Comparative expression analysis of primary tumors and cell lines reveals distinct patterns of expression of membrane-associated protein genes

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Motivation

Much of the current knowledge in cancer biology is based on studies on tumor cell lines. As compared to primary tumors, tumor cell lines have the advantage to easily grow in vitro as monolayers, providing a virtually unlimited amount of material for different types of analysis and overcoming the limitations on the abundance of primary tissue samples. Cancer cell lines have been used to determine the phenotypic properties of cancer cells such as proliferation rates, migration capacity and ability to induce angiogenesis. Moreover, in pre-clinical drug research cell lines are normally the first biological system that is used to validate a drug target or to assess drug sensitivity and effectiveness of anti cancer drugs. Despite the wide usage of cell lines in cancer research, there is only a limited knowledge of the molecular differences between cell lines and their primary tumor counterparts. A deeper understanding of the relationships between the two biological systems is therefore essential to empower the employment of cell lines in cancer studies. In the present work, a panel of cell lines derived from different tumor tissues has been compared to the corresponding primary tumors focusing on the genes coding for the membrane-associated proteins (here referred globally as the membranome genes). Cell membrane proteins play an essential role in cell biology as they include transporters, signal transduction receptors and proteins involved in cell-cell adhesion. Most noticeable these proteins are the ideal targets for cancer Ab-based therapies.
Differences between the primary tumor and the corresponding cell line have to be carefully considered when using cell lines as in-vitro model for anti-cancer Ab studies.

Methods

To identify the set of human plasma membrane proteins within the NCBI Human Gene database we applied a combined analysis based on the Gene Ontology annotations and the Phobius transmembrane segment and signal peptide prediction algorithms. The derived gene list was manually revised by adding known membrane associated proteins from the literature and by removing proteins associated with intracellular compartments. This allowed the estimation of a total number of about 4,400 proteins exposed on the cell plasma membrane, representing about 17% of the all human genome.
The expression analysis was carried by using public data primary tumors and cell lines on nine tumor types. The data were generated using the Affymetrix Hu95a arrays carrying 12.533 probe sets corresponding to 9.059 human genes; of those 1.731 were classified as membranome genes. By using ANOVA the overall transcriptional variance in both tumor cell lines and primary tumors was assessed. To identify the membranome genes differentially expressed between the cell lines and their cognate tumor of origin the Significance Analysis of Microarrays package (SAM) was carried out.
Enriched classes of genes among the differentially expressed ones were then identified by using the Gene Set Enrichment Analysis (GSE).

Results

Our results indicate that membrane protein genes contribute, more than the not-membranome ones, to the overall transcriptional variance in tumor cell, either derived from primary tumors or cell lines. Similarities and differences in the membranome expression between cell line samples and their primary tumor counterparts were studied and membranome gene expression patterns unique to cell lines or to primary tumors could be identified. Such patterns have probably to be ascribed to factors related to the different cell culture environment. The membranome genes were classified into different groups according to their expression patterns and annotated based on the biochemical pathways. Interestingly, a number of membranome functional classes could be identified that were more relevant in defining the transcriptional differences between primary tumors and cultured cell lines. These findings contribute to the elucidation of the opportunities and limitations of the use of cancer cell lines for drug development studies, in particular the ones targeting membranome antigens such as anti-cancer monoclonal Abs.

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