CIFellows 2020-2021

Computing Innovation Fellows

NME2 and MYC Pathway Drives Resistance to Enzalutamide Treatment in CRPC Patients

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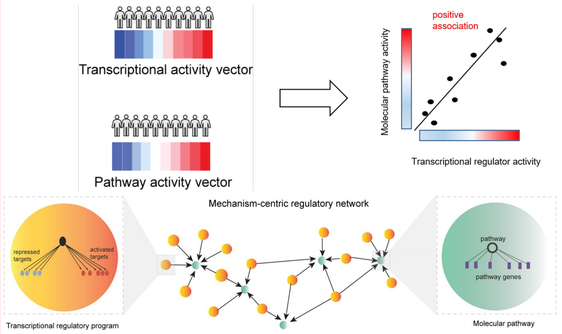
Abstract

Resistance to Enzalutamide is a serious problem in prostate cancer. Thus there is a crucial need to develop computational approaches that can help improve understanding of underlying molecular mechanisms involved in response to Enzalutamide. In this study, we have reconstructed a CRPC-specific mechanism-centric regulatory network which integrates biological pathways with their upstream transcriptional regulatory programs and mined the network to identify MYC pathway and its upstream transcriptional regulatory program, NME2 to be associated with response to Enzalutamide. Further, NME2 and MYC pathway activity have demonstrated the ability to predict CRPC patients at risk of developing resistance to Enzalutamide. Finally, we have demonstrated that the ability of our findings to predict patients at risk of Enzalutamide resistance outperforms the predictive ability of markers associated to overall prostate cancer aggressiveness and treatment response. Thus we propose that MYC associated mechanisms can be utilized to pre-screen patients who are at a higher risk of developing resistance to Enzalutamide

Background

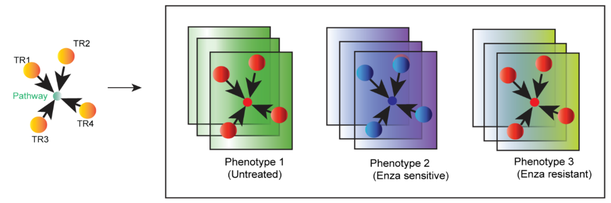
Prostate cancer patients that develop resistance to androgen deprivation therapy progress to a more lethal form of the disease known as castration resistant prostate cancer (CRPC). For such CRPC patients, Enzalutamide is most common form of treatment as it has shown to improve patient survival. However, some patients do not respond to it and develop resistance in approximately 8 months to 1.5 years. As CRPC patients that fail Enzalutamide treatment are left with no targeted therapeutic option, there is a crucial need to develop methodologies that can help improve our understanding of the underlying molecular mechanisms involved in response to Enzalutamide.

Reconstruction of the network



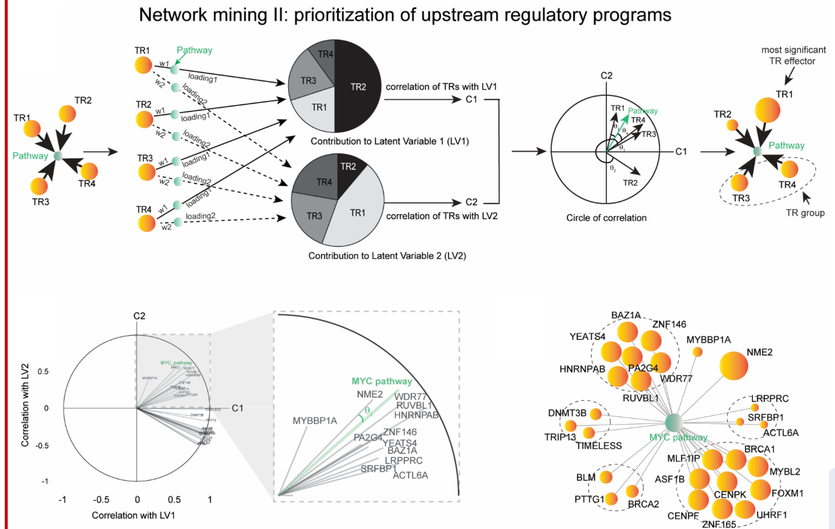
Single sample pathway enrichment analysis and transcriptional regulatory analysis identified pathway activity vector and transcriptional activity vector respectively, which where then subjected to linear regression to determine relationship between a molecular pathway and upstream transcriptional regulatory program (First row) and reconstruct a mechanism centric regulatory based network (Second row)

