A Mouse Breast Cancer Model Study for a Mathematical Model Predicting Tumor Relapse After Long Dormancy

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1. Background:

Lesi and Heilmann (2019) developed a mathematical model for how large populations of tumors of different sizes in a large cohort of patients evolve in time due to cell division, death and metastasis[1]. When ratios of data-derived parameters are in certain ranges, the model predicts reappearance of seemingly eradicated tumors after many years. The model describes experiments carried out for it on melanoma in zebrafish extremely well and provides insight into gender disparities in melanoma, but the derived parameters were not in the range for long-term recurrence. The only non-human cancer with some experimental evidence of long-term recurrence after treatment is a mouse model of breast cancer[2,3]. With this model we begin by measuring the tumor size distribution from three sets of mice, each sacrificed a different amount of time after inoculation with tumor cells. The method that we use is histology (Fig. 1). Since such cancers mainly initiate metastases to the lungs early on, we examine thin slices of the mouse lungs that have been preserved in formalin and then stained so that one can visually distinguish between tumor and normal tissue and measure tumor sizes. In order to understand the effect of immunity, we also compare tumors and metastases in three other sets of mice, normal and immune-deficient of the same strain and mice of a different strain, all inoculated with tumor cells native to the first strain. These tumors should fool the immune system of the native mouse - so we don't expect differences between the first two groups, and we will see how long it takes for the third group's immunity to recognize the cells. We also will see if there are differences in metastases between the first two groups and if any metastases survive eradication in the third.

2. Overview

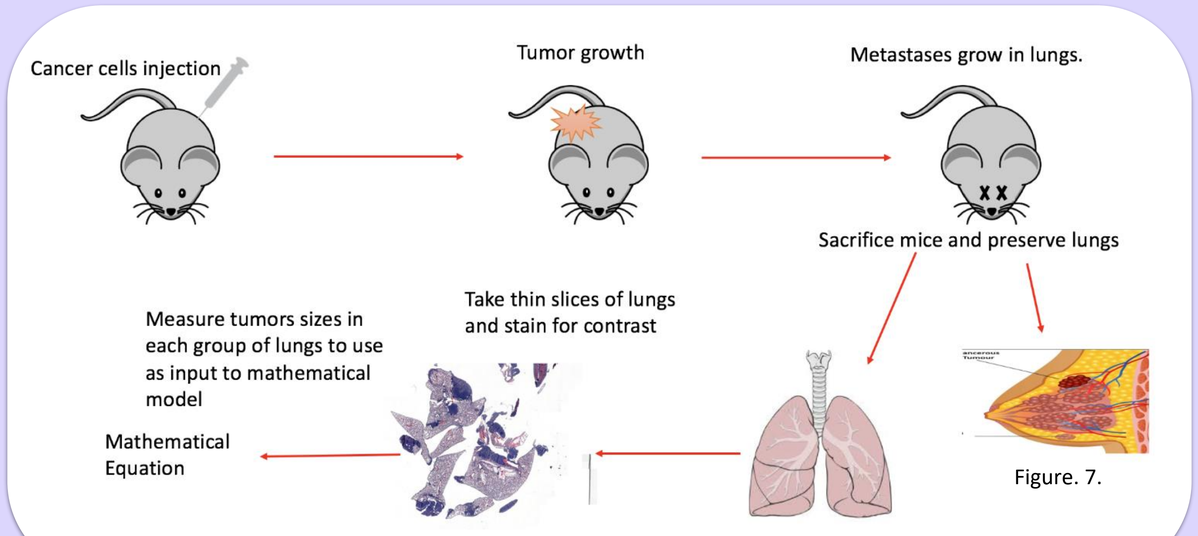

Figure. 2. Procedure for the experiment.

This is a flowchart (Fig. 2) of the procedure for the Experiment. First, each mouse is injected with breast cancer cells at day 0. They are observed for one of three different times (weighed, measured several times per week) until they are sacrificed. Their lungs are removed, preserved in formalin, thinly sliced and stained. The metastases in these sections are identified and counted The data collected is then put together in the form of histograms at three different time points that the mathematical model uses as inputs to determine its parameters.

