Integrating Proteomics of Viral Infection and Cancer Drug Resistance to Uncover Shared Mechanisms of Cell Defense

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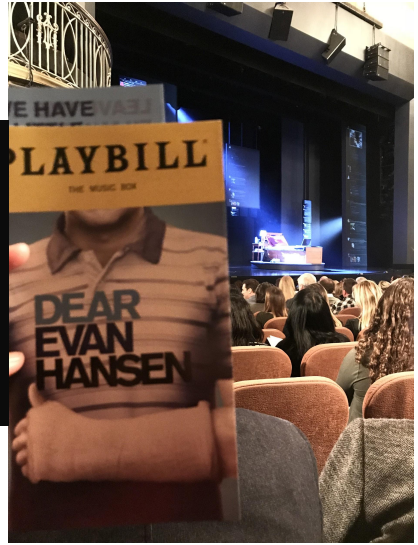
About Me

- Grew Up in Millbrae, California
- Currently Attend Mills High School
- Love spending time and interacting with kids
- Enjoy theatre and performance



Cell Defense Against Virus = Cancer Cell Defense Against Cancer Drugs?

"Now, here, you see, it takes all the running you can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!"

- Lewis Carroll, *Through the Looking Glass*

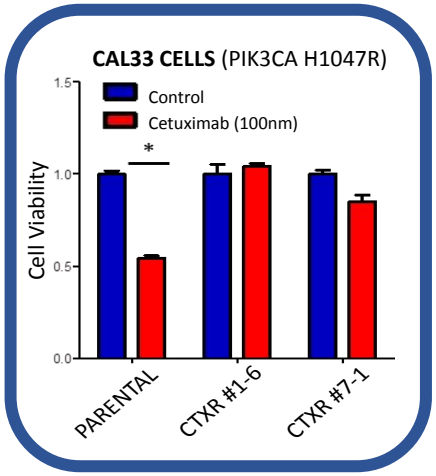
- Humans and viruses have co-evolved for millions of years.
- One of the most important properties evolved by human cells is their response to virus in order to survive.
- The Red Queen's Race illustrates this constant struggle between humans and viruses.

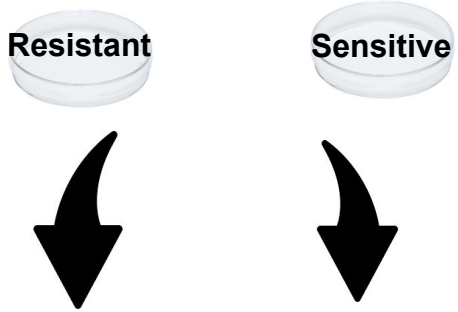
Driving Questions

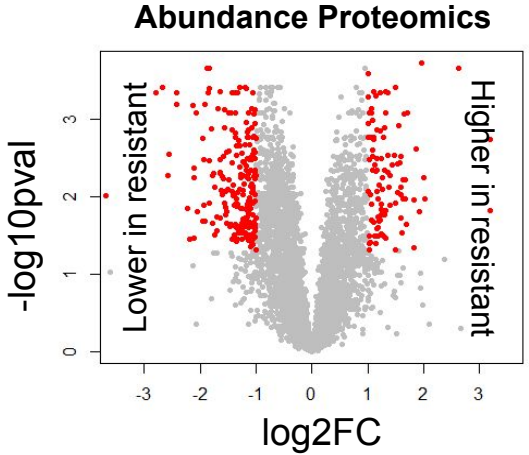
Is a cancer cell's defense against drug treatment similar to a cell's defense against a virus?

Can this similarity reveal new drug targets to fight cancer drug resistance?

