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Fronteers in Virology: Engineering viruses to target cancer cells for Destruction

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The development of tools to re-engineer viruses has led to the numerous attempts to position them as therapeutic agents for selective destruction of cancer cells. The most promising of the agents engineered to date are herpes simplex viruses. The candidate therapeutic viruses forms 2 groups. The first comprises virus mutants that lack the $\gamma_34.5$ gene. In essence, a key event in viral replication is activation of protein kinase R (PKR). In the absence of the $\gamma_34.5$ gene PKR phosphorylates the elongation factor eIF-2a and shuts off protein synthesis. The protein encoded by $\gamma_34.5$ gene recruits phosphatase 1a to dephosphorylate eIF-2a to enable the synthesis of late viral proteins. A more attenuated version in clinical trials (G207) lacks the gene encoding ribonucleotide reductase and hence it replicates only in dividing cells in which PKR is not activated. Ionizing radiation delivered within 24 h after virus delivery enhances the effectiveness of the virus by activating p38 that in turn, activates late gene promoters thereby enhancing viral replication. The effectiveness of this class of viruses stems in part on the induction of local antitumor activity. Indeed incorporation into the viral genome of genes encoding immune modulators such as IL4 or IL12 significantly increases the antitumor activity in immunocompetent experimental animal systems. The second group of candidate therapeutic viruses have a wild-type genome except that glycoprotein D has been modified to enable entry into cells solely via novel receptors uniquely present in cancer cells. Current viruses in this group target the IL13 a2 receptor commonly present in Glioblastoma multiforme. Other receptors have also been targeted.

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