Liver Toxicity of Immune Checkpoint Inhibitor Drugs in Mice with a Humanized Immune System

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Immune checkpoint inhibitors (ICIs), including ipilimumab (Yervoy®) and nivolumab (Opdivo®), work by blocking specific immune checkpoint proteins, which are often hijacked by tumor cells to evade immune surveillance. Inhibiting the checkpoint activates lymphocytes to destroy tumors, but results in immune-related adverse events (irAEs) in healthy tissues. To study irAEs in the kidneys and liver, newborn BRGS mice were injected with human stem cells to develop a humanized immune system (HIS) and subsequently implanted with triple negative breast cancer cells. Non-humanized (BRGS) and humanized (HIS-BRGS) mice were treated by vehicle or a combination of ipilimumab and nivolumab (10 mg/kg, weekly, ip) for four weeks. Tumor weights were measured, and kidneys and livers were isolated to determine the concentrations of irAE biomarkers, B Cell Activating Factor (BAFF) and granzyme A, using sandwich-based ELISAs. Compared to non-treated mice, the tumor weight was 50% of decrease in humanized HIS-BRGS mice treated with ipilimumab/nivolumab. Humanizing the immune system significantly increased BAFF and granzyme A protein concentration in the kidneys, but not in the livers. ICI treatment significantly increased granzyme A and BAFF concentrations in the kidneys by 400% and 50%, respectively, while there was no significant effect on concentrations in the liver. These data suggest that lymphocyte proteins are differentially regulated in the liver and kidney toxicity associated with ICIs. As a result, pharmacological targeting of BAFF and granzyme A using inhibitors may reduce the nephrotoxicity, but not the hepatotoxicity, associated with immune checkpoint inhibitor therapy. Supported by R25ES020721, R01CA277313, and Society of Toxicology Intern Program.