Combination therapy with TLR7 agonist and radiation is effective for the treatment of solid cancer

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Toll like receptors (TLRs) are well-conserved pattern recognition receptors required for sensing pathogenic elements such as bacterial lipopolysaccharides, DNA, or viral RNA. TLR1, TLR2, TLR4, TLR5, and TLR6 are present on the surface of cells and recognize bacterial and fungal components. In contrast, TLR3, TLR7, and TLR9 function intracellularly by recognizing of the nucleic acids (DNA or RNA) of pathogens. The host innate immune responses are enhanced through the recognition of pathogen-associated molecules by these TLRs. Moreover, the activation of innate immunity by TLR agonists effectively drives adaptive immunity via the production of several cytokines [e.g., interleukin (IL)-12b] and the activation of antigen-presenting cells (APCs). IL-12b is a pivotal cytokine for the induction of Th1 immune response and antigen-specific cytotoxic T cells (CTLs) (1). These inductions are extremely important for cellular immune response in the host and may lead to elimination of viruses or establishment of several cancer therapies. The expression of costimulatory molecules (CD40, CD80 and CD86) on APCs is enhanced after stimulation by several TLR agonists (2,3). These costimulatory molecules are intricately involved in the induction of acquired and antigen-specific immune responses. Therefore, TLR agonists can induce cellular immune response in viral infection and cancer and have the potential to treat cancer. Indeed, the anti-tumor effects of several TLR agonists were recently evaluated in basic studies and clinical trials (4,5). In particular, one TLR7 agonist, imiquimod (Aldara 5% cream, 3M), has been approved for clinical use by the FDA. This agent is topically used for the treatment of basal cell carcinoma and other skin tumors. However, many investigators have confirmed that monotherapy by some TLR agonists was not sufficient to completely eliminate the tumor in animal studies and clinical trials. Therefore, combination therapy with TLR agonists and other anti-cancer treatment is being evaluated. Traditional treatments for patients with cancer are surgery, chemotherapy, and radiation. Although these traditional treatments are effective for early stages of cancer, they have a limited role in advanced cancer. Recently, cancer immunotherapy has received attention as a new strategy of cancer therapy. Several studies have evaluated the anti-cancer effects of the combination of TLRs agonists and traditional cancer therapy (6).

In the study by Dovedi *et al.* published in Blood, the anti-tumor effect of combination therapy with a TLR7 agonist and traditional radiation therapy was evaluated in murine T cell and B cell lymphoma models (7). These data demonstrated that systemic administration of a TLR7 agonist combined with local radiation could suppress the progression of tumor growth and improve the survival rate in tumor-bearing mice. In particular, the combination of weekly administration of a TLR7 agonist and 5 fractions of 2 Gy local radiation could completely inhibit the subcutaneously established lymphoma. In many basic animal studies, it is extremely difficult to eliminate a tumor by chemotherapy, radiation, cancer immunotherapy, or any other cancer therapy in several murine lymphoma models. In general, the suppression of tumor growth but not the completely rejection of tumor is valued as cancer therapy. Therefore, this cancer treatment regimen comprising a TLR7 agonist and radiation may help establish a new strategy against chemotherapy-resistant lymphoma in clinical sites.

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In previous studies, TLR agonists have been locally administrated by intratumoral injection in animal cancer models, because the anti-tumor effect of a TLR agonist was significantly higher following local administration than systemic administration (8). Topical administration of imiquimod is also approved for clinical use. However, direct intratumoral administration of TLR agonists to non-cutaneous tumors is often difficult, frequently requiring image-guided delivery systems, such as ultrasound or computed tomography. Therefore, it is interesting that systemic administration of a TLR7 agonist combined with radiation therapy had greater anti-tumor activity in murine lymphoma model than intratumoral injection. As previously reported, the authors also indicated that a single systemic injection of TLR7 agonist had no anti-tumor effect. Repeated injection of a TLR7 agonist as monotherapy slightly improved survival rate in tumor-bearing mice. The therapeutic efficacy can be dramatically increased by combination with local radiation therapy. This improvement was observed in three different murine T cell and B cell lymphoma models.

With respect to the mechanism for augmentation of anti-tumor effect by the combination of systemic administration of a TLR7 agonist and local radiation, the authors demonstrated the significance of tumor antigen-specific CD8 T cells. CD8 T cell depletion assay by anti-CD8 antibody treatment indicated that CD8 T cells were required for the enhancement of anti-tumor effect in the TLR7 agonist/radiation combination therapy. In contrast, CD4 T cells and B cells were not involved in the anti-tumor effect of this combination therapy. Many studies have indicated the importance of tumor antigen-specific CD8 T cells, also known as CTLs, in suppressing tumor growth by cancer immunotherapy (9). Several factors are critical in the induction and augmentation of tumor antigen-specific CD8 T cells. For example, IL-12b and IL-2 are critical cytokines for the induction of antigen-specific T cells. In particular, IL-12b is intricately involved in the establishment of Th1 response and cellular immunity in viral infection and cancer. Th1 response induces antigen-specific CD8 T cells via the production of IFN-γ. The antigen presentation by APCs such as dendritic cells is also involved in the generation of Th1 immune response and antigen-specific CD8 T cells. The authors also examined the DC function after combination therapy of systemic administration of TLR7 agonist/local radiation. Systemic administration of a TLR7 agonist up-regulates the costimulatory molecules (CD80 and CD86) on the surface of DC, and the efficacy of phagocytosis by DC enhanced after irradiation. The up-regulation of phagocytosis of tumor antigen and co-stimulatory molecules on DC may also be pivotal in the induction of tumor antigen-specific CD8 T cells and the enhancement of anti-tumor effect after the combination therapy.

