Development of an improved humanized patient-derived xenograft, Hu-PDX, mouse model for evaluation of antitumor immune response in lung cancer

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ABSTRACT

Human tumor xenograft models are unable to replicate the human immune system and tumor microenvironment. We developed an improved humanized mouse model, derived from fresh cord blood CD34+/HSCs, and combined it with lung cancer cell line derived human xenografts or patient-derived xenografts (Hu-PDXs). Reconstitution of human leukocytes (CD45+) was detected as early as four weeks without the onset of graft vs host disease (GVHD). Repopulated human T, B, Natural Killer (NK), dendritic cells (DC), and mediated antigen specific cytotoxic T lymphocyte (CTL) responses, indicating functional activity. Growth of engrafted PDAXs and xenograft tumors were not dependent on the human leukocyte antigen (HLA) status of the donor. Treatment with the anti-PD1 checkpoint inhibitor pembrolizumab inhibited tumor growth significantly, and correlated with an increase of CTL and decrease of MDSC levels, regardless of the donor HLA type. Pembrolizumab had no effect on tumor growth in non-humanized mice. Anti-PD1 inhibitor nivolumab occurred. In conclusion, fresh CD34+/HSCs are more effective than their expanded counterparts in humanizing mice, and do so in a shorter time. The Hu-PDX model provides an improved platform for evaluation of immunotherapeutics.

References & Disclosures


CONCLUSIONS

• Humanization with fresh CD34+/HSCs are more effective than their expanded counterparts.
• Reconstitution of human leukocytes (CD45+) was faster and detected as early as four weeks without the onset of GVHD.
• Reconstituted T cells in humanized mice were functionally active and displayed antigen specific CTL response.
• Growth of engrafted PDAXs and xenograft tumors were not dependent on the HLA status of the donor.
• Strong antitumor immune responses to the anti-PD1 (Pembrolizumab) were found against PDAX and xenograft tumors developed in humanized mice but not non-humanized mice.
• The Hu-PDX model provides an improved platform for evaluation of immunotherapeutics.

Strategic development for a humanized PDX mouse model

T cell functionalities and Ag specific T cell response in Hu-PDX

Immune profiling of human immune cells in humanized mice

Human PDX and cell line xenograft tumors in humanized mice

Antitumor immune effect of pembrolizumab on Hu-PDX and Hu-lung metastasis model

Infiltration of human immune cells into humanized and non-humanized PDAXs