Pathogen-associated Proteins Expressed in Drug Resistant Cancer Cells







KEGG 2019 Enrichments

Higher abundance in resistant

P-value < 0.01 & abs(Log2FC) > 1

Term	Overlap	p value
Regulation of actin cytoskeleton	5/214	0.0005682921184
Salmonella infection	3/86	0.002530717247
Toll-like receptor signaling pathway	3/104	0.004326066064
TNF signaling pathway	3/110	0.005059010487
Measles	3/138	0.009439570402
Fluid shear stress and atherosclerosis	3/139	0.009626430062
Glutathione metabolism	2/56	0.01348185914
Hepatitis B	3/163	0.01476751104
Tight junction	3/170	0.01650850628
RIG-I-like receptor signaling pathway	2/70	0.02055588695
Epstein-Barr virus infection	3/201	0.02555489067
Human immunodeficiency virus 1 infection	3/212	0.02929102737
Synthesis and degradation of ketone bodies	1/10	0.03106391882
IL-17 signaling pathway	2/93	0.03477649876
Chagas disease (American trypanosomiasis)	2/103	0.04186022507

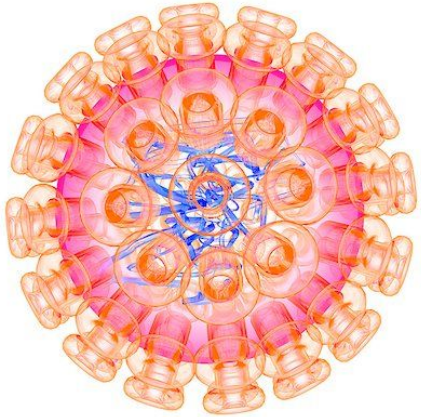
Enrichr

About Epstein-Barr Virus (EBV)

- EBV infection is associated with many cancers, including gastric cancer and lymphoma.
- EBV was the first virus shown to cause cancer.

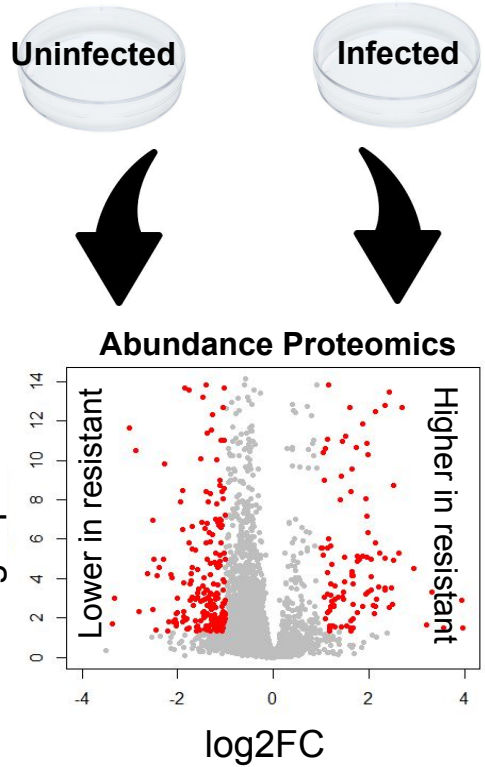
Data from Danielle Swaney, Margaret Soucheray, and Mehdi Bouhaddou

Karposi's Sarcoma-associated HerpesVirus (KSHV) Infection Upgregulates EBV Associated Proteins



Facts about KSHV

- In the same virus family as EBV: Herpesviridae.
- Known to cause Karposi's sarcoma and other cancers.



