

A functional network model of the metastasis suppressor RKIP and its regulators in breast cancer cells

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Outline

Introduction

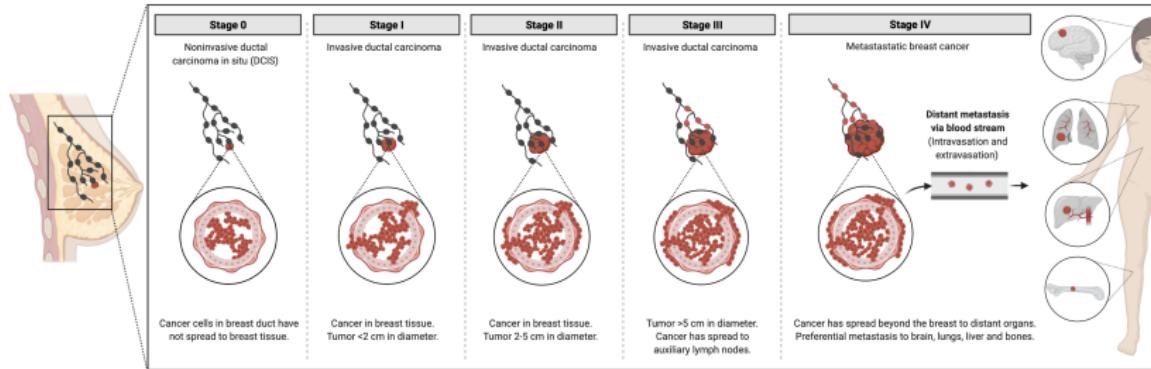
Materials and Methods

Results

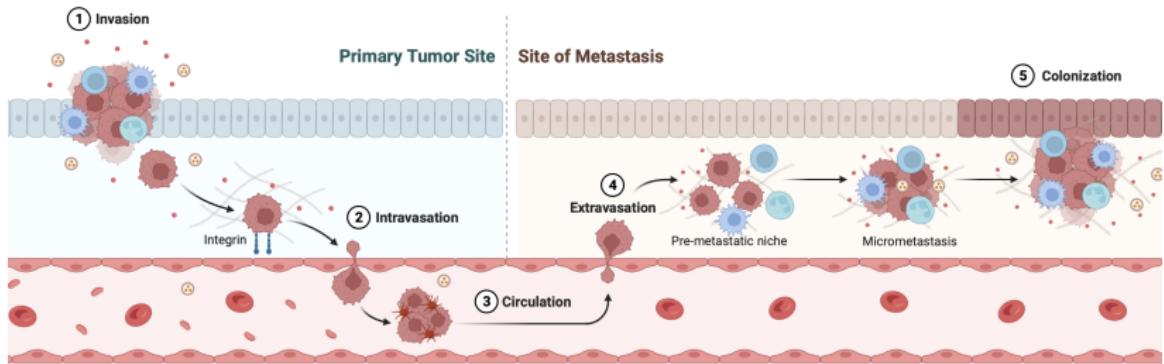
Summary

Introduction

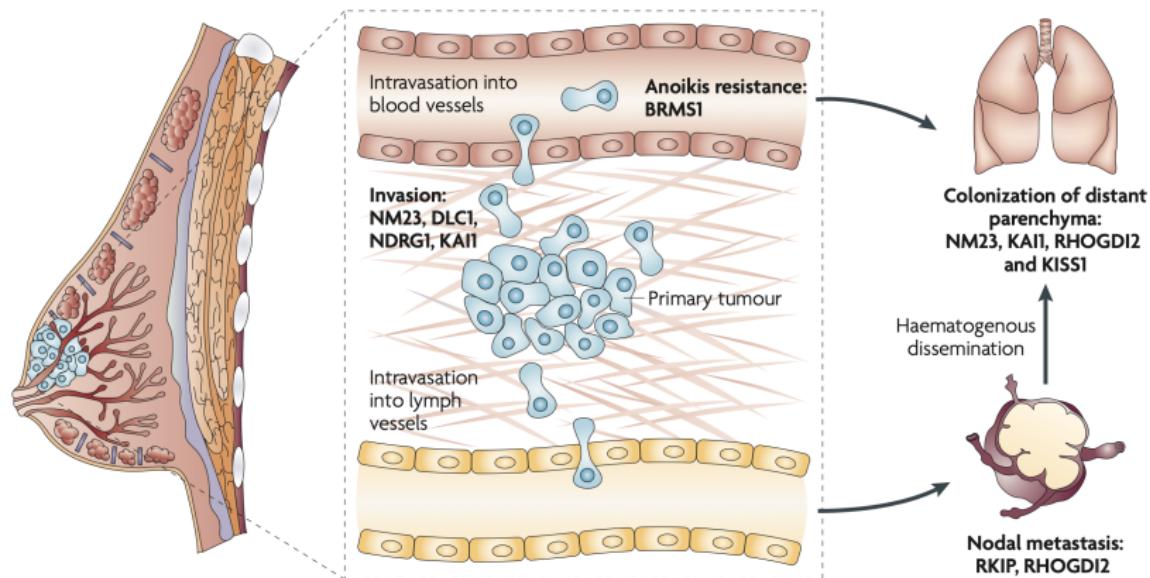
STAGES OF BREAST CANCER



Overview of Metastatic Cascade

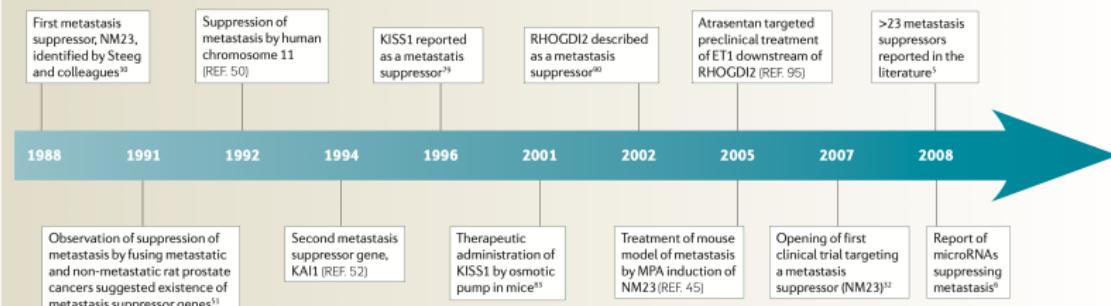


Metastasis suppressor genes and steps in the metastatic cascade in human cancer



[Smith and Theodorescu, 2009]

Timeline | Key advances in the metastasis suppressor field



MPA, medroxyprogesterone acetate; RHOGLI2, RhoGTPase dissociation inhibitor 2.

[Smith and Theodorescu, 2009]

Functions and reported targeting strategies of Metastasis suppressor genes

Symbol	Alias(es)	Function(s)	Potential targeting strategy
BMP4	BMP2B	Soluble cytokine	Direct therapeutic administration of suppressor protein*
BRMS1	None	Chromatin and transcriptional regulation; regulation of gap junctions	None published at present
CTGF	CCN2, IGFBP8	Soluble cytokine	None published at present
DLC1	ARHGAP7	Regulation of RhoGTPase signalling	Re-induction of endogenous gene through HDAC inhibition ⁶⁹
KAI1	CD82, kangai 1	Inhibition of EGFR signaling; induction of senescence through interaction with DARC	Therapeutic re-induction of endogenous gene by plant extracts ⁶² ; viral ⁶⁷ and non-viral ⁶¹ gene therapy
