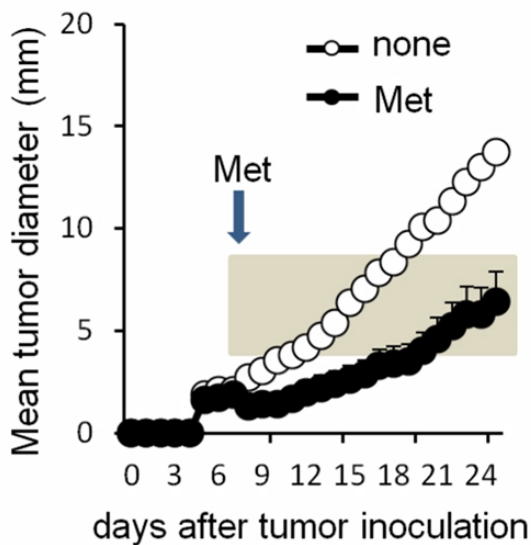


Metformin confers anti-tumor immunity by reactivating exhausted CD8T lymphocytes

24 February 2016



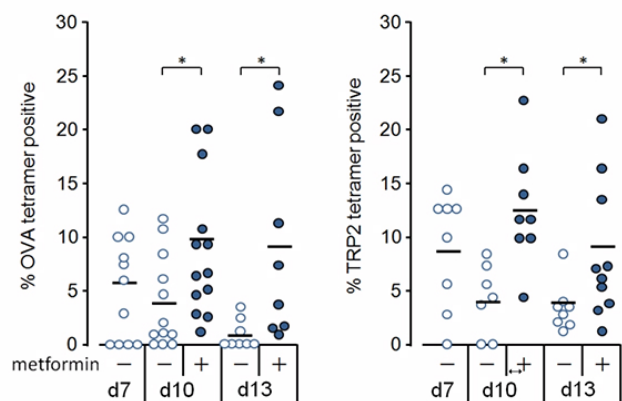
Mice inoculated with melanoma cells (MO5 expressing OVA) were treated w/o metformin (Met) from day 7, as indicated by the shadowed rectangle, and tumor growth was monitored. Metformin treated mice showed significant inhibition of tumor growth.

Anti-cancer effect of tumor infiltrating CD8+T lymphocyte (CD8TIL) is suppressed by interaction between immune-checkpoint molecules such as PD-1 and CTLA-4 expressed on CD8TIL and their ligands expressed on cancer cells, which is referred to as immune-exhaustion. Cancer immunotherapy with antibody-mediated, immune-checkpoint blockade is now promising in preventing advanced melanoma and non small cell lung carcinoma (NSCLC). Such antibody-mediated immunotherapy, however, faces their enormous financial problem and significant side effects like autoimmune diseases.

On the other hand, metformin, a safe and low cost drug prescribed for patients with type 2 diabetes,

has been recognized to have anti-cancer effect. We found that CD8TIL is a target of metformin. CD8TIL inevitably undergoes immune-exhaustion, characterized by diminished production of multiple cytokines such as IL-2, TNF α and IFN γ , followed by elimination with apoptosis. Metformin is able to counter the state. Metformin, thus, blocked immune exhaustion within [tumor tissues](#).

Mice administered metformin by free drinking water, showed significant tumor growth inhibition in 6 distinct tumor models and CD8TIL becomes resistant against apoptosis, furthermore, it begins to produce multiple cytokines. Blood concentration of metformin in those mice is almost comparable to that of type 2 diabetes patients who are taking metformin daily. Therefore, along with other cancer immunotherapies, treatment of cancer patients with [metformin](#) may significantly improve the efficacy and have a great benefit for their prognosis.



On days 7, 10 and 13, TILs were recovered from tumor masses, and CD8+ TILs were examined for K^b-OVA₂₅₇₋₂₆₄ and K^b-TRP2₁₈₀₋₁₈₈ tetramer binding (n = 7-13) by flow cytometry analysis. The population of CD8+ TILs specific for either antigen, OVA₂₅₇₋₂₆₄ or TRP2₁₈₀₋₁₈₈, was significantly increased in metformin treated mice (+), compared with non-treated mice (-). The accumulation of antigen specific of CD8+ TILs is caused

by inhibition of apoptosis by metformin treatment.

More information: Shingo Eikawa et al. Immune-mediated antitumor effect by type 2 diabetes drug, metformin, *Proceedings of the National Academy of Sciences* (2015). [DOI: 10.1073/pnas.1417636112](https://doi.org/10.1073/pnas.1417636112)

Provided by Okayama University

APA citation: Metformin confers anti-tumor immunity by reactivating exhausted CD8T lymphocytes (2016, February 24) retrieved 27 July 2022 from <https://medicalxpress.com/news/2016-02-metformin-confers-anti-tumor-immunity-reactivating.html>

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