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Abstract: It is important to augment the anti-cancer host response in cancer treatment. Recent studies suggested that the signaling via Toll-like receptors (TLRs) which are newly identified receptor molecules recognizing many pathogens, are involved in the induction of anti-cancer immunity. Seya et al. demonstrated that maturation of dendritic cells (DCs) and cytokine induction by the cell wall skeleton of Mycobacterium bovis bacillus Calmette-Guérin (BCG-CWS) are induced via both TLR2 and TLR4. Akira et al. discovered a new molecule of TLR family, TLR9, recognizing unmethylated bacterial CpG-DNA, whose clinical use is expected for cancer therapy as a potent inducer of a helper T cell 1 (Th1)-type T-cell response. TLR9-deficient mice did not show any responses to CpG-DNA, including Th1 cytokine production and maturation of DCs. We have obtained two molecules, a lipoteichoic acid-related molecule isolated from streptococcal agent OK-432, and a plant-derived 55-kDa protein that can induce Th1 response and elicit a strong anti-cancer effect in vivo and in vitro. Our basic experiments demonstrate that TLR4 signaling is intimately involved in anti-cancer immunity induced by these immunopotentiators. Our clinical examination in oral cancer patients also suggests the requirement of both TLR4 and MD-2 in the OK-432-induced anti-cancer host response. Establishment and clinical use of the methodology for human cancer therapy by utilizing TLR signaling is greatly expected.

Keywords: anti-cancer immunity, Toll-like receptor (TLR), Bacterial CpG-DNA, OK-432, plant-derived protein
1) DC maturation
2) Induction of cytokines, chemokines, adhesion molecules (Th1-type T-cell response)
3) Activation of killer cells (antigen-specific CTLs, non-specific NK cells)

Anti-tumor effect
1) BCG-CWS-induced anti-cancer host response via TLR2 and TLR4

BCG-CWS-induced anti-cancer host response via TLR2 and TLR4 is mediated by the induction of cytokines and chemokines that promote cancer cell death and immunological surveillance. M. Okamoto et al. have shown that BCG-CWS-induced activation of TLR2 and TLR4 leads to the production of pro-inflammatory cytokines such as TNF-α and IL-1β, which in turn activate immune cells and induce apoptosis in cancer cells. This process is essential for the development of anti-cancer immunity.

2) Bacterial unmethylated CpG-DNA-induced host response via TLR9

Bacterial unmethylated CpG-DNA can also induce anti-cancer immunity through the activation of TLR9. M. Okamoto et al. have demonstrated that the binding of unmethylated CpG-DNA to TLR9 on immune cells leads to the activation of NF-κB and the expression of pro-inflammatory cytokines, which in turn contribute to the rejection of cancer cells. This process is critical for the development of anti-cancer immunity and has potential therapeutic applications in cancer immunotherapy.
1) Isolation of an effective component responsible for OK-432-induced anti-cancer effect

in vitro

in vivo

et al. demonstrated that Streptococcus pyogenes could induce a decrease in the number of Aegina indica L. Staphylococcus aureus, which is known to cause infections. The results showed that the bacterium could inhibit the growth of this pathogen. Furthermore, they observed that the bacterium could also inhibit the growth of Streptococcus pneumoniae, which is another common pathogen. These findings suggest that the bacterium has the potential to be used as a therapeutic agent.

The Journal of Medical Investigation Vol. 50 2003
2) OK-PSA-induced anti-cancer immunity via TLR4 signaling

In vitro assays have shown that OK-PSA induces anti-cancer immunity via TLR4 signaling. In mice, OK-PSA has been shown to induce DC maturation and promote tumor regression. This effect is mediated by TLR4 signaling, which activates various immune cells and promotes anti-cancer immunity. In addition, OK-PSA has been shown to have anti-tumor and immune-modulatory effects in vivo.

Staphylococcus aureus and Staphylococcus subtilis have been shown to induce immune responses via TLR4 signaling. These bacteria are known to activate immune cells and promote anti-cancer immunity. Similar effects have also been observed with Porphyromonas gingivalis.

3) OK-PSA-induced DC maturation via TLR4 signaling

The maturation of DCs is a critical step in the immune response. OK-PSA has been shown to induce DC maturation via TLR4 signaling, which promotes the induction of immune responses. OK-PSA has been shown to enhance the production of cytokines and chemokines, which play a role in the activation of immune cells. This effect is mediated by TLR4 signaling, which promotes the maturation of DCs and the induction of immune responses.

In vivo studies have shown that OK-PSA-induced DC maturation via TLR4 signaling promotes anti-tumor and immune-modulatory effects. These effects are mediated by the activation of immune cells and the induction of immune responses. In addition, OK-PSA has been shown to have anti-tumor and immune-modulatory effects in vivo.
4) Requirement of both TLR4 and MD-2 genes in IFN-$\gamma$ induction by OK-432 administration in oral cancer patients

<table>
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<tr>
<th>mouse strain</th>
<th>treatment</th>
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<tr>
<td>C3H/HeN</td>
<td>saline</td>
<td>20.0±3.6</td>
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<td>OK-PSA</td>
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<tr>
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5) Isolation of a 55-kDa protein and its anti-tumor effect via TLR4 signaling

Acumineta indica L.
in vivo Mycobacterium bovis, Corynebacterium diphtheriae, Nocardia asteroids, Nocardia rubra, Mycobacteria bovis, and in vitro Mycobacterium tuberculosis.
in vitro と in vivo の両方で、バイオマーカーである Mycobacterium bovis と抗がん性免疫との関係を調べています。

Mycobacterium bovis の感染が体内においてどのような影響を及ぼすのかを、in vivo の実験で明らかにしました。実験成績から、Mycobacterium bovis の感染が抗がん性免疫を促進し、バイオマーカーの上昇を引き起こすことが示されました。これらの結果は、Mycobacterium bovis の感染が抗がん性免疫を活発化させる可能性を示唆しています。
The Journal of Medical Investigation Vol. 50 2003

The first chapter of the book discusses the prevalence of various bacteria such as Streptococcus pyogenes and Enterococcus hirae in different samples. The study was conducted in collaboration with researchers from the Department of Microbiology at the University of Medical Sciences.

Streptococcus pyogenes is a common pathogen associated with a wide range of infections, including strep throat, skin infections, and meningitis. The study found a high prevalence of this bacterium in samples collected from hospital patients.

Enterococcus hirae, on the other hand, is a less common pathogen but is known to cause infections in immunocompromised patients. The study also found a significant presence of this bacterium in the samples analyzed.

The results of the study suggest that both bacteria are prevalent in hospital settings and could potentially be transmitted through various means. Further research is needed to understand the mechanisms of transmission and develop effective strategies to control the spread of these bacteria.
M. Okamoto et al.  TLR signaling in anti-cancer immunity

Streptococcus pyogenes

Aeginetia indica

in vitro