Mining of the network – Step 1



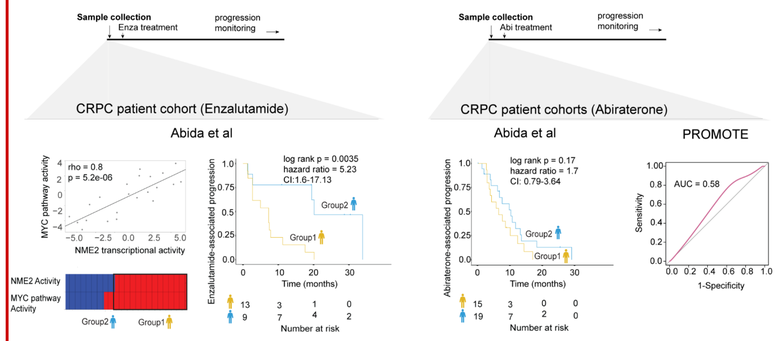
Following reconstruction of the network, our next essential step was network mining. In this study network mining was a multi-step process. In the first step, we aimed to identify parts of the reconstructed network (also referred to as subnetworks that comprises of molecular pathways and their upstream transcriptional regulatory programs) that govern response to Enzalutamide treatment . In particular, we sought to identify parts of the network that were upregulated in untreated state (i.e., phenotype 1), becomes down-regulated in Enzalutamide sensitive state (i.e., phenotype 2) and then again "recovers" and become up-regulated in Enzalutamide resistant state (i.e., phenotype 3). We hypothesized that subnetworks that showcase such "up-down-up" behavior play a role in response to Enzalutamide.

Mining of the network – Step 2



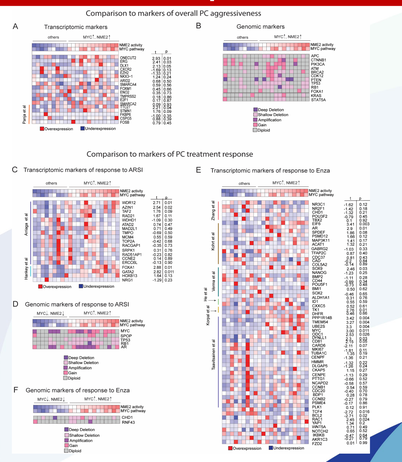
Partial least square inspired approach utilizes weights, *w*, along with transcriptional regulatory programs (i.e., TR, orange nodes) to identify latent variables (pie circles) and contribution of each transcriptional program to a latent variable (slices in a pie, colored in different shades of grey). Alongside association between each TR and a latent variable is illustrated by circle of correlation. Further utilizing the circle of correlation, correlated transcriptional regulatory programs were clustered and prioritized. Our analysis identified MYC pathway and its upstream transcriptional regulatory program NME2 to play a role in response to Enzalutamide.

NME2 and MYC pathway are associated with poor response to Enzalutamide



(Left) Kaplan-Meier survival analysis comparing CRPC patients that received post-sample adjuvant Enzalutamide from Abida et al cohort with high NME2 and MYC pathway activity (yellow) and rest of the patients (blue). Log-rank p-value, hazard ratio, and CI are indicated. (Right) Kaplan-Meier survival analysis comparing CRPC patients that received post-sample adjuvant Abiraterone from Abida et al cohort with high NME2 and MYC pathway activity (yellow) and rest of the patients (blue). Log-rank p-value, hazard ratio, and CI are indicated. ROC analysis on CRPC patients that received post-sample adjuvant Abiraterone from PROMOTE indicate cooperation indicate cooperation between NME2 and MYC pathway cannot classify CRPC patients based on their response to Abiraterone. AUROC is reported

NME2 and MYC performance



Predictive ability of NME2-MYC program outperform predictive ability of known markers of progression and known markers of treatment response (including second generation anti androgen therapy and Enzalutamide).

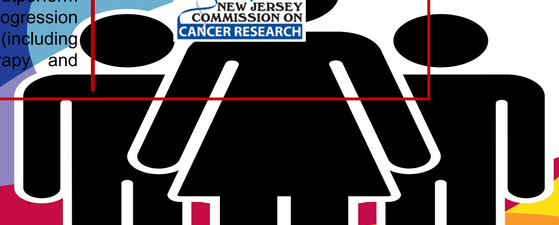
Conclusion

MYC-associated mechanisms can serve as a biomarker of primary resistance to Enzalutamide aiming to identify patients that are at risk of developing resistance.

Funding Sources

New Jersey Commission on Cancer Research Pre-Doctoral Fellowship

American Cancer Society®
NIH U.S. National Library of Medicine
NJCCR New Jersey Commission on Cancer Research



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