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論文題目	Inactivation of the PD-1-dependent immunoregulation in mice exacerbates contact hypersensitivity resembling immune-related adverse events （PD-1 依存的な免疫制御機構の抑制は、免疫関連副作用に類似する接触性皮膚炎の悪化を引き起こす）		

（論文内容の要旨）

The expression of PD-1 as a co-inhibitory receptor suppresses the effector T-cell responses and its blockade has been proven to be a durable strategy for strengthening immune responses in cancer treatment. This effective blockade of the PD-1 pathway provides a promising strategy of immunotherapy. Expanding the use of these immune checkpoint blockades in addition to unprecedented success in advanced cancer treatment, sometimes is along with detrimental disorder of immune-related adverse events (irAE). This irAE is reported in many patients who underwent PD-1 blockade therapy and among which dermatitis-like skin disease is the most frequent. Inflammatory tissue damage in irAE is progressive in some patients and in rare cases irAE reported critically dangerous in which cancer-immunotherapy was discontinued. Therefore, proactive management of irAE to prevent exacerbation is essential.

In this study, I evaluated that in what respect inactivation of the PD-1/PD-L1 pathway causes aggravated skin inflammation. To this end, an exacerbated oxazolone-induced contact hypersensitivity (CHS) by anti-PD-L1 mAb treatment has been used. This murine model consists of two distinct phases, a sensitization phase which begins by a topical application of oxazolone on the shaved abdomen, and an elicitation phase following frequent challenges with the same hapten on the ear. As a result, anti-PD-L1 mAb treatment in both phases caused a massive infiltration of CD8+ T cells into the inflamed tissue associated with significant ear edema. Consistent with that, an elevated number of CD8+ T cells and remarkable ear swelling has been observed in PD-1-/- mice.

Along with T cells, NK and dendritic cells were found to express a distinct level of PD-1 in the inflamed tissue. However only PD-1+ expressing T cells may have an indispensable role in exaggerating dermatitis following anti-PD-L1 mAb treatment. Multiple episodes of anti-PD-L1 mAb treatment in RAG2-/- mice did not enhance the ear inflammation.

The blockade of PD-L1 during the sensitization phase remarkably promoted the development of oxazolone-reactive effector T cells in draining Lymph nodes. Since an intensified CHS was guaranteed by the presence of oxazolone-specific T cells even though anti-PD-L1 mAb treatment was withheld during the elicitation phase.

Enhancement of local CD8+ T cell-dominant immune responses by PD-L1 blockade was correlated with the upregulation of CXCL9 and CXCL10 ligands of CXCR3. As neutralization of CXCR3 prevented the induction of vigorous dermatitis by anti-PD-L1 mAb. Non-hematopoietic CD45- cells identified as predominately responsible for upregulation of CXCL9 and CXCL10 in the inflamed ear following inactivation of the PD-1/PD-L1 pathway.

To generate skin inflammation similar to that observed in human dermal irAE a suboptimal dose of oxazolone has been used and as a result, neither a significant tissue swelling nor T cell accumulation in the ear was recognized. As opposed, immunopotentiation by anti-PD-L1 mAb helped to rise the subtle level of inflammation to visible dermatitis and increased CD4+ and CD8+ T cell numbers. Therefore, blockade of the PD-1 pathway can transform concealed skin irritation to significant dermatitis. Moreover, induction of T cell-dominant inflammation by anti-PD-L1 mAb was inhibited by the blockade of CXCR3.

In conclusion, the role of PD-1/PD-L1 inactivation in the regulation of skin inflammation was a matter of debate in this study. In this regard, I reproduced a CD8+ T cell-dominant form of cutaneous inflammation by the blockade of PD-L1 to evaluate the emergence mechanism of skin irAE. This exaggerated CHS shares common features with clinical observations in human dermal irAE. Results produced by this study can help a better management of skin irAE to improve the quality of immunotherapy in cancer patients.

（論文審査の結果の要旨）

本研究は、免疫チェックポイント阻害によるがんの免疫治療における炎症性の副反応、免疫関連副作用（irAE）に着目し、実験動物モデルを作成した上で発症メカニズムを考察したものである。irAE の重症化は比較的稀ではあるが、生命に関わる増悪も有るため、この治療を行う際には irAE を適切に管理することの重要性が認識されている。

irAE に対する適切な対処法、薬剤を開発するためには、その発症メカニズムを再現した実験動物モデルが必要である。irAE が最も頻繁に観察されるのは皮膚であり、治療前には炎症の徴候が見られなかった部位に出現することも多いが、この状況を再現できる実験モデルは確立されていない。申請者はマウスでの接触性皮膚炎が抗 PD-L1 抗体投与によって増強される事に着目した。その分析結果は、irAE を起こした患者の皮膚組織のものと一致しており、irAE に特徴的な T 細胞主導の炎症反応が再現されていると言える。

この実験モデルは実際のがん治療における irAE と同様に、PD-1/PD-L1 系のブロックによって誘導される点、類似した炎症像を示していて発症メカニズムも共通と考えられる点、無症状の皮膚組織においても誘導される点の全てを実現しており、既知の irAE モデルと比較しても利点が多い。irAE に対する対処は、がんに対する免疫反応との兼ね合いも考える必要があるが、その解決のために本研究の利用価値は高いと考えられる。

したがって、本論文は博士（医学）の学位論文として価値あるものと認める。

なお、本学位授与申請者は、令和３年３月２日実施の論文内容とそれに関連した試問を受け、合格と認められたものである。

要旨公開可能日：　　年　　月　　日　以降