The VIMM, established in 2008 by Paul B. Fisher, M.Ph., Ph.D., the Founding Director, is comprised of outstanding scientists/clinicians from VCU School of Medicine focusing on important medical-related research in cancer, neurodegeneration and infectious diseases. The purpose of this NEWS & VIEWS is to highlight the exciting research being performed by the VIMM members.

Promoting protective antitumor immunity for cancer eradication

- Management of localized prostate cancer (PC) through surgical, radiation and chemotherapeutic approaches can be successful, but metastatic prostate cancer remains essentially incurable because no effective and safe treatment modality is available.
- Melanoma differentiation associated gene-5 (MDA-5), a type I interferon (IFN)-inducible gene, was originally cloned in human melanoma. This study indicates that MDA-5 can induce a direct tumoricidal or type I IFN-promoting effect in PC cells.
- This is the first demonstration of antitumor immunity induced by targeting the viral-sensing MDA-5 signaling pathway in prostate tumors. Therapeutic activation of MDA-5 at the tumor site is exploited to mobilize systemic innate and adaptive antitumor immune responses to eradicate metastatic PC.
- This MDA-5-targeting immunotherapy can be used either alone or in combination with other approaches to treat PC and other malignancies.

Counteracting the immunosuppressive tumor microenvironment (TME) and restoring immune effector cell functions remains a major challenge for successful cancer immunotherapy. In a study recently published in the journal of Cancer Research*, investigators in the VCU Institute of Molecular Medicine (VIMM) developed a novel strategy targeting the TME, which results in destruction of PC cells and concurrent induction of an antitumor immune response.

Melanoma differentiation associated gene-5 (MDA-5) was initially identified and cloned by Dr. Paul B. Fisher as a type I interferon (IFN)-inducible gene in human melanoma. Subsequent studies showed that MDA-5 represents a major innate immune receptor critically required for sensing viral pathogens and initiating an anti-viral host response involving production of type
IFNs. Dr. Fisher and his colleagues previously reported that forced expression of the MDA-5 gene kills cancer cells without harming normal cells. In this study involving a collaboration between Dr. Xiang-Yang (Shawn) Wang’s laboratory and Dr. Fisher, the investigators provide new insights into the biological impact of MDA-5 activation in cancer cells by defining the structural domains that confer a direct tumoricidal or type I IFN-promoting effect, which advances the understanding of the selective pro-apoptotic activity of MDA-5 in cancer cells, and not normal cells. A striking finding of this work is that intra-tumoral delivery of MDA-5 using an adenovirus results in regression of pre-established PCs and development of long-term protective antitumor immunity in immune competent mouse models. The mechanistic studies showed that this superior antitumor efficacy is primarily due to the activation of tumor-reactive cytotoxic T lymphocytes and/or natural killer cells, which is dependent on the type I IFN pathway in the TME. These findings underscore a previously unappreciated role of the MDA5-mediated viral sensing pathway in the induction of antitumor immunity, offering a new opportunity for therapeutic targeting of the immunosuppressive TME to restore systemic antitumor immunity for cancer eradication and prevention of relapse. Although this research was conducted in prostate cancer mouse models, it is believed that these data may have broad implications in the treatment of other malignancies and metastatic diseases. These promising preclinical results provide a strong scientific rationale to support potential translation of MDA-5-based immunotherapy. This study was supported in part by NIH grants CA175033, CA154708 (X.-Y. Wang), Department of Defense W81XWH-11-0480/0481, W81XWH-13-0409/0455 (P.B. Fisher and X.-Y. Wang), the National Foundation for Cancer Research (P.B. Fisher).

Figure legend: Targeting the MDA-5–IPS-1 pathway in tumors to potentiate protective antitumor immunity. Overexpression of MDA-5, a sensor for viral dsRNA, in cancer cells triggers activation of IRF-3 and caspase-3 in an IPS-1–dependent manner. The interaction between MDA-5 and its downstream adapter protein IPS-1 results in the production of type I IFNs and concomitant cancer cell death. The type I IFNs promote the activation and effector functions of NK cells and/or CTLs. Collaborative action of tumor-reactive innate and adaptive immune cells leads to effective tumor eradication. [Yu et al., Cancer Res. 2016 April 15, PMCID: PMC4873369].

Publications:


Kang DC, Gopalkrishnan RV, Wu Q, Jankowsky E, Pyle AM, Fisher PB. mda-5: An...

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