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Cancer immunotherapy impedes skeletal muscle repair

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Objective To observe the difference of the capacity of skeletal muscle repair and the corresponding immune response in melanoma mice treated with cancer immunotherapy after acute skeletal muscle contusion.
Methods 96 males C57BL/6 mice were used in this experiment. They were divided into control group and injury group. The control group included normal control group (C group, n = 8), tumor control group (T group, n = 8) and tumor immunotherapy group (A group, n = 8).The skeletal muscle injury group was divided into normal injury group (D group, n = 24), tumor mice injury group (DT group, n = 24) and cancer immunotherapy injury group (DA group, n = 24). B16 cells were injected subcutaneously into the dorsum of C57/BL mice to prepare melanoma mice model. Immunotherapy is the injection of anti CTLA-4 and anti PD-1 antibodies. The model of gastrocnemius muscle contusion was established. At different time points after damage, mice were sacrificed. The gastrocnemius muscle of mice was made into cryosections. After HE staining and Mason staining, the regeneration of skeletal muscle and the healing of fibrotic scar were observed. The expression of CD8 T Cells and Regulatory T Cells (Treg) were detected by immunofluorescence.
Results 1.H&E staining of muscle slices at 7 days after injury showed that myofibers in the non-injured muscles are polygonal in shape with peripheral nuclei. Quantitative evaluation of the skeletal muscle in the cancer immunotherapy injury group (DA group) showed that the number of centrally nucleated fibers was significantly lower than that in the other injury groups（D group，DT group）and there was an enlarged interstitial space. Immunotherapy leads to greater muscle degeneration: vacuolated myofibers could be seen. Collagen deposition was detected by Masson trichrome staining, and collagen deposits were found in the injury group. However, the regenerated muscles of the cancer immunotherapy injury group (DA group) showed more collagen deposits than those of the other injury groups（D group，DT group）, no collagen deposits were found in the control group.
2. On 14 day after injury, the density of muscle fibers in the other injury groups（D group，DT group ） was higher than that in immunotherapy group (DA group), which was about 1.5 times of that in immunotherapy group (DA group). The other injury groups（D group，DT group） showed a larger proportion of regenerated muscle fibers with different diameters, whereas the cancer immunotherapy injury group (DA group) had fewer regenerated muscle fibers. Compared with the control group, the mice in the other injury groups（D group，DT group）still had a small amount of collagen deposits, the mice in the cancer immunotherapy injury group (DA group) had more collagen deposits.
3.On 21 day after injury, the average diameter on 21 day higher than that on day 7 in the three injury groups. The mean muscle fiber diameter in the other injury groups（D group，DT group） was significantly larger than that in the immunotherapy injury group. In addition, the regenerated muscle fibers in the other injury groups（D group，DT group） showed better organization and basically returned to normal compared with the immunotherapy group (DA group). There were still some collagen deposits in the immunotherapy group (DA group) mice, but no collagen deposits were found in the other injury groups（D group，DT group）mice.
4.Immunofluorescence staining showed that CD8 T cells were continuously expressed and no Treg cells were found in the immunotherapy group (DA group) mice at 7, 14 and 21 days after contusion. In the other injury groups（D group，DT group）, Treg and CD8 T cells were expressed in skeletal

muscle tissue adjacent to the regenerated muscle fibers on 7 days. On day 14, a small number of CD8 T cells and a large number of Treg cells infiltrated the damaged muscles. On day 21, almost no CD8 T cells were detected, and Treg cells continued to express. There was no expression of Treg cells and CD8 T cells in the control group.
Conclusions Cancer immunotherapy will delay the repair of damaged skeletal muscle and reduce the capacity of skeletal muscle repair and regeneration.