

Selective drug sensitivity score (DSS) for indolent and aggressive prostate cancer cell lines

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Introduction

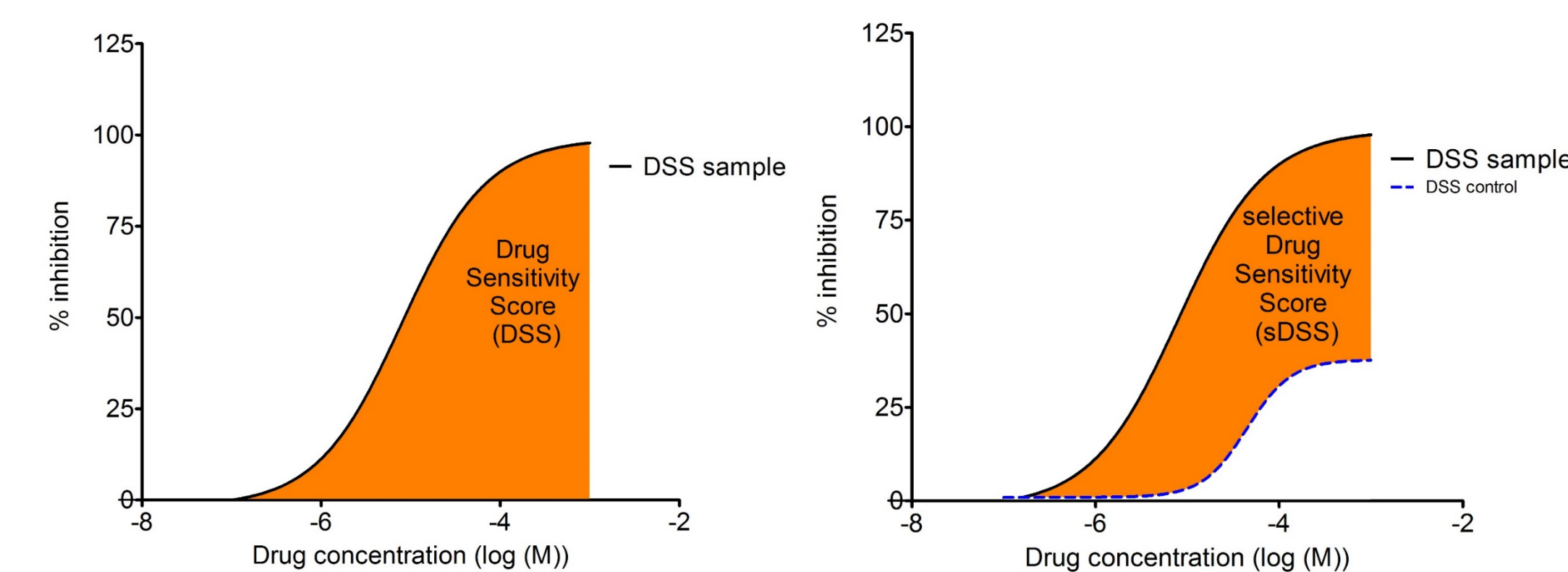
Prostate cancer (PC) is the most common malignancy in men and the second leading cause of cancer-related deaths. The majority of PCs are classified as adenocarcinomas characterized by the expression of androgen receptor (AR) and prostate-specific antigen (PSA). Two of the most commonly used cell lines are LNCaP and PC-3 cells, derived from lymph node and bone metastases, respectively. In addition to these, VCaP cells, derived from vertebral metastases, are widely used in prostate cancer research. It has been well established that LNCaP and VCaP cells represent the conventional indolent form of PC expressing AR and PSA and are androgen-dependent. PC-3 cells, on the other hand, do not express AR and PSA, are androgen-independent, and represent the highly aggressive form of PC.

Aim of the Study

Our goal was to compare the response of LNCaP, VCaP and PC-3 cells to a large panel of known anti-cancer compounds and determine the differences and similarities in sensitivity between these cell lines.

