Method of lethally sensitizing human and animal cells

Technology

Radiation therapy is a common way to treat solid tumors in cancer patients. However, the cell killing efficiency of radiation therapy is not 100%. Therefore chemical adjuvants are often used in combination with radiation to increase the lethality of cancer cells. As molecular biology tools are emerging as novel therapeutics, we propose the use of specific siRNA to inhibit a cancer therapy target, namely poly(ADP-ribose) glycohydrolase (PARG). The inhibition of PARG in an animal cell that is treated with ionizing radiation dramatically sensitizes it and kills it more efficiently. Morevover, siRNA are extremely target-specific, therefore avoiding side effects.

Cellular DNA damage response and/or DNA repair pathways are targets of choice to enhance the potency of DNA damage agents such as ionizing radiation. Poly(ADP-ribosyl)ation is one of the first cellular response to DNA damage. Polymers of ADP-ribose (PAR) are synthesized by poly(ADP-ribose) polymerases in the presence of DNA damage. PAR are covalently attached to a multitude of nuclear proteins, including some DNA repair enzymes, causing the protein to momentarily loss their function (inhibition). The proteins regain their function within minutes by the action of poly(ADP-ribose) glycohydrolase (PARG), which specifically hydrolyzes PAR inro free ADP-ribose units. Inhibition of PARG would prevent the hydrolysis of PAR on critical proteins, therefore inhibiting many cellular processes, including repair and cell division. Thus, the presence of PAR for a long period of time in a cell is toxic and provoke its death. The use of a PARG inhibitor will lethally sensitizes human and animal cells toward ionizing radiations.

Applications

Poly(ADP-ribose) glycohydrolase is an ideal target for radiation therapy because of the central role it plays in DNA damage response. Without a functional PARG, damaged cell die quickly because of the presence of PARG's substrate, PAR. Therefore, PARG inhibition would be used as an adjuvant to DNA damage-induced cancer therapies.

Competitive advantages

This technology is a member of the nucleic acid-based therapies family. It is targeting a specific gene using specific siRNA, harnessing the power of RNAi. Therefore, side effects and/or off target is decreased to a minimum. Specificity of action is at its maximum.

State of development

Proof of principle in the nematode C. elegans

Business opportunity

Université Laval is seeking partners for co-development and /or commercialization of this technology.

Intellectual Property

Serge Desnoyers
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