Triple checkpoint blockade targeting PD-1, TIM-3, and LAG-3 reinvigorates ovarian cancer-infiltrating T cells by increasing T cell polyfunctionality and effector function

BACKGROUND

OBJECTIVE

METHODS

CONCLUSIONS

REFERENCES

ACKNOWLEDGEMENTS

T cells acquire multiple checkpoint receptors in response to chronic activation, including PD-1, TIM-3, and LAG-3, eventually resulting in cell dysfunction or death. Previous attempts to remove these checkpoint receptors in vitro or in vivo have been ineffective due to receptor compensation. Understanding how each checkpoint receptor is modulated or reinvigorated during triple checkpoint blockade can provide critical insight into the underlying mechanisms that drive triple checkpoint blockade.

Triple immune checkpoint blockade using inhibitory antibodies targeting PD-1, TIM-3, and LAG-3 has previously been found to improve tumor control and favorably modulate the composition of immune infiltrates in various syngeneic and humanized mouse models.1–5 Dendritic cell (DC) tumor vaccines and triple checkpoint blockade are in clinical development to target PD-1, TIM-3, and LAG-3, respectively.1 Here, we assessed how ex vivo triple checkpoint treatment with these antibodies modulates the function of tumor-infiltrating leukocytes isolated from primary ovarian cancer resections.

To achieve this goal, we defined the functional profile of ovarian cancer infiltrating T cells isolated from resection specimens by flow cytometry and mass cytometry, and then ex vivo treated these cells with triple checkpoint blockade. Our observations support the concept that triple checkpoint blockade reinvigorates multiple checkpoint receptors on T cells, thereby enhancing the functional strength of T cells at the tumor microenvironment.

REFERENCES


ACKNOWLEDGEMENTS

Edited support was provided by Heather Ondrach-Koch and Irenna Yaya and was accomplished by Kristin G. Schneider, elf of TDI/MA, Inc, Waltham, MA, USA.