Transmembrane proteases are suitable markers for successful propagation of human tumor cells infection caused by Sendai oncolytic virus

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Background

Oncolytic viruses specifically infect and kill tumor cells without harming healthy cells. Currently, many viruses are being studied extensively for their oncolytic and immunotherapeutic properties in clinical and preclinical trials. *Sendai virus* (SeV) is a murine respiratory virus of considerable interest as it is considered nonpathogenic in humans. Preliminary data indicated that transmembrane serine proteases II that are active in cells from many tumor types participate in the replication cycle of the virus. Therefore, it seemed plausible to assume that differential expression of proteases in various cell types might serve as a basis for varying degrees of susceptibility to infection by Sendai virus.

Results

Our research showed that it was indeed the case. We studied the ability of 15 tumor cell lines to support replication and production of infection competent virions. We uncovered a correlation between the susceptibility of cell lines and expression of a number of genes that regulate protease signaling pathways. The susceptibility of cell lines positively correlated with the expression of 4 genes encoding TMPRSS2 and also CPM, CTSL2, DPP4. Of all these genes TMPRSS2 had the most significant impact on susceptibility to infection by Sendai virus compared to the other genes. In conclusion we demonstrated that expression of transmembrane serine proteases by cells derived from various tumors allows Sendai virus to selectively infect human tumor cells. That property makes Sendai virus well suited for virotherapy since it doesn't infect normal human cells.

Methods

Trancriptome data (RNA-Seq) of 26 model and primary tumor cell lines was analyzed using elastic net algorithm

$$\min_{(\beta_0,\beta)\in P^{p+1}} R_\lambda(\beta_0,\beta) = \min_{(\beta_0,\beta)\in P^{p+1}} \left[\frac{1}{2N} \sum_{i=1}^{N} \left(y_i - \beta_0 - \sum_{j=i}^{p} \left(x_{i,j}\beta_j \right) \right)^2 + \lambda \left((1-\alpha)\frac{1}{2}\|\beta\|_{l_2}^2 + \alpha\|\beta\|_{l_1} \right) \right]$$

were $Y \in P^{N,1}$ is vector of sensitivity to SeV, $X \in P^{N,p}$ - normalized expression of protease genes (127 genes), α determines penalties L1 и L2, λ - correction strength of regularized regression models.

After theoretical analysis, the impact of most relevant proteases (TMPRSS2 ,CTSA, CPM, CTSL2, DPP4, PRSS21, PRSS53) was validated by analysis of sensitivity changes after knock-out of a particular protease using shRNAs in model cell lines.

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Acknowledgments:
The research was supported by Russian Ministry of Education grant RFMEFI57714X0033