INHIBITION OF INTEGRIN $\alpha\text{v}\beta 8$ IN COMBINATION WITH LOW DOSE RADIATION INDUCES ANTITUMOR EFFECT IN ADVANCED IMMUNE CHECKPOINT BLOCKADE REFRACTORY TUMOR MODEL

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Background Integrin $\alpha\text{v}\beta 8$ activates TGF β in immune cells. $\alpha\text{v}\beta 8$ inhibitors have been shown to potentiate immune checkpoint blockade (ICB) in preclinical models [1]. Radioimmunotherapy (RIT) induces immunogenic cell death and antigen presentation, however it concurrently activates immunosuppressive pathways. Interestingly, $\alpha\text{v}\beta 8$ immunosuppressive activity was implicated in radiotherapy resistance [2]. We have explored whether antagonizing $\alpha\text{v}\beta 8$ overcomes the suppressive effect of TGF β and restores anti-tumor immunity in advanced ICB and RIT resistant tumors.

Methods Efficacy was evaluated after combination treatment with low dose radiation, $\alpha\text{v}\beta 8$ (clone C6D4) and PD-1 (clone J43) mAb in an advanced CT26 colon cancer syngeneic mouse model. Mice were treated at tumor volume of >120 mm³ and euthanized at 2,000 mm³. Flow cytometry and transcriptomic analysis were used to assess the mechanism of action. Tumor volumes are presented as mean $\pm$ SEM. Statistics were performed by one-way ANOVA, or log-rank test. Bone marrow derived dendritic cell (BMdDC) cultures were isolated from C57BL/6 mice.

Results Cell death, including radiation-induced apoptosis, induced immunoregulatory and maturation program in a population of ex vivo cultured BMdDC, recently described as mregDC/DC3 [3,4]. mregDC/DC3 signature was associated with increased $\alpha\text{v}\beta 8$ expression, suggesting a role of this integrin in inducing an immunosuppressive phenotype. A CT26 model was established to mimic the progression of late-stage tumors and was unresponsive to radiation, ICB and RIT. In CT26 implanted mice, $\alpha\text{v}\beta 8$ is expressed on tumor stroma, and is not detectable on cancer cells. Addition of $\alpha\text{v}\beta 8$ mAb to RIT markedly increased tumor regression ($P=0.0067$) and survival ($P<0.0001$). There were 8/10 complete responders with addition of $\alpha\text{v}\beta 8$ mAb relative to 3/10 in RIT alone. Improved efficacy correlated with enhanced T cell activation and improved DC functionality. Consistent with a recent report in a less advanced CT26 model [5], $\alpha\text{v}\beta 8$ mAb + radiation resulted in similar efficacy as conventional RIT although the effect was modest in more advanced tumors (Figure 1, A, B).

Conclusions Inhibition of $\alpha\text{v}\beta 8$ in combination with RIT eradicated an advanced tumor, unresponsive to the respective monotherapies or conventional RIT. The anti-tumor effect was driven by enhancement of adaptive immunity, improvement of DC function and reduced tumor tolerance. These data provide evidence that $\alpha\text{v}\beta 8$ inhibition enhances RIT and may be effective against ICB refractory tumors.

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REFERENCES

- Reszka-Blanco NJ, Yadav V, Krumpoch M, Cappellucci L, Cui D, Dowling JE, et al., Inhibition of integrin $\alpha\text{v}\beta 8$ enhances immune checkpoint induced anti-tumor immunity by acting across immunologic synapse in syngeneic models of breast cancer. AACR; Cancer Res 2021;81(13_Suppl):Abstract nr 1559.
- Jin S, Lee WC, Aust D, Pilarsky C, Cordes N, $\beta 8$ integrin mediates pancreatic cancer cell radiochemoresistance. Mol Cancer Res. 2019; 17(10): 2126–2138.
- Maier B, Leader AM, Chen ST, Tung N, Chang C, LeBerichel J, et al., A conserved dendritic-cell regulatory program limits antitumor immunity. Nature. 2020; 580 (7802): 257–262.
- Garris CS, Arlauckas SP, Kohler RH, Trefny MP, Garren S, Piot C, Engblom C, et al., Successful anti-PD-1 cancer immunotherapy requires T cell-dendritic cell cross-talk involving the cytokines IFN- γ and IL-12. Immunity. 2018; 49(6): 1148–1161.
- Dodagatta-Marri E, Ma H-Y, Liang B, Li J, Meyer DS, Chen S-Y, et al., Integrin $\alpha\text{v}\beta 8$ on T cells suppresses anti-tumor immunity in multiple models and is a promising target for tumor immunotherapy. Cell Report. 2021; 36(1): 109309

Ethics Approval All animal work was approved by the site Institutional Animal Care and Use Committee and was performed in conformance with the Guide for the Care and Use of Laboratory Animals within an AAALAC-accredited program. Humane euthanasia criteria were predetermined on the basis of body weight and defined clinical observations.

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