KEGG 2019 Enrichments

Higher abundance in infected

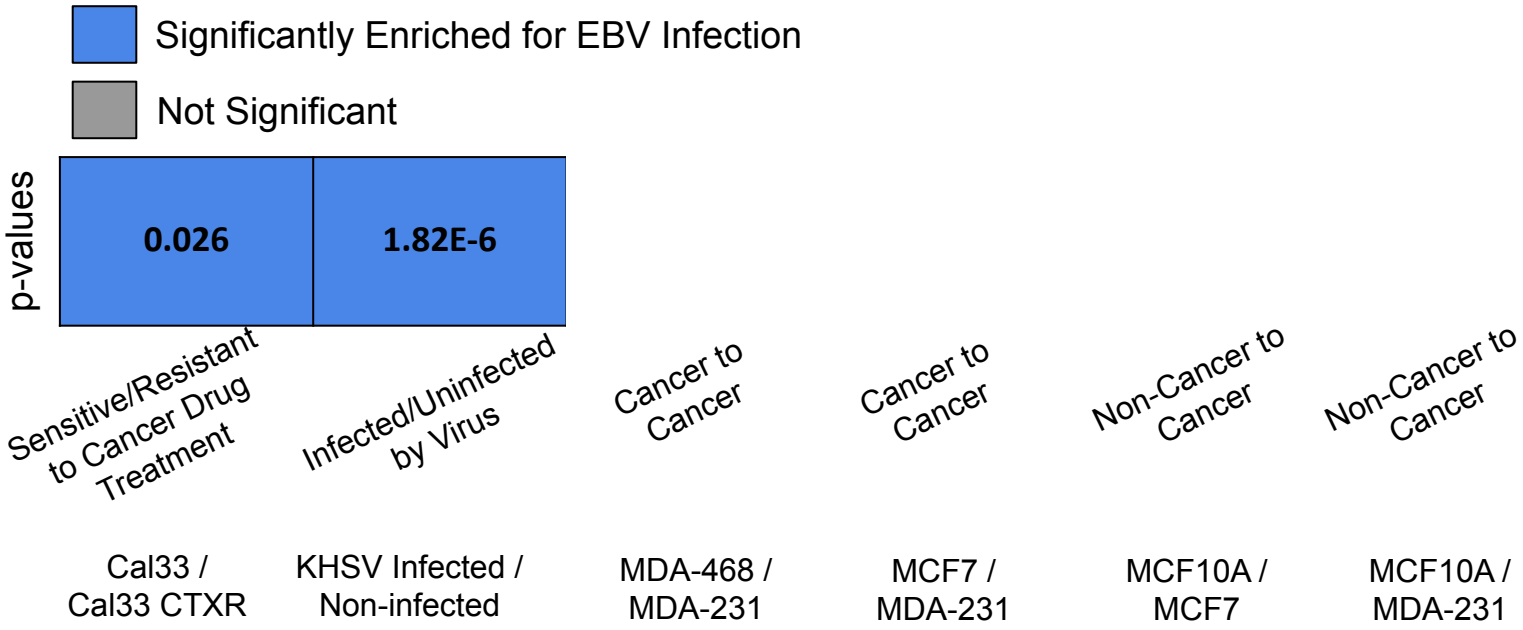
P-value < 0.05 & abs(Log2FC) > 1

Term	Overlap	p value
Epstein-Barr virus infection	7/201	1.82E-06
Herpes simplex virus 1 infection	8/492	8.25E-05
Antigen processing and presentation	3/77	0.001453953641
HIF-1 signaling pathway	3/100	0.003066197306
Human immunodeficiency virus 1 infection	4/212	0.003329077805
Human cytomegalovirus infection	4/225	0.004114925302
Hepatitis C	3/155	0.0103179745
Glutathione metabolism	2/56	0.01151301931
Influenza A	3/171	0.01343613594
Neomycin, kanamycin and gentamicin biosynthesis	1/5	0.01441745034
Central carbon metabolism in cancer	2/65	0.0152937291
Human papillomavirus infection	4/330	0.01535735218
Glycolysis / Gluconeogenesis	2/68	0.01665714571
RIG-I-like receptor signaling pathway	2/70	0.01759392339
Complement and coagulation cascades	2/79	0.02207697631

Enrichr

Data from Jeff Johnson

Enrichment of EBV Infection Across Various Cellular Conditions



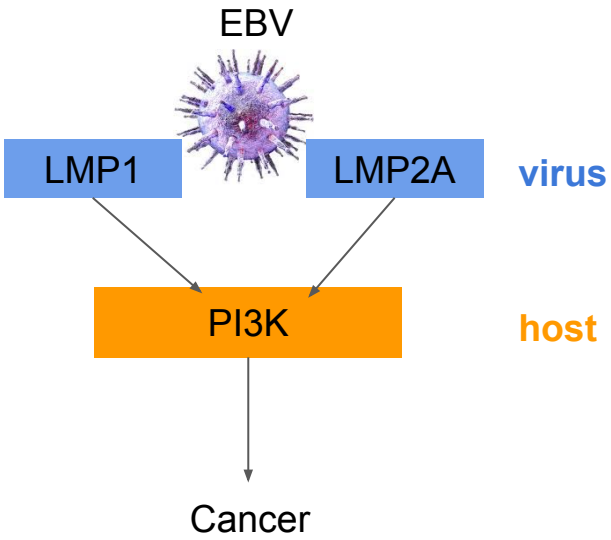
Cancer Cell Lines: **MDA-468, MDA-231, MCF7**

Non-Cancer Cell Line: **MCF10A**

Conclusion: Host response to EBV may lead to oncogenesis as well as cancer drug resistance.

