Molecular Pathology of Patient Tumors, Patient-Derived Xenografts and Cancer Cell Lines

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In life for life

Introduction

Cancers are heterogeneous diseases with diverse pathogenesis. Clinical diagnosis is primarily based on anatomic location (organs) and histopathology (morphology of cancerous tissues and cells), and may not be accurate. For example, a metastasis could be misdiagnosed if the morphology is insufficient to identify its origin. An improved diagnostic method is therefore needed. Transcriptome sequencing (RNA-seq) profiles gene expression, which may be used to describe molecular pathology and diagnose cancers. However, first, it is necessary to systematically demonstrate that good correspondence exists between histopathology and molecular pathology, which has been made possible by the availability of pathology and genomic data from The Cancer Genome Atlas (TCGA) project that profiled thousands of cancer samples of various histopathology types.

Patient derived xenografts (PDXs), never manipulated *in vitro,* are considered patient avatars and used as experimental models to study pathogenesis, assess pharmaceutical effects, and guide precision medicine. Various anecdotal reports have shown that the xenografts mirror corresponding patient disease in histopathology and molecular pathology. If such similarity is systematically verified and, further, quantified, the translational utility of PDXs can be immensely explored and expanded. We have built a large library of PDXs over the years and performed transcriptome sequencing. The pathological relevance of PDXs to patient tumors, both histologically and molecularly, can now be examined by combining data from TCGA and PDXs.

In this study, we established a new diagnostic method based on pairwise comparison of TCGA cancers using transcriptome data. We then systematically compared similarities of TCGA cancers both within and between histopathology types, explored the relationships of diverse types, and developed algorithms to classify human and xenograft diseases. Our data showed that PDXs are indeed similar to their original diseases in various cancer types, which does not hold true for cancer cell lines.

Results

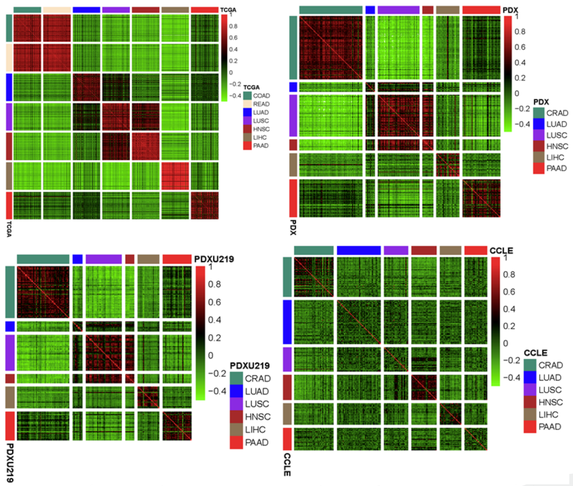

Figure 1: Heatmaps representing Pearson correlation coefficient between samples within 4 datasets when the number of pairwise DEGs is 50. DEG: differentially expressed genes. PDX: PDX with RNA-seq data. PDXU219: PDX with Affymetrix U219 data. CCLE: Cancer Cell Line Encyclopedia, cancer cell lines with Affymetrix U133 Plus 2 data.

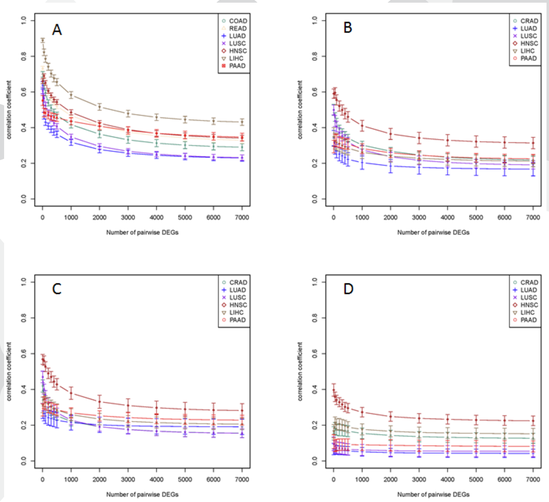

Figure 2. Change of within-type Pearson correlation coefficient by the number of pairwise DEGs in 4 datasets: TCGA (A), PDX(B), PDXU219(C), and CCLE(D).

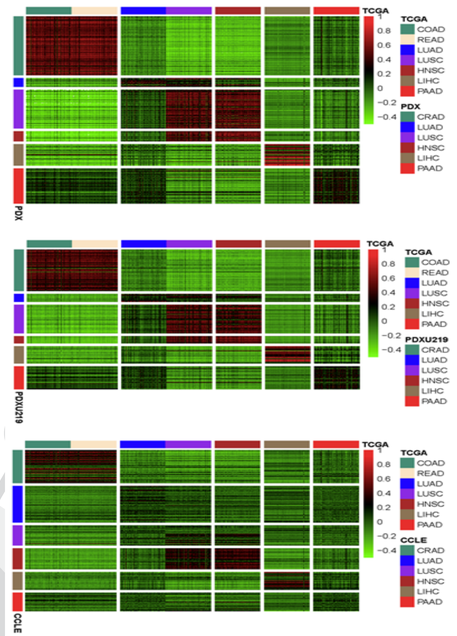

Figure 3. Heatmaps representing Pearson correlation coefficient between TCGA samples and samples in the other 3 datasets.

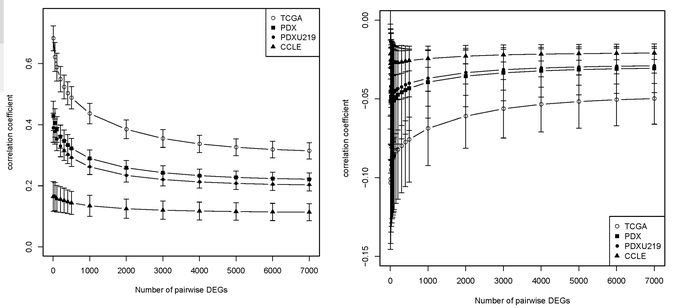

Figure 4. The within-type (left) and between-type (right) Pearson correlation coefficients in 4 datasets, with average and standard error plotted.

Conclusions

1. The relatively high within-type, as opposed to between-type coefficients, demonstrate cancer type specificity, which is largely in accordance with histopathology classification.

2. The within-type correlation coefficients initially decrease rapidly then stabilize for all cancer types as the number of DEGs increases, in both TCGA patient samples and PDX models, but much less so in cell lines.

3. Patient derived xenografts (subcutaneously engrafted tumors) still maintain reasonable specificity, although not to the extent of human tumors, and are markedly better than cancer cell lines.

4. Colon adenocarcinoma (COAD) and rectum adenocarcinoma (READ) are virtually indistinguishable. Head and neck squamous cell carcinoma (HNSC) is highly similar to lung squamous carcinoma (LUSC) by expression profiles.

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