The use of replication-competent viruses for the treatment of cancers is a rapidly growing area of research and offers an important strategy to specifically target tumor cells (1–5). A number of viruses, which can specifically infect cancer cells, have been explored in this context and have shown promising results. Identification of the optimal characteristics of such viruses is, however, a challenging task. Mathematical models and computer simulations can offer important insights and influence the design of such treatment regimes. A recent article by Wein et al. (6) provides a mathematical analysis of this question, assuming the spread of a virus through a tumor in three-dimensional space. Their model suggests that tumor reduction is promoted by efficient distribution and spread of the virus through the tumor, by elimination of immune responses, and by rapid virus-induced killing of infected tumor cells.

Recently, I have studied the same question with simpler mathematical models that did not take spatial considerations into account (7, 8). Although many of the basic results of this study agree with the findings of Wein et al. (6), there is an important difference regarding the rate of virus-induced tumor cell killing. My models (7) suggest that maximizing the death rate of infected tumor cells can be detrimental to success because a high death rate of infected cells can impair the ability of the virus to spread through the tumor. Depending on the particular assumptions about the dynamics of infected cells (7, 8), the model predicted an optimal rate of virus-induced cell killing. Similarly, for immune effector mechanisms that kill infected cells, the model suggested an optimal strength of these responses.

Wein et al. (6) point out that the higher complexity of their model such as the explicit treatment of space is an important difference between the two approaches. A closer look at their model suggests, however, that the difference in outcome is not the result of the higher complexity but the result of a difference in assumption of the basic viral dynamics underlying the models. Wein et al. (6) assume that the rate of virus release from infected cells is linearly proportional to the death rate of the cells and given by $\Delta P$, where $N$ denotes the number of virus particles released and $\delta$ denotes the death rate of infected cells. That is, the faster the death rate of infected cells (higher value of $\delta$), the larger the rate of virus production. This appears to be an unrealistic assumption. It means that infected cells produce a certain fixed number of viruses during their life, independent of their life span (the basic reproductive ratio of the virus is independent of the life span of infected cells). Furthermore, this number of viruses can be present in the cells and ready for release immediately upon infection. Thus, according to Wein et al. (6), an infinitely short life span of the infected cells, brought about by the virus, is most beneficial for therapy. My model, on the other hand, assumes that virus accumulates inside the infected cells over time. Thus, killing the cell too early (higher value of $\delta$) can result in the release of fewer virus particles and in a suboptimal outcome of treatment.

In summary, these arguments show that simply maximizing the rate of virus-induced cell killing is not a correct strategy for treatment and that the relationship between tumor reduction and virus-induced cell killing can be more complicated and merits additional experimental investigation. Similarly, abolishing lytic immune responses might also be detrimental for therapy because these responses modulate the death rate of infected cells and can push it toward an optimum value in defined parameter regions. The notion that a reduced or an intermediate death rate of virus-infected cells can lead to most efficient tissue destruction has been shown experimentally in a different context: an intermediate strength of the CD8 T-cell response can maximize T-cell-induced pathology in murine lymphocytic choriomeningitis virus infection (11).

References


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Letter to the Editor


Letter

The use of replication-competent viruses for the treatment of cancers is a rapidly growing area of research and offers an important strategy to specifically target tumor cells (1–5). A number of viruses, which can specifically infect cancer cells, have been explored in this context and have shown promising results. Identification of the optimal characteristics of such viruses is, however, a challenging task. Mathematical models and computer simulations can offer important insights and influence the design of such treatment regimes. A recent article by Wein et al. (6) provides a mathematical analysis of this question, assuming the spread of a virus through a tumor in three-dimensional space. Their model suggests that tumor reduction is promoted by efficient distribution and spread of the virus through the tumor, by elimination of immune responses, and by rapid virus-induced killing of infected tumor cells.

Recently, I have studied the same question with simpler mathematical models that did not take spatial considerations into account (7, 8). Although many of the basic results of this study agree with the findings of Wein et al. (6), there is an important difference regarding the rate of virus-induced tumor cell killing. My models (7) suggest that maximizing the death rate of infected tumor cells can be detrimental to success because a high death rate of infected cells can impair the ability of the virus to spread through the tumor. Depending on the particular assumptions about the dynamics of infected cells (7, 8), the model predicted an optimal rate of virus-induced cell killing. Similarly, for immune effector mechanisms that kill infected cells, the model suggested an optimal strength of these responses.

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In summary, these arguments show that simply maximizing the rate of virus-induced cell killing is not a correct strategy for treatment and that the relationship between tumor reduction and virus-induced cell killing can be more complicated and merits additional experimental investigation. Similarly, abolishing lytic immune responses might also be detrimental for therapy because these responses modulate the death rate of infected cells and can push it toward an optimum value in defined parameter regions. The notion that a reduced or an intermediate death rate of virus-infected cells can lead to most efficient tissue destruction has been shown experimentally in a different context: an intermediate strength of the CD8 T-cell response can maximize T-cell-induced pathology in murine lymphocytic choriomeningitis virus infection (11).

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