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Regulatory mechanisms of nucleic acid-mediated innate immune responses in tumor microenvironments

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Abstract

We identify novel mechanisms whereby TIM-3 suppresses the innate immunity induced by nucleic acids. Interaction of TIM-3 with HMGB1 inhibits the recruitment of nucleic acids to endosomal compartments in dendritic cells, leading to impairment of innate immune signals. Thus, TIM-3 is an effective target for enhancing antitumor immunogenicity of nucleic acids.

Innate immunity serves as a well-organized pattern recognition system for infectious and stress-induced components derived from inflammatory microenvironments. In particular, nucleic acids derived from infectious agents or dying host cells are detected by pattern-recognition receptors such as Toll-like receptors (TLRs) and cytosolic sensors for DNA and RNA, leading to the induction of cytokines and proinflammatory mediators essential for innate immune responses[1].

Discrimination between foreign and self nucleic acids serves as a key mechanism protecting the host from pathogens while maintaining tissue homeostasis, as exposure of self-nucleic acids to the innate immune system frequently results in severe inflammation and autoimmune reactions[2]. However, several studies have unveiled mechanisms by which self-nucleic acids gain access to innate immune systems. Endogenous proteins released from inflammatory environments, such as danger-associated molecular patterns (DAMPs), can preferentially interact with self-nucleic acids. The formation of complexes with DAMPs enables nucleic acids to gain access to endosomal compartments in which innate immune systems recognize nucleic acids and orchestrate proinflammatory responses[3]. In addition, recent studies reveal that exogenous nucleic acids mediate immunogenic activities by

interacting with pattern recognition systems. For example, DNA released from dying host cells has a key role in triggering the adjuvant effects of aluminum, thus facilitating dendritic cell (DC) migration and antigen-specific T cell responses[4]. Moreover, cellular damage induced by ultraviolet irradiation results in the structural modification of self-RNAs, by which innate immune signals are activated in a TLR3-dependent manner[5]. Thus, nucleic acids generated from host cells have the potential to activate innate immune signals under various pathogenic situations.

Transformed cells are assumed to be a mixture of self and "non-self" nucleic acids derived from cellular products bearing genetic mutations. In addition, tumor microenvironments consist of fibroblasts and myeloid cells, which produce multiple milieus of inflammatory mediators including DAMPs[6]. However, it remains largely unclear whether inflammatory mediators activate innate immune signals by releasing 'immunogenic' nucleic acids in tumor microenvironments. Thus, it is critical to address the molecular mechanisms by which tumor microenvironments affect the ability of nucleic acids to interact with proinflammatory signal machinery and activate the innate immune system.

TIM-3 is upregulated on T-helper type 1 CD8$^+$ T lymphocytes during the chronic phase

of infection or cancer and triggers apoptosis of T-helper type 1 T cells upon ligation with galectin-9 [7].

We identified an unexpected function of TIM-3 on DCs in negatively regulating nucleic acid-mediated innate immune responses in tumor microenvironments [8]. TIM-3 is expressed on DCs infiltrating tumors at much higher levels than on DCs in normal tissues, and preferentially binds with the major DAMP, high mobility group box-1 (HMGB1), which has a critical role in stimulating nucleic acid-mediated innate immune signals [9]. TIM-3 negatively regulates HMGB1-mediated recruitment of nucleic acids to endosomal compartments in DCs, thus shutting down the downstream innate immune cascades mediated by TLRs and cytosolic sensors[8]. TIM-3 on DCs thereby enables tumors to evade innate immunosurveillance by attenuating nucleic acid-mediated innate immune sensing, which is potentially triggered by tumor-associated inflammation (**Figure 1**).

Why TIM-3 on DCs is preferentially recognized by HMGB1 rather than galectin-9 remains largely obscure, but multiple mediators derived from tumors may regulate the repertoires of endogenous danger signals that contribute to the creation of inflammatory tumor microenvironments. Interestingly, a recent report revealed that pattern recognition ligands including DAMPs may serve as driving forces that trigger the release of

exogenous HMGB1 from the nucleus of host cells[10]. This suggests that DNA vaccination or endogenous nucleic acids released from dying cells upon cytotoxic chemotherapy may increase exogenous HMGB1 in tumor microenvironments, thus contributing to the generation of HMGB1-DNA complexes and activation of innate immune signals. In this regard, tumors utilize TIM-3 on tumor-infiltrating DCs as one strategy to evade innate immune responses elicited by anticancer therapeutic regimens.

Further elucidation and deeper understanding of mechanisms linking innate immune signals with tumor-associated inflammation and the impact of negative regulatory pathways of innate immune systems within tumor microenvironments will provide new strategies to augment endogenous antitumor immune responses and improve anticancer regimens in the future.

References

1. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell 2010; 140: 805-820.

2. Blassius AL, Beutler B. Intracellular Toll-like receptors. Immunity 2010; 32: 305-315.

3. Desmet CJ, Ishii KJ. Necleic acid sensing at the interface between innate and adaptive immunity in vaccination. Nat Rev Immunol 2012; 12: 479-491.

4. Marichal T, Ohara K, Bedoret D, Mesnil C, Sabatel C, Kobiyama K, et al. DNA released from dying host cells mediates aluminum adjuvant activity. Nat Med 2011; 17: 996-1002.

5. Bernard JJ, Cowing-Zitron C, Nakatsuji T, Muehleieisen B, Muto J, Borkowski AW, et al. Ultraviolet radiation damage self noncoding RNA and is detected by TLR3. Nat Med 2012.

6. Kuraishy A, Karin M, Grivennikov SI. Tumor promotion vis injury- and death-induced inflammation. Immunity 2011; 35: 467-477.

7. Zhu C, Anderson AC, Schubart A, Xiong H, Imitola J, Khoury SJ, et al. The Tim-3 ligand galectin-9 negatively regulates T helper type 1 immunity. Nat Immunol 2005;

6: 1245-1252.

8. Chiba S, Baghdadi M, Akiba H, Yoshiyama H, Kinoshita I, Dosaka-Akita H, et al. Tumor-infiltrating dendritic cells suppress nucleic acid-mediated innate immune responses through interactions between the receptor TIM-3 and the alarmin HMGB1. Nat Immunol 2012; published online July 29; doi: 10.1038/ni.2376.

9. Yanai H, Ban T, Wang Z, Choi MK, Kawamura T, Negishi H, et al. HMGB proteins function as universal sentinels for nucleic acid-mediated innate immune responses. Nature 2009; 462: 99-103.

10. Anderson Y, Tracy KJ. HMGB1 is a therapeutic target for sterile inflammation and infection. Annu Rev Immunol 2011; 29: 139-162.

Figure legend

Figure 1

This scheme illustrates the molecular machineries whereby TIM-3 on DCs negatively regulates innate immune signals, which would be activated by endogenous danger signals under normal conditions. Tumor microenvironments frequently generate endogenous danger signals such as HMGB1 due to smoldering inflammation. HMGB1 binds nucleic acids and facilitates the interaction of nucleic acids with pattern recognition receptors such as TLRs and cytosolic sensors, activating innate immune signals. However, tumors counteract innate immune systems by upregulating TIM-3 on tumor-infiltrating DCs. The interaction between TIM-3 and HMGB1 inhibits the recruitment of nucleic acids into the endosomal compartments in DCs. Thus, the interaction between TIM-3 and HMGB1 serves as an evasion strategy used by tumor microenvironments to escape innate immunosurveillance.