Materials and Methods

Drug sensitivity of the cell lines was assessed by applying a large panel of drugs covering both cancer chemo-therapeutics and many clinically available and emerging molecularly targeted drugs including conventional chemotherapy, kinase inhibitors, metabolic modifiers, rapalogs, differentiating/epigenetic modifiers, kinesin inhibitors, apoptotic modulators, NSAIDs, hormone therapy, immunomodulators and HSP inhibitors. A panel of about 460 compounds was tested in five concentrations covering a 10,000-fold drug-relevant concentration range in 384-well format. Cells were seeded to pre-drugged plates, followed by cell viability measurements (CellTiter-Glo) after 72 hours. Maximal and minimal responses to drugs were analyzed, the EC50 values were calculated and Drug Sensitivity Score (DSS) was calculated for each drug as a measure of reduced viability (1-3). A selective Drug Sensitivity Score (sDSS) was calculated to identify the selective drug response pattern of a cancer cell line (1-3).



Results / Drug sensitivity score (DSS)

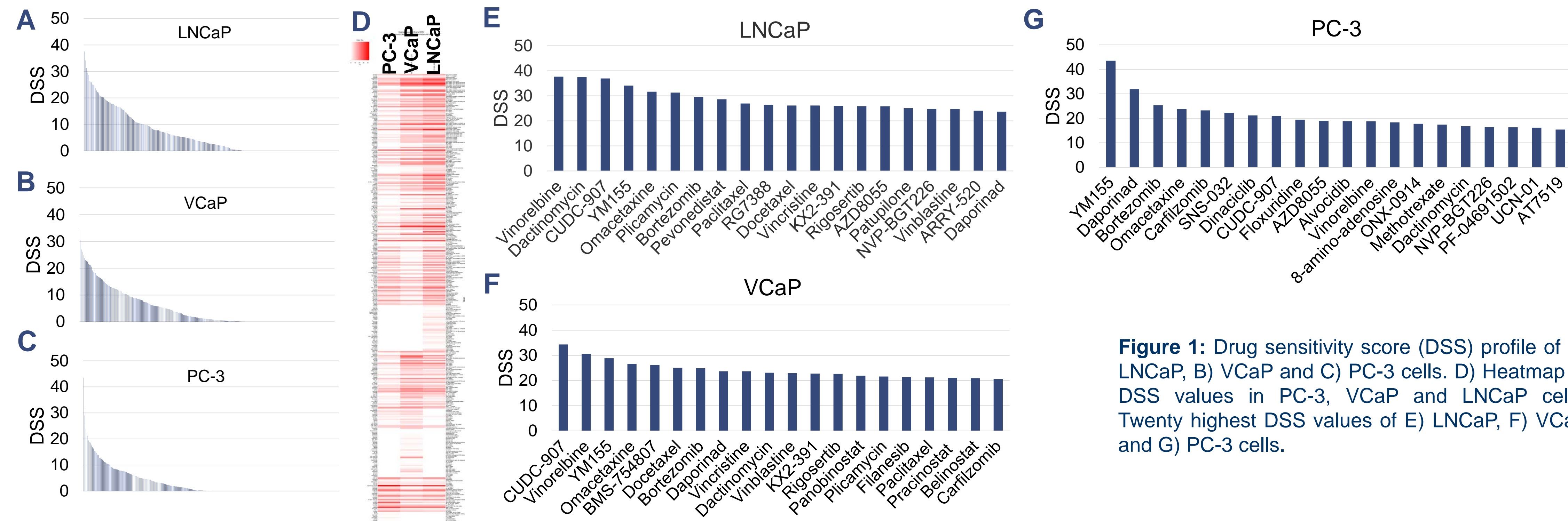


Figure 1: Drug sensitivity score (DSS) profile of A) LNCaP, B) VCaP and C) PC-3 cells. D) Heatmap of DSS values in PC-3, VCaP and LNCaP cells. Twenty highest DSS values of E) LNCaP, F) VCaP and G) PC-3 cells.

