868 CD122-DIRECTED IL-2/ANTI-IL-2 COMPLEXES MASSIVELY EXPAND STEM-LIKE TUMOR-SPECIFIC T CELLS AND ENHANCE ABSCOPAL RESPONSES TO RADIATION AND ANTI-PD-1

Kateryna Onyshchenko*, Ren Luo, Liqun Wang, Gabriele Niedermann. *University Hospital Freiburg, Freiburg im Breisgau, Germany*

Background Early clinical trials have provided evidence for RT-induced systemic effects in conjunction with aPD-1 or IL-2 in metastatic patients, but strong abscopal responses are clinically rare. Dual combinations of aPD-1 with more effective and less toxic IL-2 derivatives, e.g., CD122-directed pegylated IL-2, are also currently under investigation. Whether a combination of RT, aPD-1, and CD122-directed IL-2/anti-IL-2 complexes (IL-2c) can increase abscopal effects against established non-irradiated tumors is unknown. Also, in-depth analyses of the differentiation of tumor-specific $CD8^+$ T cells have not yet been reported for aPD-1/IL-2c. We investigated how adding IL-2c to hRT/aPD1 affects tumor-specific $CD8^+$ T cell differentiation and the potential of this triple combination to enhance the abscopal effect compared to the respective dual treatments.

Methods Mice bearing bilateral tumors were treated with two fractions of 8 Gy (C51 colon carcinoma model) or 12 Gy (B16 melanoma model); aPD1 was given weekly; IL-2c was given for five consecutive days. CD8 T cell-depleting and CXCR3-blocking antibodies were used to determine if the therapeutic effects depend on $CD8^+$ and $CXCR3^+$ T cells. Differentiation stages of tumor-specific $CD8^+$ T cells in tumor-draining lymph nodes, spleen, blood, and tumors were determined flow cytometrically using MHC-I tetramers and various antibodies.

Results The abscopal effect was significantly stronger in triple-treated mice compared to mice treated with RT/aPD1 (C51 model: $p < 0.01$; B16 model: $p < 0.05$), RT/IL-2c (C51 model: $p < 0.01$; B16 model: $p < 0.001$) or aPD1/IL-2c (C51 model: $p < 0.0001$, B16 model: $p < 0.01$). Moreover, triple therapy improved survival and resulted in complete cures of 3/12 mice in the C51 model and 2/12 mice in the B16 model. These anti-tumor effects were associated with dramatic expansion of tumor-specific $CD8^+$ T cells. Undifferentiated stem-like and effector-like but not terminally differentiated exhausted cells particularly strongly increased. Moreover, IL-2c induced CXCR3 mainly on non-terminally differentiated $CD8^+$ T cells. Both $CD8^+$ (C51 model: $p < 0.0001$; B16 model: $p < 0.01$) and $CXCR3^+$ (C51 model: $p < 0.0001$) T cells were crucial for the RT-induced abscopal effect upon RT/aPD-1/IL-2c treatment.

Conclusions RT/aPD-1/IL-2c triple treatment resulted in superior local and systemic expansion of tumor-specific $CD8^+$ T cells with stem- and effector-like phenotypes. Also, IL-2c strongly increased $CXCR3^+$ CD8+ T cells that were associated with pronounced abscopal responses in models with an established metastasis resistant to aPD-1/IL-2c and only transiently responding to RT/aPD-1 or RT/IL-2c. Therefore, such triple combinations appear promising for clinical evaluation in metastatic patients.

Ethics Approval All animal experiments were approved by the Regierungspräsidium Freiburg, Germany (registration numbers: G18/066, G20-016).

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