Selective activation of the TLR3/TICAM-1/IRF-3 pathway for safe and effective immunotherapy in mouse models

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Many forms of RNA duplexes with agonistic activity for pattern-recognition receptors have been reported, some of which are being applied in clinical trials for adjuvant immunotherapy for cancer. These RNA duplexes induce cytokines, interferons (IFNs) and cellular effectors mainly via two distinct pathways, TLR3/TICAM-1 and MDA5/MAVS. In knockout (KO) mouse studies, robust cytokine or IFN production is dependent on systemic activation of the MAVS pathway, and as a consequence, MAVS-activating dsRNA often causes endotoxin-like cytokinemia. In contrast, TLR3 expression is restricted to several types of cells, including myeloid cells, such that activation of the TICAM-1 pathway leads to maturation of dendritic cells (DCs) and drives cellular effectors (i.e. NK and CTL) without incremental serum cytokine/IFN levels. Notably, this pathway not only results in activation of the immune system but also exhibits protumor activity. The effect in human patients of MAVS-activating or TICAM-1-activating RNA duplexes remains undetermined, and the design of a TLR3 agonist with optimized toxicity and dose is an important goal for human immunotherapy. Here we summarize current knowledge on available RNA duplex formulations, and offer a possible approach to developing a promising RNA duplex signature for clinical tests.

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1979-1984	Hokkaido University, Pharmaceutical Sciences PhD 1984
1984-1987	Washington Univ. School of Medicine Research Associate
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POSITIONS AND HONORS

1987-1998	Associate Director, Department of Immunology, Osaka Medical Cancer for Cancer and Cardiovascular Diseases.
1994-1997	A chief investigator of PRESTO (directed by K. Toyoshima)
1998-2004	Professor (concurrently), Nara Institute of Science and Technology.
1998-2001	Director, Depart ment of Immunology, Osaka Medical Center for Cancer and Cardiovascular Diseases.
2001-2004	Director-in-Chief, Research Institute of Osaka Medical Center for Cancer.
2002-2007	A chief investigator of CREST (directed by T. Kishimoto)
2002-2004	Professor (concurrently), Osaka University School of Medicine.
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RECENT PUBLICATIONS

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