3.

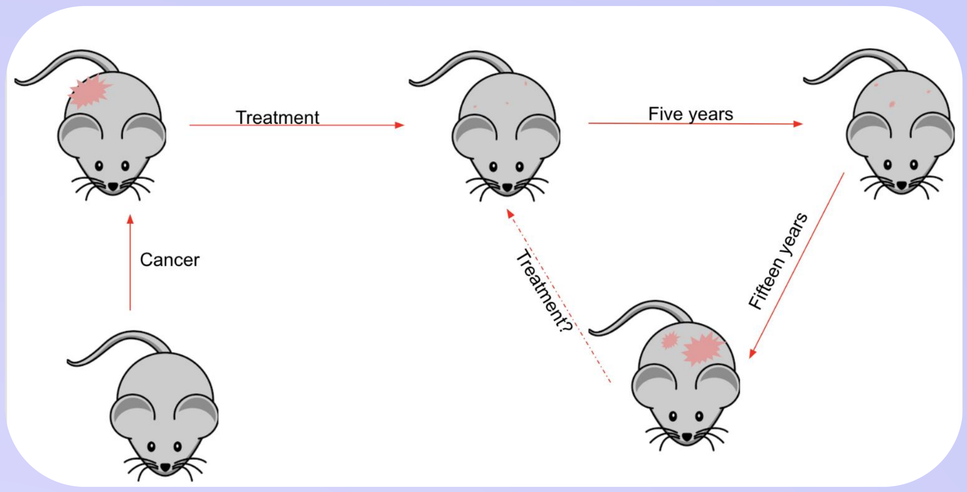

Figure. 1. A diagram of dormancy in cancer.

4. The Balb/c and SCID Mice Hosted Tumors that Gradually Grew while the C-57 Mice Eventually Terminated the Tumors

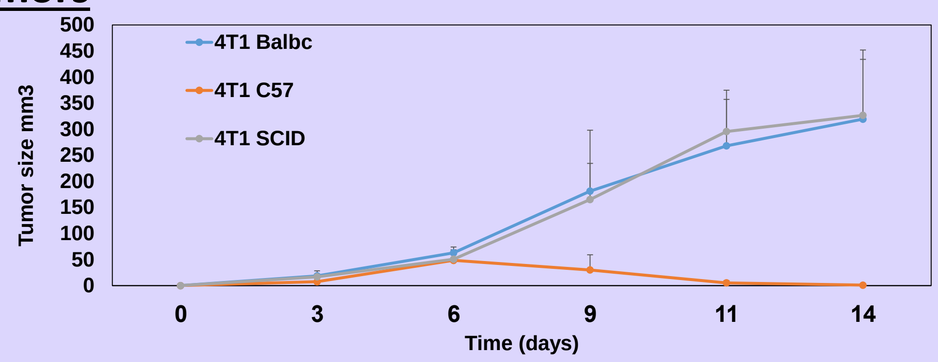

Figure. 3. Illustration of the relationship between time and size of tumors, comparing different mice types, Balb/C, SCID and C-57.

5. Average Area of Metastases Relative to the Overall Lung Area

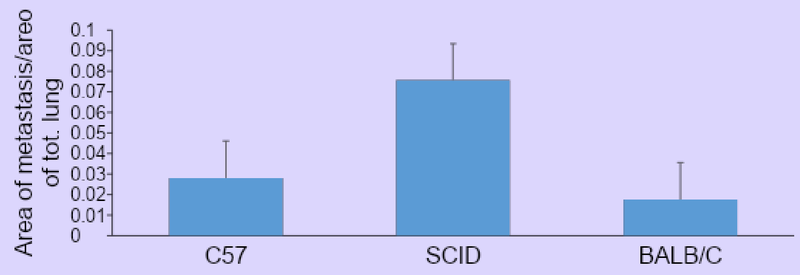

Figure. 4. Immune background of the mice interfere in the number of metastasis.

