthetic lethality, the observation that combinations of mutations can be lethal, while both single mutations are viable. In selected tumors, the specific DNA repair defect can be targeted in such a way that the tumor cells can be killed without causing severe side effect on normal tissues. The combination of PARP inhibitors and homologous recombination deficient hereditary breast and ovarian cancer is on its way to the clinic (phase III trials scheduled to start this year) and more combinations are currently in the preclinical phase. Although many hurdles still have to be taken (such as efficient patient selection and finding the most effective combinations of gene defects and drugs), these concepts may change cancer medicine in a fundamental way, from a one-size-fits-all concept to an individualized treatment strategy based on the molecular make-up of the tumor for each patient.

Biography

Dik C. Van Gent did his PhD at the Netherlands Cancer Institute (NKI) and postdoctoral studies at the National Institutes of Health (USA). He is now associate Professor at the world-renowned DNA repair group at the Department of Genetics of the Erasmus MC Rotterdam, one of the largest university medical centers in The Netherlands. He has published more than 50 papers in reputed journals, including Cell, Science and Nature and serves as an editorial board member of 'DNA Repair' and 'Genome Integrity'.

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