EBV and Drug Resistant Cancer Cells Both Activate PI3K Pathway

Epstein-Barr Virus (EBV)



Chen, World Journal of Virology, 2012

Drug Resistant Cancer Cells

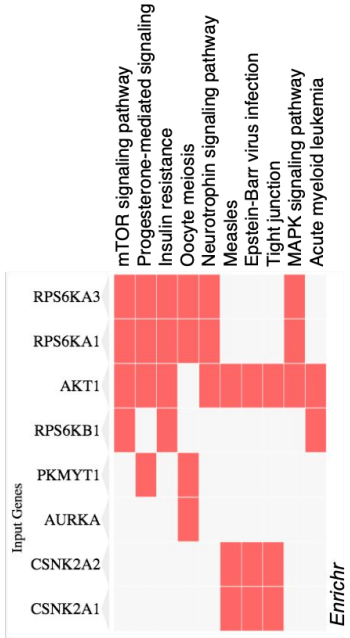
Predicted Changes in Kinase Activity

(from Phosphoproteomics Data)

Significantly **higher** in Resistant

kinase	activity	p-value
AKT1	3	0.001
CSNK2A1	3	0.001
RPS6KB1	2.69897	0.002
SGK1	2.30103	0.005
RPS6KA1	1.88605665	0.013
PKMYT1	1.65757732	0.022
STK38L	1.63827216	0.023
CSNK2A2	1.50863831	0.031
STK38	1.43179828	0.037
RPS6KA3	1.4202164	0.038
AURKA	1.39794001	0.04
PRKG1	1.30103	0.05

Phosphoproteomics data reveals activation of ***PI3K/mTOR pathway*** in cetuximab resistant cells.



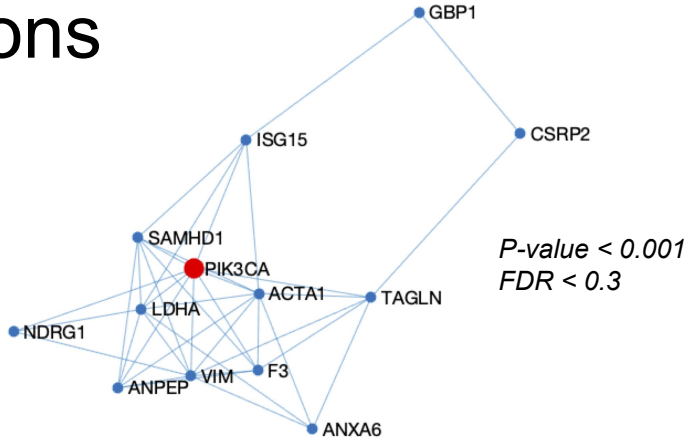
phosfate.com: Ochoa, D, et al. Molecular Systems Biology (2016)

Conclusions

- Drug resistant cells express Epstein-Barr related proteins.
- These proteins may contribute to the activation of the PI3K pathway.

Future Directions

- Use Network Propagation, a network analysis technique, to look for overlap between viral proteomics and cancer resistance proteomics datasets.
- This could reveal novel drug targets with strong evolutionary roots to fight cancer resistance.



What I Learned

- I learned how to code in R from no prior experience.
- I used Cytoscape to map PPI networks.
- I learned how to use Network Propagation Analysis.

Acknowledgments

Krogan Lab

Nevan Krogan**
Mehdi Bouhaddou**
Diego Quintero**
Minkyu Kim
Danielle Swaney**
Manon Eckhardt
Gwendolyn Jang
Robyn Kaake
Kelsey Haas
Paige Haas
Vincenzo Pierotti
Ernst Pulido
Margaret Soucheray**
Jeff Beck
Jacqueline Fabius
Gina Nguyen
Alexa Rocourt
Jeff Johnson

CCMI Cancer Cell Map Initiative

UCSF Quantitative Biosciences Institute

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