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To cite this version:


HAL Id: pasteur-01135735
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Submitted on 25 Mar 2015

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How informative is the immune response against surrogate tumor antigens to assess antitumor immunity?

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A commentary on

The strength of the T cell response against a surrogate tumor antigen (TA) induced by oncolytic vesicular stomatitis virus (VSV) therapy does not correlate with tumor control

The last decade has seen the development of numerous antitumor therapeutic approaches. Concomitantly, the interest for using oncolytic viruses (OV) against cancer has grown tremendously and a number of promising candidates are now in preclinical and clinical studies. Tumor regression in vivo following viral infection has been shown to be a multifactorial process (1). The reductionist view of viruses simply causing direct lysis of infected cancer cells has now been replaced by a view including the complex interplay between viruses and the tumor environment. The important role of the immune response in either limiting or enhancing OV treatment is also now well recognized (2, 3). The prototypic Rhabdoviridae VSV has generated encouraging results in various experimental tumor models and is now used in a phase I clinical trial in patients with liver cancer (www.clinicaltrials.gov; #NCT01628640).

VSV possesses intrinsic oncolytic properties as it replicates more efficiently in type-I interferon (IFN)-defective cells, a pathway frequently impaired during tumorigenesis (4). Cancer therapy using VSV has been shown to generate a variety of immune responses including tumor-specific CD8+ T cells that are induced following the release of TA by infected cells (5). However, the tumor-specific immune response generated following VSV treatment is usually weak and often only leads to transient tumor control. Experimental tumor models expressing various surrogate non-self-TA have been developed over the years to more easily assess the magnitude and quality of immune responses generated against tumors. However, whether these responses are always representative of physiological antitumor immune responses is unclear.

Recently, our group characterized various VSV glycoprotein (G) mutants capable of interfering with host cell metabolism by inhibiting cellular transcription and translation in a kinetic similar to WT VSV as opposed to the prototypic matrix (M) mutant (Mmutant) that is slightly attenuated in vitro (6). Furthermore, VSV G mutants proved to be more cytolytic for B16 melanoma cells in vitro than the M mutant. To analyze their oncolytic potential in vivo, we used an immunocompetent mouse model implanted with B16 tumors transfected with a DNA minigene encoding the immunodominant CD8+ T cell epitope of the lymphocytic choriomeningitis virus (glycoprotein aa 33–41) (7) as a surrogate non-self-TA (B16gp33) (8). Mice were injected subcutaneously into the flank with B16gp33 cells and when tumors reached a palpable size (day 7), animals were treated intratumorally every second day with three doses (days 7, 9, and 11) of WT VSV or of the G or M mutants. Tetramer and intracellular cytokine staining analysis revealed that CD8+ T cells harvested from mice treated with WT VSV or the G mutants developed a polyfunctional gp33-specific immune response. Surprisingly however, the strength of the gp33-specific immune response generated did not correlate with the ability of a particular strain of VSV to slow down parental B16 growth and improve mice survival. Treatment with WT VSV was the poorest at controlling B16 tumor progression even though it induced a strong CTL response against gp33. On the other hand, Mmutant was more efficient than WT VSV at slowing down B16 growth despite the fact that this virus induced the lowest gp33-specific T cell response. We therefore determined whether CD8+ T cell responses directed against endogenous self-TA were involved in limiting tumor progression. CTL responses against self-TA, such as TRP-1 and gp100, were barely detectable ex vivo when analyzed separately. However, adoptive transfer of purified CD8+ T cells harvested from Mmutant-treated B16gp33 melanoma-bearing mice into naive mice provided better protection against parental B16 tumor implantation compared to CTLs taken from WT or G mutant-treated mice. These results suggest that the M mutant, despite being the weakest at inducing a T cell response against the surrogate non-self-TA gp33, induces the broadest antitumoral CTL response.

B16 melanoma is a highly aggressive tumor model in part because major histocompatibility complex class I (MHC-I) surface expression is very low on these...
WT VSV of the G mutants (8). The matrix
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response against gp33 (see Figure 1
of B16 TA proportionally reducing the
leads to presentation of a broader pool
by this mutant. This may subsequently
poor gp33-specific CTL response induced
T cell-dependent survival despite the
explains the significantly improved CD8

This leads to inhibition of antigen pre-
station to natural killer T (NKT) cells
(11). Thus, VSV matrix protein could
participate in the retention of MHC-
I molecules within infected cells while
the mutated protein in M<sub>M51R</sub> may lack
this ability. Thus, surface MHC-I upreg-
ulation following M<sub>M51R</sub> treatment likely
explains the significantly improved CD8<sup>+</sup>
T cell-dependent survival despite the
poor gp33-specific CTL response induced
by this mutant. This may subsequently
lead to presentation of a broader pool
of B16 TA proportionally reducing the
response against gp33 (see Figure 1
for model).

In a recent study, Pedersen et al.
compared vaccine-induced CD8<sup>+</sup> T cell
responses directed against self and non-
self-TA and showed that vaccination with
adenoviral vectors encoding endogenous
TA had little or no effect on the growth of
B16 melanomas whereas vaccination
with a similar vector construct expressing
a surrogate non-self-TA induced effi-
cient tumor control (12). Although vacci-
nation against both self and non-self-TA
induced comparable CD8<sup>+</sup> T cell responses
in terms of cell numbers and effector func-
tions, CTLs directed against self-TA were
of lower functional avidity. These results
are in agreement with our study and pro-
vide a potential mechanism explaining why
T cell responses against self and non-
self-TA are different and might not be
induced at proportional levels during OV
therapy.

Taken together, these results highlight
a considerable limitation of many experi-
mental systems used to assess antitu-
mor immunity and warrant caution when
extrapolating responses against surrogate
TA to the overall antitumoral immune
response. This may prove critical for the
development of novel or improved OV,
which may be biased by incorrectly esti-
mating immune response correlates using
such experimental systems. Therefore,
great efforts will need to be made to develop
improved methods for analyzing the anti-
tumoral immune response induced by OV's
against a broader array of TA in order
to better appreciate their full therapeutic
potential.

ACKNOWLEDGMENTS

This work was supported by the Canadian
Institutes of Health Research and by the
J.-Louis Lévesque Foundation.

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to exploit tumor specific defects in innate immune

cells. Strikingly, B16 infection with VSV M
mutant induced the upregulation of sur-
face MHC-I both in vitro and in vivo, a
phenomenon that was not observed for
WT VSV of the G mutants (8). The matrix
protein of VSV was previously shown to
alter trafficking of a molecule structurally
similar to MHC-I, namely CD1d (9, 10).
This leads to inhibition of antigen pre-
sentation to natural killer T (NKT) cells
(11). Thus, VSV matrix protein could
participate in the retention of MHC-
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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 13 March 2014; accepted: 21 May 2014; published online: 04 June 2014.


This article was submitted to Tumor Immunity, a section of the journal Frontiers in Oncology.

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