INNATE IMMUNE SENSING OF NUCLEIC ACIDS AND APPLICATION FOR OLGONUCLEOTIDE-BASED IMMUNOTHERAPY

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Summary: Nucleic acids are sensed by specialized innate immune receptors, including a subgroup of TLRs and the family of RIG-I-like receptors. For example, viruses are detected based on the recognition of viral nucleic acids. Immunorecognition of viral nucleic acids leads to the initiation of early innate immune responses that limit viral replication and are essential for eliciting adaptive responses to virus-specific protein antigens. RNA with a triphosphate group at the 5′-end (5′pRNA) is the ligand for RIG-I. By using a new chemical approach for 5′triphosphate oligoribonucleotide synthesis, we found that short double-strand conformation with base pairing of the nucleoside carrying the 5′-end is the ligand for RIG-I. We found that a conserved histidine in the 5′-end of the bound RNA. This explains how RIG-I detects negative strand RNA viruses, which lack long double-stranded RNA but do contain panhandle, blunt, short double-stranded 5′triphosphate RNA in their single-stranded genome. The crystal structure of the RIG-I CTD domain bound to the blunt-end of the 5′-ppp dsRNA was resolved. The structure, supported by mutation and functional studies, defines how a lysine-rich basic cleft within the RIG-I CTD domain sequesters the 5′-ppp end of the bound RNA. We found that a conserved histidine in RIG-I controls immune tolerance of 2′-O-methylated cap1 self RNA. Furthermore, we demonstrate that RIG-I-RNA ligand interaction not only activates type I IFN but also induces inflammasome activation and pro-apoptotic signaling. Based on these activities, RIG-I ligands are promising candidates for the therapy of viral infection and cancer. Specifically, cytoplasmic innate immune sensors endogenously expressed in all tumor cells help to overcome the limitations of conventional prophylactic vaccine strategies. The activation of the RIG-I–like helicase pathways in tumor cells can revert the immunosuppressive tumor microenvironment into an immune-permissive state. Such immune intervention not only has the potential to turn tumors into tumor vaccines, it will enable tumor antigen–specific T cells induced through other tumor vaccination approaches to become effective inside otherwise immunosuppressive tumor environments.

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References

ANTI-ANGIOGENIC THERAPY: NEW INSIGHTS

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Summary: Angiogenesis, the development of blood vessels, is a fundamental pathophysiological process. Vascular endothelial growth factor (VEGF)-A is a key regulator of blood vessel growth during embryonic development and in a variety of physiological processes. VEGF inhibitors have been shown to block tumor growth in numerous preclinical models, consistent with an important role of VEGF-A in tumor angiogenesis. We developed a humanized anti-VEGF-A monoclonal antibody (bevacizumab) to test the hypothesis that blocking VEGF-A-induced angiogenesis may result in a clinical benefit in tumor patients. Bevacizumab has been approved by the FDA and worldwide for the treatment of several malignancies. Furthermore, blocking VEGF-A prevents vision loss and had a major impact on the progression of neovascular age-related macular degeneration and ischemic retinal disorders.

We have recently been studying the mechanisms of resistance to anti-VEGF therapies in various tumor models. These studies indicate that multiple pro-angiogenic mechanisms may be implicated. We identified factors produced by tumor-infiltrating myeloid cells or by fibroblasts identified as key mediators of angiogenesis. Efforts are ongoing to determine the translational and clinical significance of such findings.

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IMMUNE MECHANISMS OF ATHEROSCLEROSIS

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Summary: Atherosclerosis is a chronic inflammatory disease of the arterial wall responsible for most ischemic cardiovascular diseases. Circulating levels of several cytokines are associated with disease burden, and CRP levels predict the risk of future cardiovascular events. Atherosclerosis is initiated in response to various stimuli, mostly modified lipids. Innate immune responses involving both vascular and immune cells, mostly monocytes/macrophages, are rapidly activated in response to vascular injury, play important roles in vascular remodeling, and orchestrate the development of a more specific adaptive immunity. Most lymphocytes of atherosclerotic plaques are CD4+ T cells of the Th1 cell type. They recognize epitopes on native ApoB100 in a MHCII-dependent manner, produce interferon (IFN)-γ and promote pro-atherogenic T cell responses. They are counter-regulated by the anti-inflammatory and homeostatic properties of regulatory T cells (Tregs), mainly through IL-10 and TGF-b–dependent pathways. The development of atherosclerosis is also associated with signs of B lymphocyte activation, particularly manifested by enhanced production of natural IgM type and adaptive IgG type antioxidant low-density lipoprotein autoantibodies. Recent studies have redefined the roles of the different B-cell subsets in atherosclerosis. Innate B1-cell subset protects against lesion development in an IgM-dependent manner (Kyang, 2011 #17924), whereas B2 cells promote atherosclerosis, at least in part through activation of adaptive T-cell responses. I will briefly discuss the most recent advances in our understanding of pro- and antiatherogenic pathways and suggest several new and promising immune-based therapeutic strategies to limit disease progression and severity.

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