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Innate sensing of cancer's non-immunologic hallmarks

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A cancer mass consists of a complex composition of cancer cells, stromal cells, endothelial cells and also immune cells, which can represent more than half of the cellularity of a solid cancer. These immune cells become activated when they sense cancer antigens and stress ligands. Innate immune cells also detect various aspects of cellular stress that characterize a growing tumor mass. These key hallmarks of cellular stress are also detected by the cancer cell itself. In this review, we highlight studies that show that the cancer cell itself could be considered an 'innate cell' that senses and reacts to non-immunologic hallmarks of cancer, including displaced nucleic acids, proteotoxic stress, oxidative stress, and metabolic alterations.

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Introduction

Although cancer cells can display unique neoantigens that drive personalized approaches to cancer therapy, they can also exhibit shared 'hallmarks' which accompany uncontrolled cellular proliferation. These hallmarks include not only cellular processes such as resistance to apoptosis and autonomous replication [1] but also subcellular characteristics such as oxidative stress, DNA damage, and aberrant metabolism [2,3]. Notably, evading immunity and inflammation-driven cancer progression also are hallmarks of cancer [4], but how these hallmarks relate to the non-immunologic hallmarks is not clear. In this review, we highlight recent studies that demonstrate that the non-immunologic hallmarks of cancer can be sensed in the tumor microenvironment, leading to immunologic effector activities of innate cells.

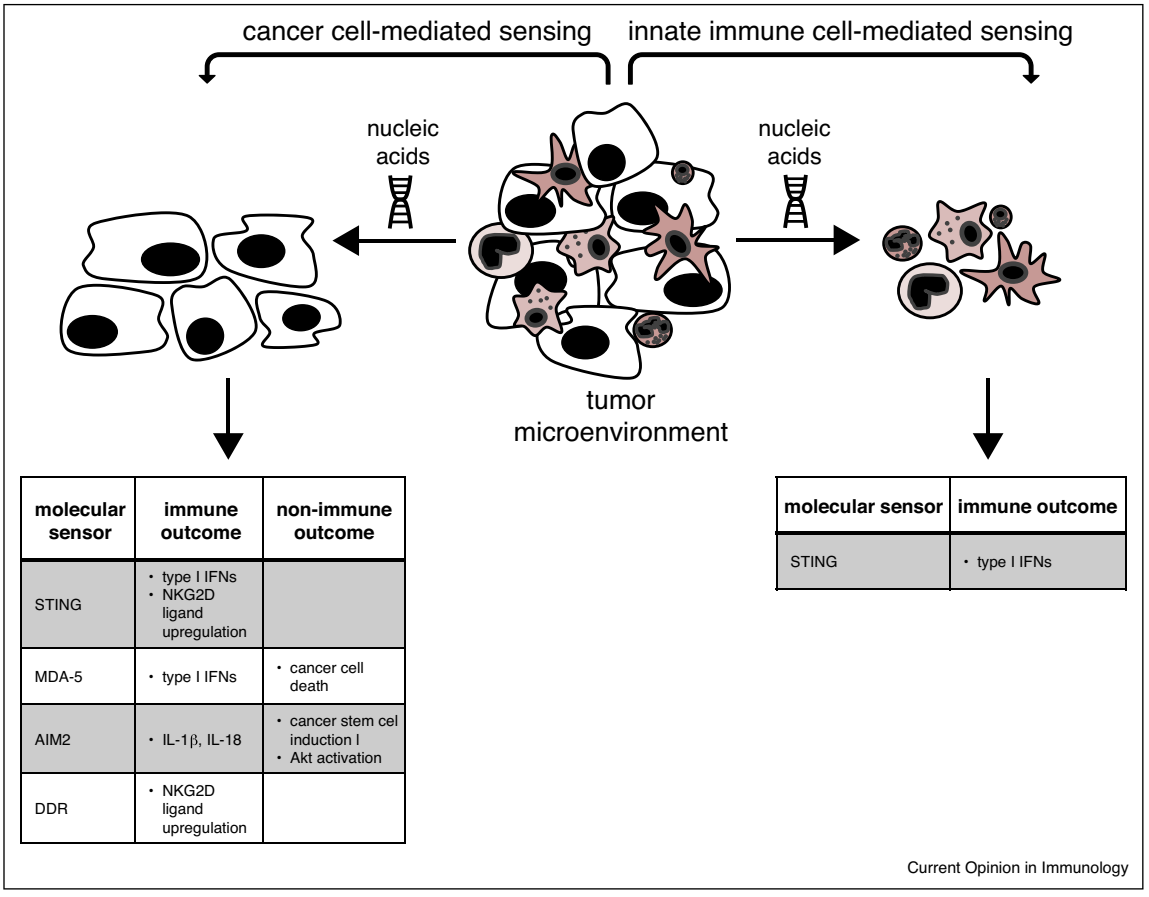
Previous reviews have summarized how innate immune cells sense antigens, stress, or changes in the microenvironment during cancer immune surveillance. We will briefly cover the newest insights into this well-known concept at the end of every section below. However, we begin each section by focusing on the idea that cancer cells themselves can function as 'innate cells' by sensing intrinsic or extrinsic changes in their microenvironment, leading to direct immune effector functions. We will focus on sensing of various hallmarks of cancer, including ectopic nucleic acids (Figure 1), aneuploidy and proteotoxic stress (Figure 2), oxidative stress (Figure 3), and metabolic aberrations (Figure 4), with specific regard to the anti-tumor effector activities downstream of innate sensing.

