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ORIGINAL ARTICLE

Entropic analysis reveals a connection between the recurrence of cancer and chemotherapy

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Abstract In this study, we proposed an entropic analysis to overcome limitations of conventional statistical methods to analyze clinical data for cancer patients who experienced relapse of tumors following chemotherapy. We have applied this entropic method to reveal potential mechanisms that lead to a relapse of Wilms' tumor in pediatric patients. Results indicate β-tubulin isotype III up-regulation is likely the primary cause of the relapse.

1. Introduction

Relapse of tumors has been a major clinical challenge after patients received treatments either involving surgical removal, radiotherapy or chemotherapy (Boisgerault et al., 2013). Researchers and clinical practitioners have attempted to correlate clinical results and potential risk factors to identify molecular mechanisms of relapse including EGF-like growth factor over-expression (Tagliabue et al., 2003) in breast cancer and up-regulation of several genes (e.g. CLDN16 and TJP3) in ovarian cancer (Laios et al., 2008). Besides biological factors, healthcare providers have reported that a common question from patients is whether stress factors may be playing a role in triggering the relapse of tumors. However, some studies did not find any relationship between stress response and cancer relapse (Todd et al., 2014).

Therefore, many attempts have been subsequently focused on determining biological mechanisms of relapse at a molecular level aimed at eventually developing improved treatments. For example, an integrative model for relapse in ovarian cancer was developed to identify genes that can be related to the relapse and can become the target for better therapy aimed at decreasing drug resistance and optimizing the efficacy of existing drugs (Laios et al., 2008).

Our goal is to develop an information-driven approach in order to interpret clinical data based on the available information relevant to binding properties of drugs and biological targets. Results of this approach may reveal deeper insights into mechanisms of the relapse of cancer after patients receive chemotherapy. We hope this will unveil new directions in the redesign of drugs to overcome cancer recurrence.

The foundation of the proposed approach is based on information theory. Information theory has been shown to be an appropriate and robust method to make inference from insufficient data to resolve problems in complex systems

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(biological systems and drug discovery are but two examples of numerous applications) with the least bias (Tseng and Tuszynski, 2014). Particularly, the method of maximum entropy (ME) has been proved to be a powerful tool for inductive inference to objectively process information (Giffin et al., 2007; Caticha et al., 2007). Tseng and Tuszynski further reviewed and demonstrated that drug discovery can substantially benefit from the method of ME (Tseng and Tuszynski, 2014). Therefore, based on this method, we proposed an entropic analysis approach. Since the method of ME is a universal inductive inference tool (Giffin et al., 2007; Caticha et al., 2007), the proposed method can be applied to study the relapse of different types of tumors as long as information used is relevant to the problem of interests.

To demonstrate the use of the entropic analysis approach, we consider a case study, which was designed to uncover possible mechanisms of the relapse of Wilms' tumor in pediatric oncology patients. As has been already shown through metastudies, although the treatment protocols developed either by the National Wilms' Tumor Study Group (NWTSG) or the International Society of Pediatric Oncology (SIOP) over the years have an increased patient survival rate, there is still approximately 15% of WT patients who developed relapse of the disease (Geller and Dome, 2010). Therefore, one clinical challenge in treating Wilms' tumor is to investigate mechanisms of the relapse of Wilms' tumor in patients who received tubulin-target based chemotherapy including the drug vincristine. Specifically, the meta-study conducted by Grundy in the Pediatric Oncology Group at the Cross Cancer Institute, Edmonton, was aimed to determine whether variations in the tubulin isotype expression may be responsible for drug resistance and correlate these findings with two stages of relapse (early and late).