Recently, several other investigators have examined the anti-tumor effect of combination therapy with a TLR7 agonist and local radiation (10,11). In subcutaneous and orthotropic mouse models of colorectal and pancreatic cancer, combined treatment with local irradiation and systemic administration of a TLR7 agonist was highly effective against established tumors. These studies also demonstrated that the combination of radiation therapy and TLR7 agonist administration could stimulate the processing and presentation of locally released tumor antigens. Moreover, T cells and NK cells markedly contributed to the enhancement of anti-tumor efficacy of the combination therapy. In a spontaneous lung metastasis model, the combination therapy of primary tumors significantly reduced metastatic burden in the lung and improved survival (10). Lung metastatic lesions were never exposed to radiation directly. The reduction of lung metastasis was thought to be due to the indirect effect of the combination therapy. In the studies that evaluated the combination of systemic administration of TLR7 agonist and local radiation therapy against cancer, the combination therapy induced tumor antigen-specific CD8 T cells. Application of combination therapy to primary tumors could induce a systemic adoptive immune response to cancer cells, and the tumor antigen-specific immune response could reduce present and future metastatic lesions. Dovedi *et al.* also demonstrated that long-term surviving mice after the combination therapy are protected against subsequent tumor rechallenged by the induction of a tumor-specific memory immune response. The tumor specific induction of memory immune response might be involved in the improvement of survival in tumor-bearing mice or mice with any metastatic lesions.

Dovedi *et al.* demonstrated that the combination of repeated systemic injection with TLR7 agonist and fractionated radiation therapy strongly induced anti-tumor immune response and improved the prognosis of tumor-bearing animals. A previous report indicated that multiple IFN-related genes were up-regulated after fractionated radiation therapy (12). The up-regulation of IFN-related genes might lead to the induction of tumor antigen-specific immune response and remission of cancer. However, no

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comparable analysis was performed on the host immune response after combination therapy with repeated TLR7 agonist administration and fractionated radiation therapy. Moreover, it is unclear how the mechanism differs between single systemic injection and repeated injection of a TLR7 agonist in terms of the host immune response in tumor-bearing animals. If these questions can be resolved and the mechanism of anti-cancer effect of combination therapy determined, the combination therapy with TLR7 agonists and radiation could be translated to early phase clinical trials immediately. In particular, because TLR7 agonist is systemically injected not locally administered, translation to clinical studies would be relatively easy.

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Footnote

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References

1. Trinchieri G. Interleukin-12: a proinflammatory cytokine with immunoregulatory functions that bridge innate resistance and antigen-specific adaptive immunity. Annu Rev Immunol 1995;13:251-76.
2. Hathcock KS, Laszlo G, Pucillo C, et al. Comparative analysis of B7-1 and B7-2 costimulatory ligands: expression and function. J Exp Med 1994;180:631-40.
3. Ito H, Ando K, Ishikawa T, et al. Role of Valpha14+ NKT cells in the development of Hepatitis B virus-specific CTL: activation of Valpha14+ NKT cells promotes the breakage of CTL tolerance. Int Immunol 2008;20:869-79.
4. Zamarin D, Postow MA. Immune checkpoint modulation: rational design of combination strategies. Pharmacol Ther 2015;150:23-32.
5. Vacchelli E, Eggermont A, Sautès-Fridman C, et al. Trial Watch: Toll-like receptor agonists for cancer therapy. Oncoimmunology 2013;2:e25238.
6. Adams S. Toll-like receptor agonists in cancer therapy. Immunotherapy 2009;1:949-64.
7. Dovedi SJ, Melis MH, Wilkinson RW, et al. Systemic delivery of a TLR7 agonist in combination with radiation primes durable antitumor immune responses in mouse models of lymphoma. Blood 2013;121:251-9.
8. Kawarada Y, Ganss R, Garbi N, et al. NK- and CD8(+) T cell-mediated eradication of established tumors by peritumoral injection of CpG-containing oligodeoxynucleotides. J Immunol 2001;167:5247-53.
9. Gajewski TF, Fuertes MB, Woo SR. Innate immune sensing of cancer: clues from an identified role for type I IFNs. Cancer Immunol Immunother 2012;61:1343-7.
10. Adlard AL, Dovedi SJ, Telfer BA, et al. A novel systemically administered Toll-like receptor 7 agonist potentiates the effect of ionizing radiation in murine solid tumor models. Int J Cancer 2014;135:820-9.
11. Schölch S, Rauber C, Tietz A, et al. Radiotherapy combined with TLR7/8 activation induces strong immune responses against gastrointestinal tumors. Oncotarget 2015;6:4663-76.
12. Tsai MH, Cook JA, Chandramouli GV, et al. Gene expression profiling of breast, prostate, and glioma cells following single versus fractionated doses of radiation. Cancer Res 2007;67:3845-52.

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