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Immunity

The DNA Structure-Specific Endonuclease MUS81 Mediates DNA Sensor STING-Dependent Host Rejection of Prostate Cancer Cells

Highlights

- Presence of cytosolic DNA in prostate cancer cells depends on *Mus81*
- *Mus81* induces STING-dependent type I interferon expression
- Immune rejection of prostate cancer cells relies on *Mus81* and STING
- *Mus81* enhances innate and adaptive anti-cancer immune responses

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In Brief

The mechanisms leading to the presence of cytosolic DNA in cancer cells are unknown. Gasser and colleagues find that the DNA structure-specific endonuclease *Mus81* promotes the shedding of genomic DNA into the cytosol of prostate cancer cells. *Mus81* stimulates STING-dependent DNA sensor pathways and immune rejection of prostate cancer cells.

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The DNA Structure-Specific Endonuclease MUS81 Mediates DNA Sensor STING-Dependent Host Rejection of Prostate Cancer Cells

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SUMMARY

Self-DNA is present in the cytosol of many cancer cells and can promote effective immune rejection of tumor cells, but the mechanisms leading to the presence of cytosolic DNA are unknown. Here, we report that the cleavage of genomic DNA by DNA structure-specific endonuclease MUS81 and PARP-dependent DNA repair pathways leads to the accumulation of cytosolic DNA in prostate cancer cells. The number of nuclear MUS81 foci and the amount of cytosolic dsDNA increased in tandem from hyperplasia to clinical stage II prostate cancers and decreased at stage III. Cytosolic DNA generated by MUS81 stimulated DNA sensor STING-dependent type I interferon (IFN) expression and promoted phagocytic and T cell responses, resulting in type I and II IFN-mediated rejection of prostate tumor cells via mechanisms that partly depended on macrophages. Our results demonstrate that the tumor suppressor MUS81 alerts the immune system to the presence of transformed host cells.

INTRODUCTION

Prostate cancer is a leading cause of cancer-related death among men and the incidence of prostate cancer has steadily increased over the last decade (Nelson et al., 2003). Genetic and environmental factors have been linked to prostate cancer, and evidence implicates inflammatory processes in the pathogenesis of prostate cancer (De Marzo et al., 2007). Signs of inflammation are present in the majority of prostate cancer biopsies (De Nunzio et al., 2011). Prostate tumors developing in the transgenic adenocarcinoma of the mouse prostate (TRAMP) model of autochthonous prostate cancer are infiltrated by leukocytes and components of the innate immune system control the development of the most aggressive form of prostate cancer in TRAMP mice (Raulet and Guerra, 2009). However, the factors that contribute to inflammation and immune recognition of prostate tumors remain poorly understood.

Stimulator of interferon (IFN) genes (STING) induces the production of type I IFNs and other pro-inflammatory cytokines following the detection of double-stranded DNA (dsDNA) by cytosolic DNA sensors (Ishikawa et al., 2009). Type I IFNs induce cell-intrinsic defense mechanisms, promote the activation of natural killer (NK) cells, NKT cells, and other immune cells, and stimulate adaptive immune responses (Ivashkiv and Donlin, 2014). Activated NK cells, NKT cells, and T cell subsets produce IFN-γ, which amplifies the pathogen-specific immune response by enhancing the antigen-presentation capabilities of dendritic cells and increasing the activation of macrophages (Billiau and Matthys, 2009).

Emerging evidence supports a role for STING-dependent cytosolic DNA-sensing pathways in cancer (Woo et al., 2015). STING and type I IFNs contribute to anti-glioma immunity (Ohkuri et al., 2014) and the elimination of B16 melanoma tumors (Woo et al., 2014). Mice deficient in *Tmem173*, the gene encoding STING, are susceptible to colitis-associated colorectal cancer (Zhu et al., 2014), but nearly resistant to inflammation-driven skin carcinogenesis (Ahn et al., 2014). The presence of cytosolic DNA in B cell lymphoma cells correlates with type I IFN-dependent rejection of these cells (Shen et al., 2015). Type I IFNs were also shown to be critical in the rejection of prostate cancer and other cancers (Dunn et al., 2006), but the signals that induce the production of type I IFNs have not been defined in the context of cancer.

Mutations in oncogenes and tumor suppressors induce sustained proliferation, a hallmark of cancer (Hanahan and Weinberg, 2011). The deregulated replication of cancer cells can result in widespread stalling of replication forks (Branzei and Foiani, 2010). Aberrant replication fork structures activate a replication