Increasing Immunotherapy Efficacy of Anti PD-L1

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Overview

Immunotherapy has revolutionized cancer treatment by activating the immune system to attack tumor cells. However, notable limitations remain, including differential responses between individuals and cancer types. Dr. Rony Dahan and his group found a method to significantly enhance the currently FDA-approved anti-PD-L1 treatment by combining it with RcÎ³RIIB inhibitor or by introducing specific modifications in the Fc region.

Background and Unmet Need

Checkpoint inhibitors are drugs used to activate the immune system against cancer tumor cells. Immune T cells can detect cancerous cells and eliminate them. However, to protect normal cells from attack, this process is highly regulated by several checkpoint molecules, namely programmed cell death protein-1 (PD-1) and ligand-1 (PD-L1), which induce self-tolerance. Cancer cells use these checkpoints to evade T cells. Checkpoint inhibitors are antibodies (mAbs) that bind and block these checkpoint molecules, thus promoting antitumor response.

Nevertheless, these mAbs still exhibit notable limitations. Not all cancer types are suitable for this type of therapy, and only a portion of patients respond to the treatment. Therefore, effective treatment with anti-PD-1/L1 mAb therapy remains an unmet clinical need.

The Solution

The group of Dr. Rony Dahan found a method to increase anti-PD-L1 efficacy by combination with RcÎ³RIIB inhibitor or by introducing specific mutations or post-translational modification to the Fc region of the mAbs.

Technology Essence

Antibodies targeting immune checkpoints in tumor microenvironment have an Fc domain that interacts with immune cells by binding their FcÎ³ receptor (FcÎ³R). Interaction of therapeutic antibody with FcÎ³Rs can either promote activation of immune cells (through activating FcÎ³RI, FcÎ³RIIA and FcÎ³RIIIA receptors) or result in an inhibitory effect (RcÎ³RIIB). The IgG1 anti-PD-L1 antibodies currently approved by the FDA have limited efficacy since they have a high affinity towards the inhibitory receptor, FcÎ³RIIB, while having a poor affinity to the activating receptors, FcÎ³RIIA and FcÎ³RIIIA. To overcome this, the researchers co-administered the anti-PD-L1 antibody with the FcÎ³RIIB blocking antibody. Thus the second antibody prevents the binding of anti-PD-L1 Fc domain to FcÎ³RIIB, improving the activation of the immune cells in response to anti-PD-L1 treatment. Alternatively, the present inventors engineered the Fc region of Avelumab, a commercial anti-PD-L1 antibody, to comprise an enhanced affinity towards the activating FcÎ³Rs (compared to the unmodified antibody). The removal of fucose from the mAb Fc glycan, substantially increased the affinity of the antibody to FcÎ³RIIIA and improved its antitumor effect (Figure 2). Both these modalities resulted in enhanced antitumor activity compared to that of the IgG1 anti-PD-L1 antibody

when administered alone.

Applications and Advantages

- Improvement to anti-PD-1/L1 treatment
- Potential treatment for cancer, inflammatory disease, or infectious disease

Development Status

The researchers demonstrated that co-administration of anti-huFcÎ³RIIB and Avelumab increased the therapeutic potential of Avelumab in a mouse in-vivo MC38 tumor model (Figure 1).

The researchers developed a next-generation Fc-engineered version of Avelumab with improved therapeutic antitumor activity compared to the parental Avelumab antibodies. This is a fully human antibody readily available for evaluation in human patients. Moreover, this optimized IgG scaffold can be introduced to any human anti-PD-L1 antibody to improve its efficacy.

