NATURAL KILLER CELLS IN IMMUNOTHERAPY-INDUCED MHC-I TUMOR ESCAPE

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Background Cancer immunotherapy including immune checkpoint blockade (ICB) has been successful in inducing durable responses in a variety of cancers. However, a proportion of patients who receive ICB undergo tumor relapse, putatively as result of tumor escape. A potential tumor escape mechanism is mutation of the antigen processing and presentation pathway, resulting in decreased surface major histocompatibility complex class I (MHC-I) levels. These escaped tumor cells then become invisible to CD8 T cells, which are central in the anti-tumor immune response to ICB therapy. Indeed, this type of tumor escape has been observed in relapsed patients in longitudinal studies in which mutations in $B2M$ (encoding b2-microglobulin), an essential component of classical and non-classical MHC-I, have been detected. As a result, $B2M$-deficient tumor cells lack cell surface MHC-I expression that should result in activating natural killer (NK) cells through a mechanism termed “missing-self”. Yet, the NK cell response does not appear to be strong enough to clear escaped tumor cells in all patients, as mutations in the antigen processing and presentation machinery are detected in relapsed patients. It is unclear why NK cells are unable to eliminate escaped MHC-I-deficient tumors and whether NK cells can be harnessed to prevent emergence of these escaped tumors.

Methods To address these prominent questions, we developed a methylcholanthrene-induced mouse tumor model in which $B2m$ loss can be induced with tamoxifen. The selected $B2m$ inducible knockout tumor (named BIKOT) lines were validated to lose surface MHC-I in response to tamoxifen administration by oral gavage in vivo.

Results To investigate MHC-I escape in the context of ICB therapy, we treated BIKOT-challenged mice with anti-PD1 and anti-CTLA4. Consistent with established MCA tumor models, tumors grew out progressively in untreated mice, while tumors in ICB-treated mice initially grew out after which they regressed until completely receded. The combination of suboptimal tamoxifen administration with ICB resulted in initial control of tumor outgrowth, which was followed by progressive outgrowth between week 2-3 in a proportion of animals suggesting immune escape. Indeed, relapsed tumors displayed loss of surface MHC-I.

Conclusions Taken together these preliminary data strongly suggest that the novel inducible MHC-I-deficient tumors are uniquely suited to investigate how tumors can escape T-cell recognition in face of a functional NK cell response, and furthermore provide a platform for development of NK cell-targeting therapeutics that aim to prevent tumor immune escape.

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Ethics Approval This study was approved by Washington University in St. Louis institution's Ethics Board; approval number 21-0090


Abstracts