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POSTER ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Application of State Transition Theory and Treatment Modeling for Predicting Response to Chemotherapy in a Mouse Model of Acute Myeloid Leukemia

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Acute myeloid leukemia (AML) is a cancer of the myeloid line of blood cells, and the cancer originates in the bone marrow (BM) and circulates the body through the peripheral blood (PB), which can rapidly lead to BM failure and death. AML initiation and progression are composed of multiple biological properties, and we have previously shown that the state transition theory, state-space, and a model of the stochastic differential equation (SDE) could predict AML disease evolution using the mRNA of a conditional Cbfb-MYH11 (CM) knock-in mouse model. The model of the SDE represents AML evolution from health to disease as a state transition of the transcriptome state described as a particle undergoing Brownian motion in a double-well quasi-potential, where critical points define states of healthy state, c1, transition to AML, c2, and overt AML, c3. Along with the disease evolution of AML, prediction, and understanding of AML disease responses from chemotherapy aiming to provide optimized therapeutic strategies are required. Analyzing disease responses to chemotherapy from the state transition theory perspective will give us an understanding of post-chemotherapy disease dynamics and useful predictions which have the possibility to optimize treatment processes.

To test the applicability of the AML state transition model, a time-series experiment using the conditional CM knock-in mouse model and state-transition modeling were performed. The mouse model was designed to recapitulate the human inv(16) AML, the leukemogenic fusion gene Cbfb-MYH11 (CM) in conditional CM knock-in mice (Cbfb56M/+/Mx1-Cre) cause the development of AML with a median survival of approximately 4 months after induction of CM. To induce CM expression, 6-8 weeks old CM knock-in mice were injected intraperitoneally with polyinosinic-polycytidylic acid [poly (I:C)] (InvivoGen, tlrl-picw-250) at 14 mg/kg/dose every other day for a total of 7 doses. CM leukemic mice were treated with a combination of cytarabine (50mg/kg/day; 5 days) and daunorubicin (1.5mg/kg/day; 3 days) after detection of overt leukemia, which is monitored by circulating leukemia blast (cKit+ > 20%) to model the 7+3 standard of care treatment for newly diagnosed AML. We used three independent experiments of mice as training and test cohorts (Group 1, Group 2, and Group 3). We collected 42 PBMC and 1 BM from CM-induced mice from Group 1 (4 AML and 1 control), 68 PBMC and 2 BM from Group 2 (4 AML), and 64 PBMC from Group 3 (3 AML and 2 control). The samples were collected weekly before, during, and following chemotherapy and subjected to RNA sequencing.

The effects of chemotherapy were observed in the AML state-space with chronological time points as the transcriptome particle moving from leukemia state, c3, towards a state of healthy state, c1, crossing the unstable state, c2. The relapse was defined as the time of the first observation after the particle crosses back over unstable state, c2, towards the leukemic state, c3. The 10 AML mice out of 11 AML mice achieved a partial response with a mean time to relapse of 5 weeks. All 11 AML mice showed the anti-correlation between AML state in the state space was anti-correlated with the blast percentages (ckit%).

We modified the state transition treatment model by introducing a parameter, γ, and the half-life of cytarabine (31.1 hours) and daunorubicin (21.9 hours). The gamma parameter is a force that works against the double-well quasi potential ($\gamma > 1$) and represents the anti leukemogenic effects of cytarabine and daunorubicin. Gamma was determined by fitting the model to 6 AML mice data from the training cohort. The value was determined to be γ=2.7, providing a novel quantification of the treatment effect. We performed a mean arrival time analysis using simulations of the state transition treatment model, which accurately predicted the time to relapse with a prediction error of 6.6 days for the 3 AML mice from the test cohort.
We could apply the state transition theory and propose the state transition treatment model to simulate the treatment process and the response from chemotherapy. Our model accurately predicted the time to respond to chemotherapy, from leukemia to health, and relapse, from health to leukemia, in the CM mouse model after chemotherapy. The state transition treatment model has implications for improving therapeutic strategies by targeting transcriptome state transition critical points in human AML.

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