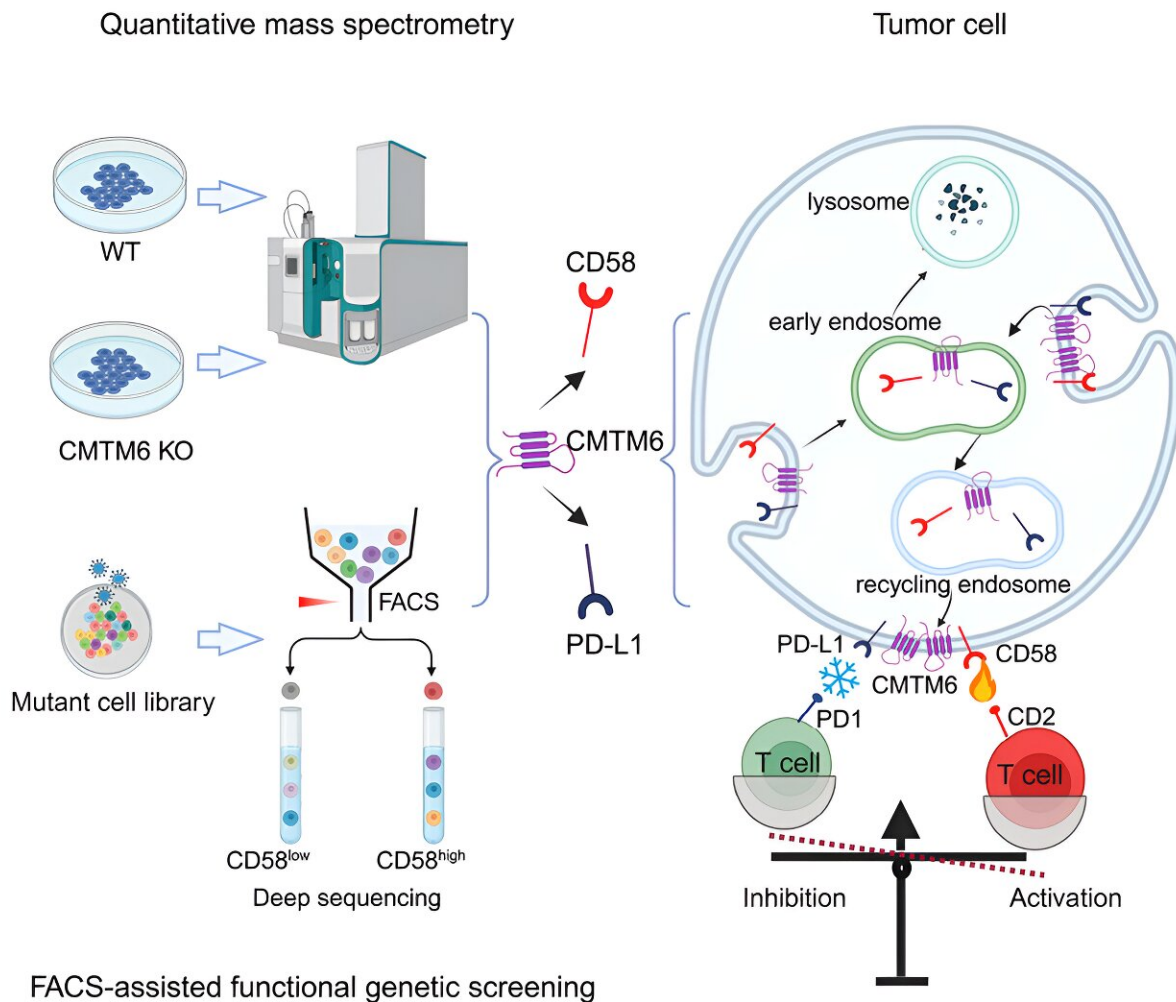


# Scientists identify a protein on cancer cells that supports the immune response against tumors

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Graphical abstract. Credit: *Cancer Cell* (2023). DOI: 10.1016/j.ccell.2023.08.008

Scientists from the German Cancer Research Center (DKFZ) identify a new and surprising function of a membrane protein on the surface of cancer cells: It supports and stabilizes an important "co-stimulatory" factor that enhances the activation of T cells, thus improving the immune response against the tumor. The study is published in the journal *Cancer Cell* and was conducted in collaboration with researchers from the Netherlands Cancer Institute.

Many types of cancer can be successfully treated with [immune checkpoint inhibitors](#) (ICI). This treatment is often simply referred to as "immunotherapy." The blockade of inhibitory immune checkpoint proteins such as PD-L1 forms the basis of this treatment. But a concomitant lack of stimulatory signaling can render the therapies useless. This is considered one of the reasons why many [cancer patients](#) do not benefit from immune checkpoint inhibitors.

T cells are the key players in the immune defense against tumors. Their activation is tightly controlled by a variety of inhibitory and also stimulatory immune checkpoints. However, [tumor cells](#) often sabotage this system by manipulating the expression of checkpoint proteins to escape destruction by the immune system.

Among the activity-promoting co-stimulatory proteins is CD58. When it binds to its receptor on an immune cell, the cell receives a stimulatory signal. If the binding of CD58 to its receptor is blocked, the [immune response](#) against many cancers is impaired.

"It is intriguing to observe that many cancer cells inherently express CD58, a molecule that essentially contradicts their own survival when they come under immune attack. We therefore wanted to understand what controls the expression of CD58," says Chong Sun, an immunologist at the German Cancer Research Center.

With their current study, the researchers found that the membrane protein CMTM6 interacts and positively regulates the expression of CD58. The surprising thing is that CMTM6 simultaneously interacts with PD-L1, the important inhibitory immune checkpoint molecule that most current ICI therapies target. CMTM6 protects PD-L1 from degradation and likewise also stabilizes CD58 via this mechanism. This mechanism potentially fine-tunes immune response.

Moreover, using a model of TCR-T cell treatment in the culture dish, the researchers showed that CMTM6 loss from tumor cells impairs T cell activation. They also found that the influence of CMTM6 on CD58 plays an important role in the antigen-specific interaction of T cells with tumor cells and also affects the response to PD-L1 blockade.

"It is fascinating that CMTM6 controls two important players in our immune system, CD58 and PD-L1, even though they have opposing functions. And what is more interesting is that when we dive into the analysis of tumor samples from patients who received ICI therapies, it appears that CD58 might just take a leading role in shaping the response, in most cases," explains Beiping Miao, one of the first authors.

Using mice to which human leukemia cells had been grafted, the team demonstrated that loss of CMTM6 protects cancer cells from CAR-T cell therapy. Additionally, in human cancer cells from tumor biopsies, widespread expression of CMTM6 and CD58 was observed, with higher expression of CMTM6 or CD58 significantly correlated with better response to immunotherapies.

"Our findings highlight the importance of CMTM6 and CD58 expression in [cancer cells](#) during an immune response against tumors. Our next step is to explore the possibility of adjusting their expression in laboratory experiments. Our goal is thereby finding a way to improve cancer immunotherapies," said Sun.

**More information:** Beiping Miao et al, CMTM6 shapes antitumor T cell response through modulating protein expression of CD58 and PD-L1, *Cancer Cell* (2023). [DOI: 10.1016/j.ccell.2023.08.008](https://doi.org/10.1016/j.ccell.2023.08.008)

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