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Proposal for Finding Treatments for Liver Cancer Using Liver Organoids

Adrianna Doggett

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PROPOSAL FOR FINDING TREATMENTS FOR LIVER CANCER USING LIVER ORGANOIDS
Adrianna Doggett
Longwood University Department of Biological and Environmental Sciences
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What is an Organoid?

• An organoid is a three-dimensional model of an organ. Liver organoids can be
  made from induced pluripotent stem cells.
• These organ-like models have been used in the clinical setting for a few years
  Before organoids were created, two-dimensional in vitro cells and mouse models
  were the common modes of modeling cancer metastasis.
• Different types of organoids
  (Fig. 1, Fig. 2, and Fig. 3)

Prevalence and Treatments

• Liver cancer is the fifth most common cancer found in men and the ninth most
  common found in women.
• In 2018 there were more than 840,000 new cases.
• Around 4% of people that are diagnosed with stage four liver cancer have a five-
  year survival rate.
• Common causes
  o Diabetes
  o Cirrhosis
• Chemotherapy treatments include cisplatin, doxorubicin, and oxaliplatin
• Immunotherapy treatments include pembrolizumab (Keytruda) and nivolumab
• With both types of treatment the 5-year relative survival rates are low
  o Localized cancer 31%
  o Regional 11%
  o Distant 2%

Specific Aim

• Find an effective model for treating liver cancer at all stages of growth by using
  tumor organoids.
• Tumor organoids will be introduced to different treatments at varying dosages in
  order to measure the changes in tumor growth.
• Hypothesis: Liver tumor organoids will be effective models for testing
  chemotherapy and immunotherapy drug effectiveness in treating liver cancer.

Potential Pitfalls

• Organoids are still relatively new concept in organ modeling.
• Expenses can add up when growing and maintaining organ models.
• Human models will require strict protocol for maintaining the organ-tike tissue.
• Potential ethical problems associated with the use of human tissues in the lab.

Potential Conclusions

1. The liver tumor organoids grown directly from patient tumors will be the more
   effective model for testing immunotherapy and chemotherapy drugs (Part A in
   Figure 4).
2. The healthy liver cells induced into cancerous cells could be a model for learning
   how cancer affects an individual and how an individual will respond to various
   treatments (Part B in Figure 4).
3. Neither cultured liver organoids will be a good model for understanding the
   mechanism of liver cancer, or how immunotherapy and chemotherapy drugs
   affect liver tissue in the human body.
   For liver tumor organoids to fit my hypothesis:
   o Tumor regression would be seen in effective drug environments.
   o No onset of tumor growth seen in a treated, cultured organoid.

Methods

- Patient liver tumor cells will be directly suspended in Matrigel. Growth factors will be added to the tumor cells, allowing them to mature in a 3-D shape (Fig. 4, part A)
  - Chemotherapy drugs at several different concentrations will be introduced
  - Immunotherapy drugs at several different concentrations will be introduced
- Healthy liver tissue will be added to the Matrigel. Gene editing will transform them into tumor organoids (Fig. 4, part B)
  - Chemotherapy drugs at several different concentrations will be introduced
  - Immunotherapy drugs at several different concentrations will be introduced
- Comparison of tumor differences between the different treatments and different growth protocols (Fig. 4, part C and Fig. 5)

Citations