Prostate cancer study provides impetus for precision medicine

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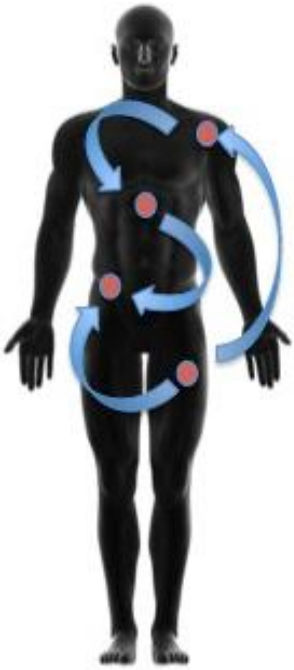

Schematic depicting that different metastases obtained from the same patient harbors limited heterogeneity, which could inform treatment options.

Image provided by Dr. Pete Nelson.

It has been more than a year since the Obama administration launched the Precision Medicine Initiative. For precision medicine to be effective for cancer treatment, molecular aberrations in cancers of the same histological classification should be distinct between patients. However, another critical feature that remains largely untested is that different tumors from the same patient should harbor limited molecular heterogeneity. A new Fred Hutch study from Dr. Pete Nelson's Laboratory (Public Health Sciences, Clinical Research and Human Biology Divisions) led by Ilsa Coleman in the Nelson Lab and Akash Kumar, a graduate student in Dr. Jay Shendure's Lab (Genome Sciences, UW) and published in *Nature Medicine*, suggests that at least for prostate cancer, this is indeed the case.

An estimated 27,000 men die of metastatic prostate cancer (mPC) each year in the United States, and the standard of care for this disease, largely unchanged for half a century, is androgen deprivation therapy (ADT). While ADT represented a pioneering precision medicine approach when first introduced it has limitations, namely, most patients undergoing ADT eventually succumb to metastatic castration-resistant prostate cancer (mCRPC). A previous study with the Nelson Lab

cataloged the suite of recurrent molecular aberrations in mCRPC, whereas the current study sought to determine whether a single metastatic tumor from any given patient provides a reliable assessment of the driver mutations for all metastases in that same patient. The study began by determining the spectrum of mutations (by whole exome sequencing), copy number alterations (by array comparative genomic hybridization) and RNA levels (microarray) from 176 primary or metastatic tumors obtained from 63 men. Recurrent alterations in genes such as *AR* (encoding the androgen receptor), *ERG*, *TP53* and *RB1*, all previously known to occur in mCRPC, were found. Despite all men having undergone ADT, robust AR activity was detected in the majority of men (88%) and AR activity scores, AR expression and *AR* genomic aberrations were highly similar between metastases derived from any single patient. Next, the researchers tested whether this concordance could be applied to other features of the tumor by incorporating copy number alterations, mutations and gene expression in their integrated analysis. Together with unsupervised clustering, these analyses revealed that all tumors taken from the same individual cluster together, whereas tumors from other men were always distinct. The investigators also evaluated a 31-gene signature of cell cycle progression (CCP), shown to be associated with prostate cancer mortality. Surprisingly, AR activity was inversely correlated with CCP, a result that was corroborated by examining the growth of cultured prostate cancer cells harboring either endogenous or overexpressed AR. Finally, genome-wide correlations of CCP revealed that elevated expression of the Fanconi Anemia pathway genes *FANCA*, *FANCI*, *FANCD2*, *BRCA1* and *BRCA2* were found in tumors with high CCP activity and that down-regulating these genes with siRNA in prostate cancer cell lines markedly reduced their growth. In summary, this study suggests that there is limited molecular heterogeneity between metastatic tumors from any given patient, a feature that might enable treatment selection based on a biopsy obtained from a single metastatic site.

Kumar A, Coleman I, Morrissey C, and Zhang X, and True LD, Gulati R, Etzioni, R, Bolouri H, Montgomery B, White T, Lucas JM, Brown LG, Dumpit RF, DeSarkar, N, Higano C, Yu EY, Coleman R, Schultz N, Fang M, Lange PH, Shendure, J, Vessella RL, Nelson PS. 2016. Substantial interindividual and limited intraindividual genomic diversity among tumors from men with metastatic prostate cancer. *Nature medicine*. Doi: 10.1038/nm.4053. [Epub ahead of print.]

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