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Trends Cancer. Author manuscript; available in PMC 2017 February 01.

Published in final edited form as:

Trends Cancer. 2016 February 1; 2(2): 67–68. doi:10.1016/j.trecan.2016.01.002.

Adding STING to the Tale of Oncolytic Virotherapy

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Abstract

The identification of STING as a key cytoplasmic innate recognition molecule for DNA viruses whose function is lost in a variety of cancers has coincided with the approval of IMLYGIC for metastatic melanoma. This represents the first replication competent viral therapy approved for the treatment of any cancer in the US. The role of STING pathway in the selectivity of HSV has been addressed for the first time in Xia et al (1).

Keywords

STING; Oncolytic Virus; HSV; Vaccinia

The identification of Stimulator of Interferon Genes (STING, TMEM173) as a key cytosolic DNA sensor for the detection of intracellular pathogens, notably DNA viruses, has provided key insights into the pathways of induction of the Interferon inflammatory response (2). Furthermore, the critical role of the STING-cGAS pathway in autoinflammatory diseases (3) and the requirement of STING for successful induction of anti-cancer adaptive immunity (4) have highlighted the importance of this molecule in a diverse range of diseases.

The possible link between STING-cGAS pathway defects and cancer is especially pertinent due to any potential role this pathway may play in the effectiveness of oncolytic virotherapies. Oncolytic viral cancer therapies, based on replication-selective viruses, have also received a lot of interest recently, driven by successful randomized clinical trial data with two vectors, one based on vaccinia (Pexa-Vec) (5) and the other on herpes simplex virus (HSV) (T-Vec, IMLYGIC) (6). Further, IMLYGIC has recently become the first approved oncolytic viral therapy in the USA. It is interesting that both of these oncolytic therapies are based on DNA-virus backbones, and so STING may play a key role in their success or failure.

This has been explored for the first time in the recent report by Xia et al (1), where it was determined that colon cancers containing mutations in the cGAS-STING pathway are highly susceptible to DNA-virus based oncolytic viral therapies. This represents a potentially

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important biomarker for sensitivity to these therapeutics, something that has been lacking to date despite the major investment in these approaches.

It is notable that STING signaling was suppressed in a high percentage of primary colon cancer samples, and was also lost in other cancer types. This would appear to implicate an important need for suppressing this pathway during tumorigenesis and could indicate STING is a novel tumor suppressor. Although more work is needed it is possible that STING-cGAS may play a key role in inducing an initial immune response subsequent to DNA damage and so its loss would prevent immune recognition of the tumor. However, cancers containing STING pathway mutations have been associated with a limited response to many immunotherapies, including both therapeutic vaccines and immune checkpoint inhibitors (7), meaning that their increased sensitivity to some oncolytic viruses could represent an Achilles heal.

This is especially interesting as it seems apparent that the primary mechanism of action of many oncolytic viral therapies is immunotherapeutic. Because these viral therapies replicate selectively in the tumor microenvironment, amplifying the therapy within the tumor itself and expressing any encoded therapeutic transgenes to high levels within the tumor microenvironment, they are uniquely effective at altering the tumor microenvironment and to sensitizing tumors that are resistant to other immunotherapies. It will therefore be interesting to further examine the role of the STING pathway in mediating response to oncolytic viral therapy and the ability to sensitize some tumors to immunotherapies.

The conflicting roles of the immune response in the activity of oncolytic viral therapies are still being uncovered, as excessive immune activation will prematurely clear the viral therapy and restrict its activity, while at the same time successful oncolytic virotherapy treatment is frequently accompanied by activation of anti-tumor adaptive immunity. The potentially pivotal role of STING in balancing oncolytic and immunotherapeutic activity of the DNA-based viral therapies remains to be fully elucidated, but this initial insight implicates this pathway as an important mediator. This is seen in Xia et al. where knock out of STING from the host immune system results in a reduction in the effectiveness of the therapy. It is therefore likely that loss of STING-cGAS signaling in the tumor allows enhanced initial oncolytic activity of the therapy, while retention of STING signaling in the host immune response is critical for optimal induction of anti-tumor immunity.

As the important role of STING-cGAS in tumorigenesis is revealed it is therefore likely to allow the development of novel targeted cancer therapies as well as the redesign of some existing therapies.

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