Metformin confers anti-tumor immunity by reactivating exhausted CD8T lymphocytes

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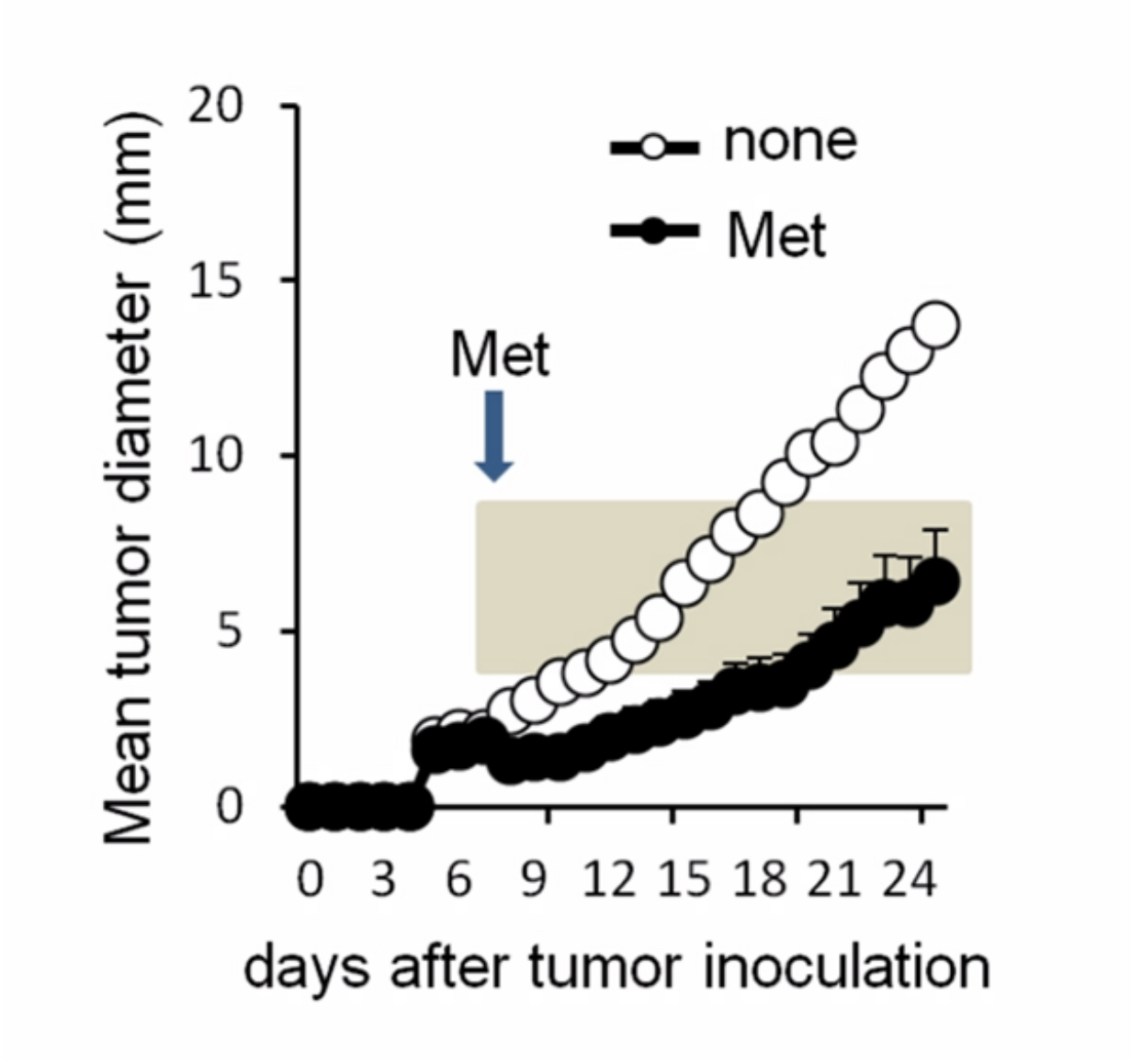


