A central challenge in cancer biology is to understand of the strategies followed by cells to overcome the effect of anticancer drugs (Smith, Khan, & Errington, 2009). Cancer, a highly complex and heterogeneous disease (Heppner, 1984; Rubin, 1990), can be described as an evolving system, that can be best illustrated by cell lineages. In experimental terms, a cell lineage reflects the relationship between descendents from a common progenitor that was exposed to a given influence, such as a bioactive drug, for a time period. The behaviour of both the progenitor and the evolving progeny reveals the time-integrated response to this influence (i.e., the pharmacodynamic response). The study of cell lineages has been, and remains, of importance in developmental biology (Stern & Fraser, 2001; Alvarez-Buylla, García-Verdugo, & Tramontin, 2001; Anderson, Gage, & Weissman, 2001; Ardaní et al., 2001; Dor, Brown, Martinez, & Melton, 2004; Kim & Shibata, 2002; Noctor, Flint, Weissman, Dammernan, & Kriegstein, 2001) and medicine (Bernards & Weinberg, 2002; Hope, Jin, & Dick, 2004; Tang et al., 2003; Weigelt et al., 2003; Yamamoto et al., 2003).

DOI: 10.4018/jkdb.2010100102
Here we select and apply appropriate data mining techniques that provide interpretable models on previously encoded cell lineage data (Khan et al., 2007), in order to reveal the degree of heterogeneity of a tumor system in response to therapy, as well as the strategies (or patterns) the resistant fraction incorporates in order to overcome the effect of the anticancer drug and thus maximize their clonal expansion potential.

DATA

Biological Sample Preparation

The human osteosarcoma cell line [U-2 OS (ATCC HTB 96)]23], derived from a 15-year-old Caucasian female and transfected with a fluorescent reporter cyclin B1 GFP, is selected. The cells are maintained at 37 °C and 5% CO2 using standard tissue culture techniques. Media used is McCoys 5A modified (Sigma) supplemented with 2 mM glutamine, 100 units/ml penicillin, 100 mg/ml streptomycin, 10% fetal calf serum and 1000 mg/ml genetin.

Cells are treated with 1 µM and 10 µM bolus dose of anticancer agent Topotecan (TPT) (Bailly, 2000). TPT is a water soluble derivative of the alkaloid Camptothecin and act as a topoisomerase I, a nuclear enzyme involved in DNA replication and repair, inhibitor (Wang, 1996). TPT is used for the treatment of a wide range of cancers, including lung (Ichinose et al., 2010), breast (Cheung et al., 2008), ovarian (Lorusso et al., 2010) and bone (Seibel et al., 2007), both in experimental and clinical contexts.

An hour post treatment, the cultured dishes are placed onto a time lapse instrument designed to capture transmission phase images from multi well plates. Image sequences are taken for 115 hours at 15-minute time intervals. The cell lineage data is encoded by ProgeniTRAK (Khan et al., 2006) and is retrieved from a cell lineage database ProgeniDB (Khan et al., 2007).

Cell Lineage Data

Information from 253 lineages is available: 168 are Control, 37 are 1µM and 48 are 10µM lineages. Each lineage is characterised as a tree where the genealogy of the Progenitor cell and its offspring is represented.

Figure 1 shows an example of a Control lineage along the experiment; we observe that Sixth Generation is reached in the 115 hours. Figure 2 shows the encoding, along with the labeling convention (refer to Table 1 for notation): an arc between two successive nodes, where both nodes represents dividing (mitosis) cells, indicates the cell cycle time or inter-mitotic-time (IMT). In labeling terms, for example, Cell1_1 and Cell1_2 in Figure 2 are sisters; both are daughters of Cell1_1, which is a daughter of Cell1_1, which is again a daughter of a Progenitor cell. The daughters of a Progenitor are termed First Generation cells (Cell1_1 and Cell1_2 in Figure 2). The daughters of the First Generation cells are termed Second Generation cells (Cell2_1,…, Cell2_4 in Figure 2), and so on.

Data Transformation. Sister cells are sorted according their statuses (following the order given in Table 2) and when both cells divide, the one with shorter IMT goes first. For example, if both First Generation cells divide, the one with shorter IMT is labeled as Cell1_1 and the other as Cell1_2. The daughters of Cell1_1 are called Cell2_1 and Cell2_2, and are sorted according their
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