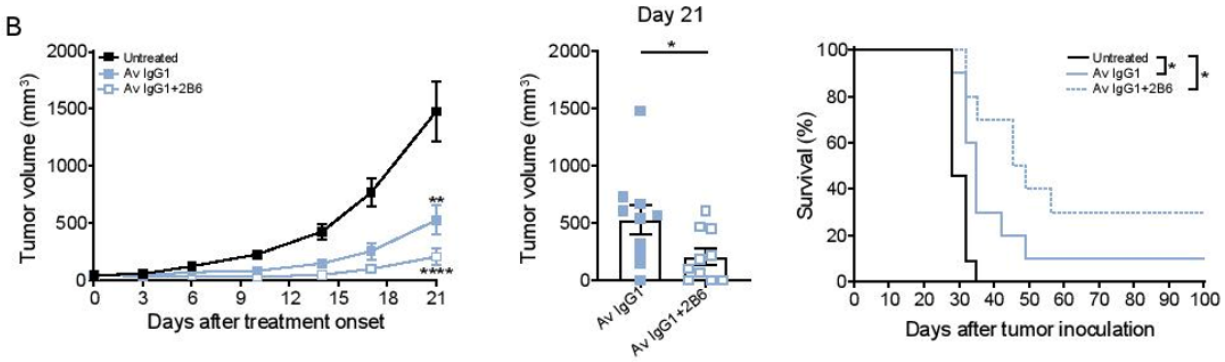

Figure 1 - Combined targeting of huFcÎ³RIIB and PD-L1 increase the therapeutic effect of Avelumab in MC38 tumor model. huFcÎ³R mice with established MC38 tumors were treated with Avelumab IgG1 in a combinatory treatment with anti-CD32B (FcÎ³RIIB) clone 2B6. Data are represented as mean Â± SEM.

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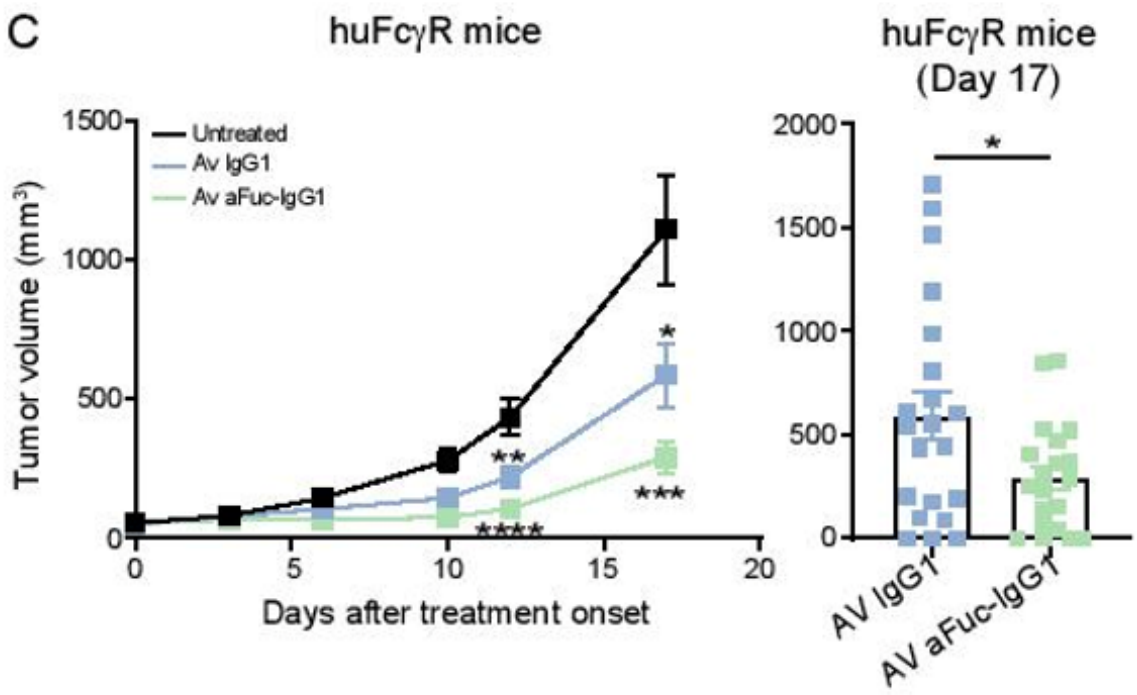

Figure 2- aFucosylation of Avelumab Fc glycan results in increased antitumor effect in vivo-in MC38 tumor model. FcÎ³R humanized mice with established MC38 tumors were treated with either Avelumab IgG1 (blue) or Fc variants: N297A (red) and Afucosylated (yellow). Afucosylation of Avelumab Fc glycan showed improved antitumor activity compared to Avelumab IgG1 or N297A variant. Data are represented as mean Â± SEM.

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Patent Status

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