Title: Impact of heterogeneity for mismatch repair activity on colon tumor development and therapeutic response

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Scientific Abstract:

Background: Colorectal cancers (CRC) that are deficient for DNA mismatch repair (dMMR) proteins have high levels of genetic instability and consequently high mutational burden, creating numerous neoantigens that can elicit an immune response. Therefore, dMMR CRC are the best candidates for immune checkpoint inhibition (ICI) compared to proficient DNA mismatch repair (pMMR) CRC. Early clinical trials revealed that only 30-55% metastatic dMMR CRC responded to ICI. Recent studies utilizing allograft models have demonstrated that tumor immune landscape can be primed with radiopharmaceutical therapy (RPT). Although early results have been quite promising, allograft models often fail to accurately predict efficacy for many reasons, but most often are due to a lack of heterogeneity.

Methods: To better understand how heterogenous MMR expression impacts tumor development and response to ICI alone or in combination with RPT, we developed a new mouse model that develops three tumor types: (1) homotypic dMMR tumors that express green fluorescent protein, (2) homotypic pMMR tumors that express red fluorescent protein, and (3) heterotypic tumors with a mixture of dMMR and pMMR cells. Surveillance bright field and fluorescent colonoscopies allow us to assess treatment response by measuring tumor size and proportion of dMMR and pMMR tumor cells in real-time. These outcomes are verified through ex vivo imaging and histological analysis.

Results: Tumor response to anti-PD-L1 ICI was dependent on MMR status. Homotypic dMMR tumors exhibited the strongest response: significantly smaller in treated mice than controls, exhibited areas of vascular congestion and increased CD8+ cytotoxic T-cells infiltration. Response of heterotypic MMR tumors varied depending on percentage of dMMR cells; tumors with a high percentage of dMMR cells remained small, whereas tumors with a low percentage of dMMR had an outgrowth of pMMR cells. Treated and untreated homotypic pMMR tumors were indistinguishable. To enhance the response of all three tumor types, mice were treated with dual ICI treatment, anti-PD-L1 and anti-CTLA-4, or RPT. Animals administered the tri-therapy (dual ICI + RPT) survived significantly longer with fewer tumors than animals treated with either dual ICI or RPT alone.

Conclusions: Our innovative mouse model allows for the highly detailed characterization of tumor response to therapies. Simplistic allograft models may not adequately account for the dynamic effects that neighboring cell death may have on radio-resistant cells, on tumor vascular perfusion and oxygenation, or on tumor immune infiltration and adaptive immune recognition of remaining cells. We begin to fill these critical gaps in knowledge and therefore the results from our studies will help guide the translation and integrated use of ICIs and RPTs in clinic.

Written Lay Abstract:

Scientists need to study how well cancer treatments work inside a living animal before we use the treatments in humans. Scientists often use mice to study cancer treatments, but sometimes it is hard to find the same type of cancers that humans have in mice. So, for this study, the scientists changed the DNA of mice so that they would grow the type of colorectal cancer found in humans.

The first colorectal cancer type they made in the mice was deficient for DNA mismatch repair (dMMR) proteins, which means that the cancer cells have immune responses and can be treated with immune checkpoint inhibition (ICI) therapy. The second colorectal cancer type in the mice was proficient MMR (pMMR), which means these cancer cells may not create an immune response and may not be well treated with ICI therapy. The third type of cancer in the mice was a mix of both dMMR and pMMR cells, which is usually seen in human colorectal cancer.

For this study, the scientists wanted to see how well ICI therapy worked on the different colorectal cancers. They then tested if treating the colorectal cancer with radiopharmaceutical therapy (RPT) would work better than just ICI therapy alone.

The scientists found that ICI therapy worked best against dMMR colorectal cancer cells. RPT therapy worked against all of the cancer types. RPT followed by ICI was most effective against the dMMR colorectal cancer cells.

This research tells us 1) how to better use mice to test cancer therapies, 2) that dMMR colorectal cancers may be best treated by RPT followed by ICI, and 3) that colorectal cancers that include pMMR cells are not well treated by ICI but can be treated with RPT. In the future, ICI and RPT therapy may be tested in clinical trials in humans with dMMR colorectal cancer.

Visual Lay Abstract:

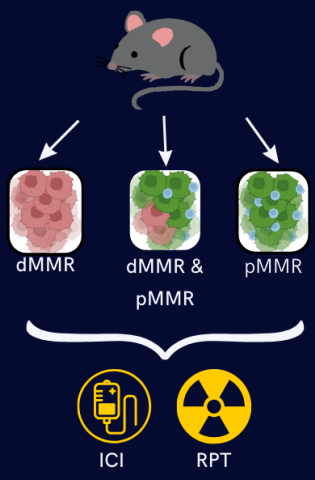
Testing Colorectal Cancer Treatments in Mice

RESEARCH ABSTRACT

WHY DO WE USE MICE TO STUDY CANCER?

Before testing cancer treatments in humans, scientists test how well they work in other animals. Mice are often used for testing because we can change their DNA, see cancers in them, and test treatments quickly. However, mice do not naturally grow all the same cancers as humans. For this study, the scientists changed mice DNA so they would grow colorectal cancers that are seen in humans.

WHAT DID WE STUDY?



Human colorectal cancer often has dMMR and pMMR cells. dMMR cells lack a DNA repair protein, while pMMR cells have the repair protein. These two types of cancer cells may need different treatments.

To study colorectal cancer treatments, scientists changed mice DNA so they would grow cancers that have dMMR, pMMR, and a mix of the two cell types.

The scientists gave these mice cancer treatments called immune checkpoint inhibition (ICI) therapy and radiopharmaceutical therapy (RPT) to see how well they worked against dMMR and pMMR cancer cells.

WHAT DID WE LEARN?

dMMR colorectal cancer cells may be best treated by RPT followed by ICI.
pMMR colorectal cancer cells are not well treated by ICI but can be treated with RPT.

WHAT'S NEXT?

ICI and RPT treatments may be tested in clinical trials in humans with dMMR colorectal cancer cells.

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