Comparison and Consequences of Different Implantation Techniques on the Orthotopic Growth of Syngeneic Hepa1-6 Liver Cancer Cells

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Introduction

Checkpoint inhibitor treatment has become a common therapy of various cancer types. Still, there is a need for well-characterized preclinical mouse models, as clinical data indicates that patients only partially respond to immune-modulatory treatments.

When compared to the classic subcutaneous or subQperior™ implantation into the mammary fat pad into syngeneic mouse models, orthotypic models are considered more predictive since the implantation of tumor cells into the organ of origin allows organotypic interaction between tumor cells and the surrounding stroma, including immune cells.

Orthotopic Hepa1-6 liver tumor growth can be followed by different means of tumor cell implantation:

- Direct injection into the liver (blue)
- Via the portal vein (red)
- Via the bile duct with subsequent removal of the spleen (green)

The growth of the luciferase-transduced Hepa1-6 cells can be monitored in vivo by bioluminescence imaging.

Results

(A) Tumor growth curve of vehicle and anti-mPD-1 treated animals (left mean values, right single growth curves).

(B) Immune cell populations present near necropsy in vehicle-treated animals were determined by flow cytometry.

Fig. 1. Hepa1-6 cells were implanted into the liver of C57BL6/N mice via spleen (blue) or portal vein (red) and the growth monitored by bioluminescence imaging (BLI). Two different cell numbers were applied: 1.0 x 10⁶ cells (solid dark color shades) and 0.5 x 10⁶ cells (light color shades). Bioluminescence signal intensity is shown as single growth curves (blue via spleen, pink directly into the liver, green via portal vein) and as mean values (right).

Fig. 2. Hepa1-6 Luc cells were ingrafted by injecting cells via spleen, directly into the liver or via portal vein in C57BL6/N albino mice. Orthotopic liver tumor growth was followed by bioluminescence imaging (BLI). Two different cell numbers were applied: 1.0 x 10⁶ cells (solid dark color shades) and 0.5 x 10⁶ cells (light color shades). Mean primary tumor volume ± SEM (mm³).

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Conclusion

- C57BL6 albino rats allow early detection of bioluminescence tumor signal.
- Orthotopic tumor growth is more homogeneous than subQperior™ subcutaneous tumor growth.
- Tumor cell transplantation via spleen or portal vein results in tumor distribution throughout the liver, whereas transplantation of tumor cells directly into the liver results in confinement to the liver.
- Injections into the portal vein leads to loss of animals because of bleeding.

- Standard application of liver cells via spleen is the method of choice if the removal of the spleen is acceptable.

References