6. EMT6 Tumor growth (breast cancer) in Balb/C mice

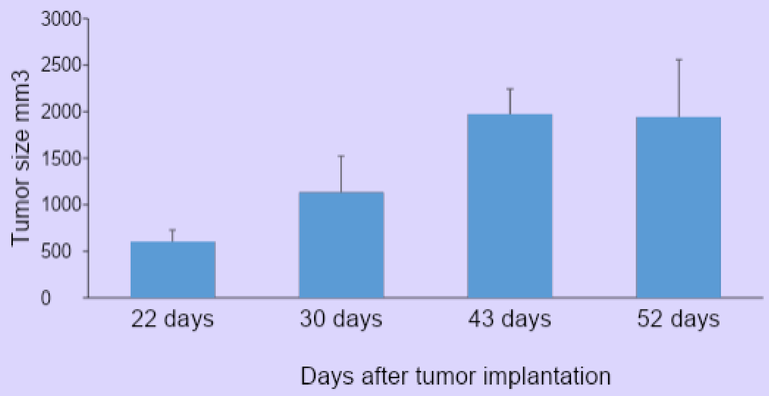

Figure. 5. Increased of tumor growth by time.

7. Average Area of Metastases over time in EMT6 tumor bearing mice

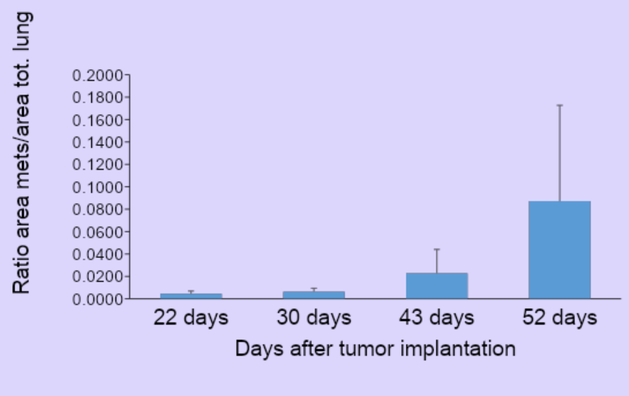

Figure. 6. Rapid growth of metastasis when compared to the tumor size.

8. Future Predictions

More data has to be gathered on the metastases in mice lungs. Additionally, after the formula is developed, More tests will have to be done to confirm the accuracy. After the formula has been deemed accurate, it could predict the likelihood of metastasis in cancer patients, allowing for the doctors and patients to have more certainty that they are healthier. This means that the doctors would know when to check up on the patients more and catch the possible new tumor before it becomes a major issue.

9. Discussion and Conclusions

1. Primary tumor in Balb/c and in immune-deficient Balb/c SCID mice grow equally fast, yet the latter seem to have far more metastases (Fig. 4).
2. C57 black mouse primary tumors grow exactly as other two groups for the first 6 days. At day 6 ,though, the C57 immune system kicks in and quickly (likely exponentially) eradicates the primary tumor. Interestingly the metastases do not seem to be eradicated (Fig. 3).
3. The metastases in the C57 mice appear to be larger than in the regular Balb/c mice (Fig. 4). This is likely due to the small amount of data gathered – only two slices per mouse lungs. We believe that with far more data per lung, the relative amounts of metastases in these mice will be quite different. Nevertheless, the fact that metastases survive in the C57 mouse despite loss of primary is interesting and may allow for long-term recurrence (Figs. 5 and 6).
4. More data is needed to get tumor size histograms needed as model inputs.

10. References

1. Adeyinka A. Lesi, Silja Heilmann, Richard M. White, David S. Rumschitzki, "A New Mathematical Model for Tumor Growth, Reduction and Metastasis, Validation with Zebra sh Melanoma and Potential Implications for Dormancy and Recurrence," bioxriv (preprint form) 2019.

2.Soledad Sosa M., Bragado P. and A. Aguirre-Ghiso J. (2014) "Mechanisms of Disseminated Cancer Cell Dormancy: an Awakening Field".

3. Furrukh M., Qureshi A. "Treatment of breast cancer; review & updates. J Ayub Med Coll Abbottabad" 2018;30(2):264–74.

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