Results / Selective drug sensitivity score (sDSS)

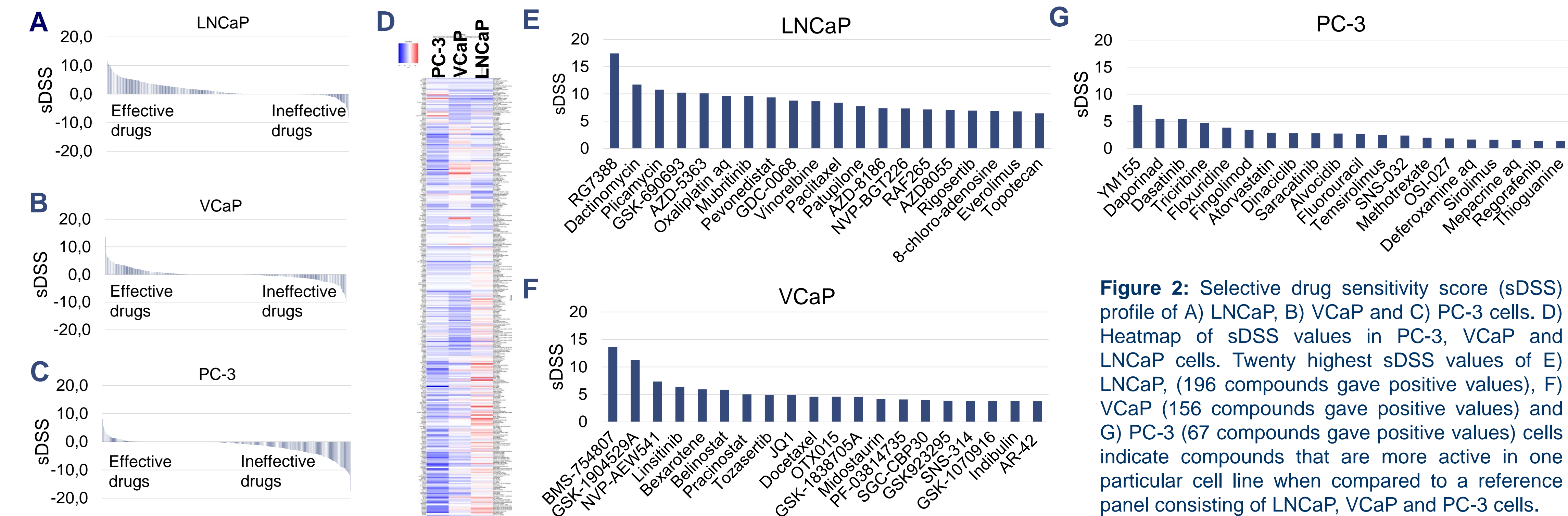


Figure 2: Selective drug sensitivity score (sDSS) profile of A) LNCaP, B) VCaP and C) PC-3 cells. D) Heatmap of sDSS values in PC-3, VCaP and LNCaP cells. Twenty highest sDSS values of E) LNCaP, (196 compounds gave positive values), F) VCaP (156 compounds gave positive values) and G) PC-3 (67 compounds gave positive values) cells indicate compounds that are more active in one particular cell line when compared to a reference panel consisting of LNCaP, VCaP and PC-3 cells.

Summary

As expected, the results indicate that LNCaP and VCaP cells in general were more sensitive to drugs of different categories than PC-3 cells. According to DSS analysis, all three cell lines showed sensitivity to conventional chemotherapy and kinase inhibitors. However, PC-3 cells were more sensitive to kinase inhibitors than conventional chemotherapy. Determining sDSS revealed specific sensitivities of each cell line:

- LNCaP cells were sensitive to conventional chemotherapy, such as anti-mitotic compounds, and kinase inhibitors, such as mTOR and AKT inhibitors.
- VCaP cells showed sensitivity to kinase inhibitors (such as Aurora kinase and IGF1R inhibitors in particular) and HDAC inhibitors.
- PC-3 cells were sensitive to kinase inhibitors (such as AKT and CDK inhibitors).

Conclusions

We conclude that the cell-based compound screening combined with DSS analysis provides a possibility to profile cellular responses to an extensive collection of anti-cancer compounds. In addition, sDSS value can be used to identify the selective drug response pattern of different cancer cell lines. This enables identification of new indications for already existing drugs, finding vulnerabilities in different types of cancer cells, and functional investigation of cellular pathways behind drug sensitivity or resistance.

References

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