Licensing Opportunity

Ref 1042-A979

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Boosting T-cell responses by inhibiting Arginase 2 expression

- L-Arginine is essential for mounting anti-tumor T cell responses. Tumors therefore tend to establish an immunosuppressive L-Arginine depleted microenvironment by increasing arginase expression.
- Researchers of the University of Geneva have developed a method to overcome this problem by abrogating arginase 2 in human immune cells, rendering them more effective, particularly in the context of T-cell transfer therapies for the treatment of solid tumors, which has been mostly unsuccessful so far.

Keywords: immunotherapy, adoptive cell therapy, CAR T-cell therapy, L-arginine, arginase II, immune checkpoint blockade, solid tumors, T-cell resopnse

In cancer, the immune system participates in suppressing the initiation of malignant neoplasms, inhibiting tumor progression and promoting tumor elimination. Tumors exploit diverse mechanisms to evade anti-tumor responses and prevent tumor elimination. Recent successful immunotherapies such as anti-PD1 monoclonal antibodies or CAR-T cell therapies (CAR-T) have emerged. CAR-T therapies have shown unprecedented success in hematological tumors, but treatment of solid tumors has been largely unsuccessful so far, in part due to the harsh immunosuppressive tumor microenvironment. Sufficient L-Arginine availability is essential for optimal function of immune cells and L-Arginine depletion via arginases contributes to the creation of an immunosuppressive tumor micro-environment impairing T cell responses.

A new approach to power-up a patient's immune system

Researchers from the University of Geneva have developed a new method to enhance the efficacy of T cell therapies for solid tumors by abolishing arginase 2 activity in immune cells. The inventors also provide a method of treatment combining impaired arginase 2 activity with blockade of negative immune checkpoints regulators (such as inhibitors of the PDL1-PD1 axis) to improve control of tumor growth and increase survival.

Reference:
A.-A. Martí i Líndez et al. 2019. Mitochondrial Arginase-2 is a cell autonomous regulator of CD8+ T cell function and anti-tumor efficacy. *JCI Insight*

Therapeutic potential - applications

- Enhancement of adoptive cell therapies that involve chimeric antigen receptor T-cells (CAR-T cells), tumor infiltrating lymphocytes (TILs), T-cell receptor-engineered T cells, natural killer cells (NK cells), innate lymphoid cells (ILCs) and dendritic cells
- Combination therapy with immune checkpoint blockade therapies such as for example inhibitors of the PDL1-PD1 or B7-CTLA4 receptor-ligand systems in oncology.

Read more overleaf

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With 460 years of history the University of Geneva is recognized today as one of the top 100 universities in the world and the second largest innovation player in Europe (Nature Innovation Index , 2017).

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Advantages

- Inhibition of Arginase 2 in ex vivo immune cells can be achieved through any means, such as for example siRNA or CRISPR-Cas9, therefore allowing flexibile integration into existing adoptive cell therapy workflows
- Arginase 2 inhibition is restricted to *ex vivo* immune cells which reduces the potential for side effects
- Particularly suited to address solid tumors which are currently not tractable through CAR T-cell therapies
- Versatile approach applicable to most immune cell-based therapies

Key data

Impaired tumor growth in Arg2$^{-/-}$ mice

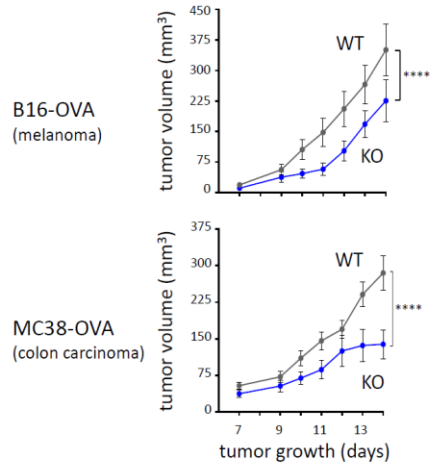

Figure 1: Impaired tumor growth in Arginase 2 deficient mice (KO, Arg2$^{-/-}$) compared to normal mice (WT)

Synergy between Arg2 deficiency and PD1 blockade

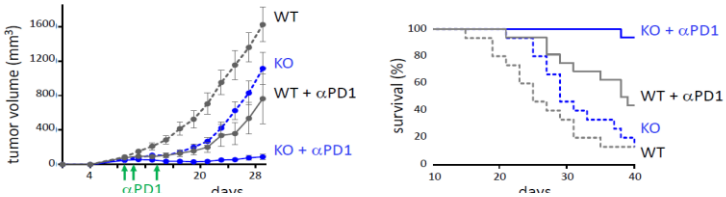

Figure 2: Normal (WT) or arginase 2-deficient (KO) mice bearing tumors were treated with anti-PD1 antibodies (immune checkpoint blockade). Combination of anti-PD1 therapy with arginase 2 deficiency results in a strong synergistic effect on tumor growth and survival.

Partnering :
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