Fig. 1 shows the mean expression levels of 13 samples (sample ID and six β-tubulin isotype types are listed in Table 1) from 78 measurements in this case study (Grundy). Fig. 2 shows the

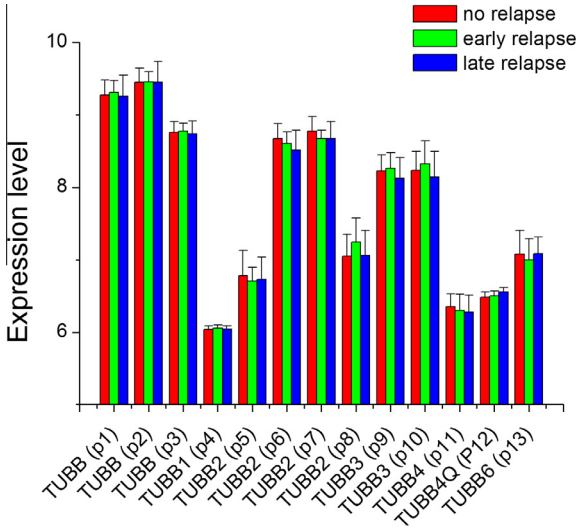

Figure 1 Histogram of mean expression level of β-tubulin isotypes, the gene names are recorded in the x-axis, for the treated patients who are at three stages of relapse of Wilms' tumor. Note that the label inside parentheses is the short annotation for probe sets used in the studies. The original annotations are shown in first column in Table 1.

detailed distribution of all expression levels in each sample. It includes 56 cases where there is no relapse of tumor after tubulin-target chemotherapy treatments, 10 cases are found to have early relapse and 12 cases show late relapse. As shown in Fig. 1, it appears that there are no significant differences in the mean expression values among the different stages of relapse of tumors for each tubulin isotype in each sample. Yet the differences in the expression level distribution for each tubulin isotype in each sample in Fig. 2 seem to disagree with the results from the mean values. Since there are no significant differences in the mean values, we can expect that commonly used statistical hypothesis tests are unlikely to provide meaningful insights. The question that arises is whether we can make any inferences based on the histograms in Fig. 2 to gain insights into the role of β-tubulin isotypes in the relapse of tumors. This question is exactly the problem that the method of ME is designed to answer based on insufficient data.

According to the proposed entropic analysis, we showed that the late relapse is primarily associated with β-tubulin isotype III expression levels. Namely, β-tubulin isotype III over-expression is likely to be the key reason for drug resistance. This result combined with the conclusions by Tseng et al. (2010), which indicate β-tubulin isotype III as the most important molecular target to inhibit microtubule polymerization and eliminate cancer cells, suggests a potential combination chemotherapy, which targets not only β-tubulin isotype III but also its possible mutations.

2. Methods and materials

2.1. Entropic analysis

The proposed approach is based on the method of ME. The foundation of the method of ME hinges on the Bayesian interpretation of probability and the rules of probability theory. The former treats probability as a measure of our state of knowledge about the system of interest rather than a frequency of occurrence of an event. The latter demonstrates that this type of probability can be manipulated by the rules of subtraction, multiplication and addition given by the standard probability theory (Giffin et al., 2007; Caticha et al., 2007). These two tools form the building blocks for inductive inference and its core is the concept of entropy. The most important factor in applying this scheme to solve specific problems is to ask "the right question". Afterward, the principle of ME indicates the most preferable inference one can make to answer that question is the one that maximizes entropy of the problem of interests. Furthermore, the method of ME indicates that given two probability distributions of a system at a specific state i, $P_1(i)$ and $P_2(i)$, the relative entropy of these two probability distributions:

$$S(P_1, P_2) = -\sum_i P_1(i) \log \frac{P_1(i)}{P_2(i)} \leqslant 0, \tag{1}$$

is shown to quantify the difference between these two probability distributions. Furthermore, when $P_2(i)$ is set to a reference distribution (for example, it can be a uniform distribution to represent our complete ignorance of the system of interest), one can utilize this relative entropy to represent a preference scale to rank possible probability distributions of the system (Tseng, 2006; Chen et al., 2007).