Sensing of nucleic acids by cancer cells and other non-immune cells

Hallmarks of cancer such as extensive replication, genomic instability and mutation, oxidative stress, or a high metabolic rate can cause damage in the cell's nuclear and/or mitochondrial (mt) DNA. Nuclear DNA damage is detected by the DNA damage response (DDR) pathway leading to activation of the kinases ATM/ATR [5]. In some instances, DNA damage can lead to displacement of endogenous nucleic acids into ectopic locations (i.e. extranuclear or extracellular). Ectopic nucleic acids are sensed by a panoply of receptors (reviewed in [6]), including toll-like receptors (TLRs), NOD-like receptors (NLRs), absent in melanoma (AIM) 2, and RIG-I-like receptors (RLRs). These receptors have independent signaling pathways that converge on activation of transcription factors such as interferon (IFN) regulatory factors (IRFs) or nuclear factor (NF)-κB, leading to the upregulation of type I IFNs (which are IFNs α, β, and the less well described ε, κ and ω) and other pro-inflammatory cytokines. Activation of the signaling module composed of cyclic GMP-AMP (cGAMP) synthase (cGAS) and stimulator of IFN genes (STING) also results in type I IFN induction (reviewed in [7]). In the case of certain NLRs and AIM2, activation leads to inflammasome activity and production of interleukin (IL)-1β and IL-18. This section will review the role of some of these nucleic acid sensors in cancer progression, with focus on their activity in non-immune cells and the outcome on innate immunity (Figure 1).

Classic studies showed that DNA damage sensed by ATM/ATR could induce NKG2D ligands, leading to NK cell activation [8]. Recent studies demonstrated that induction of the NKG2D ligand RAE required sensing of cytosolic DNA by STING [9,10]. In these studies, this sensing led to autonomous, that is, tumor derived, production of type I IFNs in lymphoma cells. Interestingly, the 'basal' level of DNA damage resulted in both

Figure 1



molecular sensor	immune outcome	non-immune outcome
STING	• type I IFNs • NKG2D ligand upregulation	
MDA-5	• type I IFNs	• cancer cell death
AIM2	• IL-1β, IL-18	• cancer stem cel induction l • Akt activation
DDR	• NKG2D ligand upregulation	

molecular sensor	immune outcome
STING	• type I IFNs

Sensing of nucleic acids by cancer cells and innate immune cells. Distinct molecular sensors mediate nucleic acid sensing by either cancer cells (left) or innate immune cells (right).

constitutive expression of NKG2D ligands and autonomous IFN secretion.

Other studies found that forced activation of STING after intratumoral injection of cyclic dinucleotides could induce anti-tumor immune responses. This study did not define which cells, tumor or dendritic cells (DCs), were the targets of STING agonists *in vivo* [11]. Another group found that activation of STING and subsequent IFN production after intratumoral injection of cGAMP controlled the growth of melanoma and colon cancers by enhancing $CD8^+$ T cell immunity [12••]. In this study, the STING-induced secretion of type I IFNs into the tumor microenvironment was mediated mostly by tumor endothelial cells rather than DCs, in contrast to another study proposing cGAMP as a cancer immune therapy agent through its activation of DCs [13].

Cancer cell expression and activity of the RLR melanoma differentiation associated protein (MDA)-5 could also mediate anti-tumor activities. Yu *et al.* showed that transducing either full-length or truncated MDA-5 led to direct cell death in cancer cells but not normal cells. Interestingly, IFNβ was induced only by full-length, but not truncated, MDA-5. Intratumoral delivery of full-length MDA-5 led to cancer regression, which was mediated by type I IFN-induced antitumor immunity. These studies suggest that ectopic dsRNA (the ligand for MDA-5) could potentially induce cancer cell death, if present in high enough levels, while also stimulating production of IFNβ by cancer cells to activate immunity [14••]. In contrast, the RLR laboratory of genetics and physiology (LGP) 2 is a negative regulator of MDA-5 and was found to be beneficial for tumor growth after radiotherapy by shutting off IFN synthesis [15,16]. This suggests that cancer cells might develop defense mechanisms targeting type I IFN production to protect themselves from immune-mediated destruction.

AIM2 is a cytosolic DNA sensor that induces inflammasome activity. In two recent similar studies, *Aim2*$^{-/-}$ mice developed more colitis-associated cancer compared to