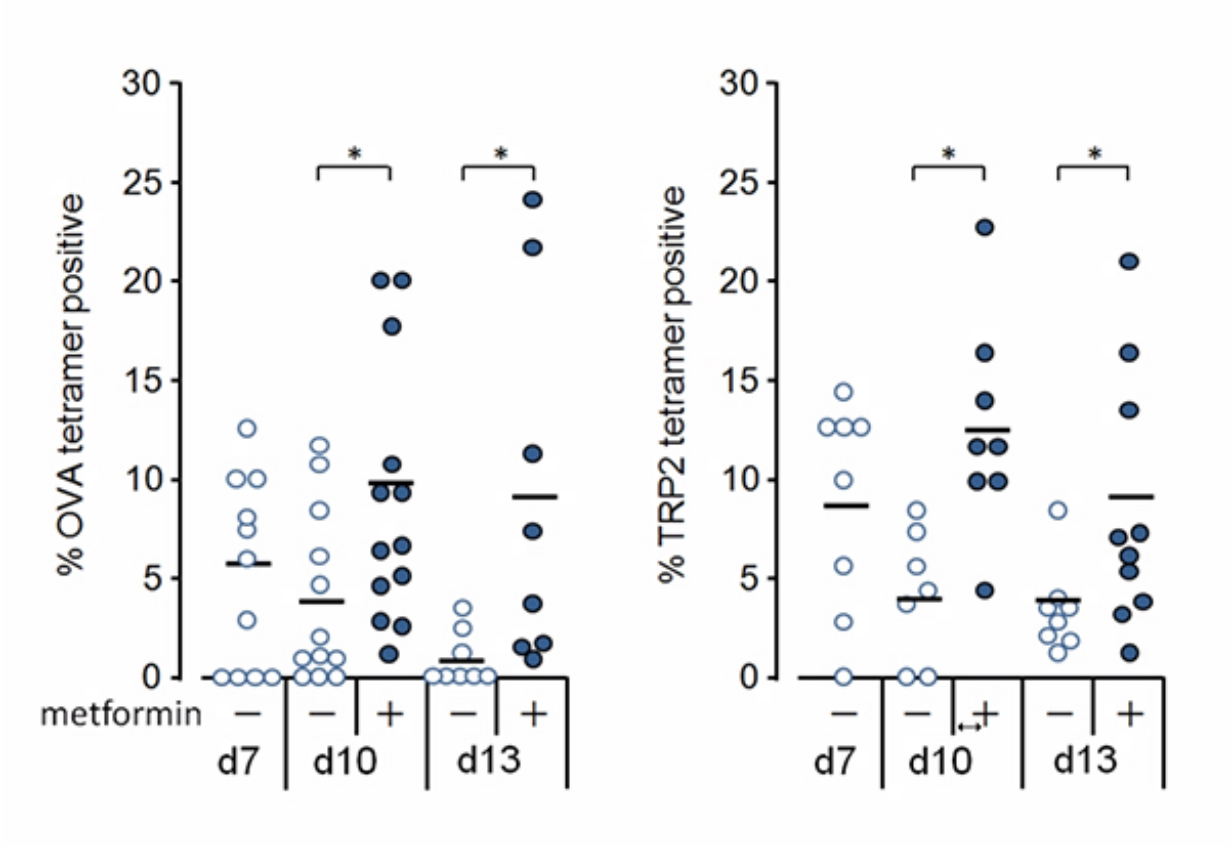
Mice inoculated with melanoma cells (MO5 expressing OVA) were treated w/o

metformin(Met) from day 7, as indicated by the shadowed rectangle, and tumor growth was monitored. Metfromin 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, TNFα and IFNγ, 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-$OVA_{257–264}$ and Kb-$TRP2_{180–188}$ tetramer binding (n = 7–13) by flow cytometry analysis. The population of CD8+ TILs specific for either antigen, $OVA_{257–264}$ or $TRP2_{180–188}$, 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

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