KISS1	KiSS-1, metastin	Soluble ligand for G-protein-coupled receptor	Direct therapeutic administration of suppressor protein ⁸³ ; possibly small molecule mimetics ⁸⁴
MKK4	MAP2K4	Signal transduction	Antibody-mediated activation pathway upstream of MKK4 (REF. 122)
NDRG1	CAP43, DRG1, RTP	Unknown	Induced by iron chelators ¹²³ , p53 (REF. 124) and PTEN expression ¹²⁵
NM23	NME1, NM23-H1	Histidine kinase activity to KSR1, decreasing Ras signalling; regulation of downstream gene expression	Re-induction of endogenous gene ^{42,47,48} ; viral gene therapy ⁶² ; inhibition of downstream genes ⁶⁰
RHOGDI2	ARHGDI2, LyGDI, GDID4	Regulation of Rho family member activation; regulation of downstream gene expression	Inhibition of downstream genes ⁹⁵
RKIP	PEBP1	Binds to and inhibits Raf kinase activity and downstream signalling	Epigenetic re-induction of endogenous gene ⁶⁷

[Smith and Theodorescu, 2009]

Materials and Methods

- Protein-protein interactions (STRINGDB), literature search and biological expression language (BEL)
- Knockdown of metastasis suppressors and transcription factors
- Pharmacological perturbations of breast cancer cell lines
- Network Perturbation Amplitude (NPA)
- Measures of consistency
- Software environment and reproducibility

Metastasis suppressor genes (MSG) [Marino et al., 2014]

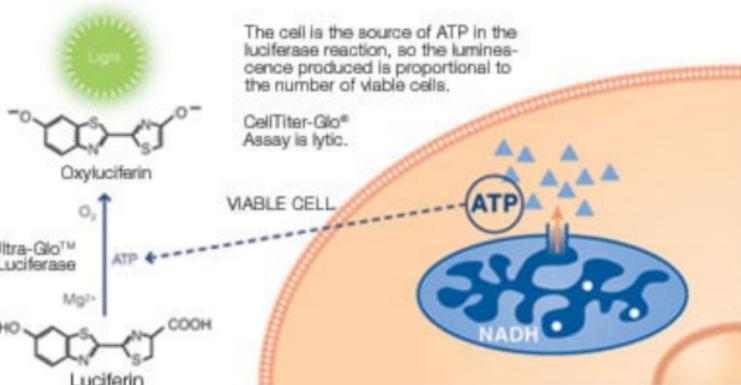
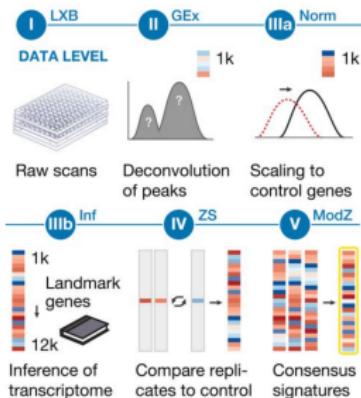
- **Cell-cell adhesion:** CD44, CD82, CDH11, CDH2, CDH1 & GSN
- **Scaffolding:** AKAP12
- **MAPK:** MAP2K6, MAP2K4, MAP2K7 & MAPK14
- **Transcription:** NME1 & BRMS1
- **GTP-binding:** ARGHDIB & DRG1
- **Other:** RRM1 & PEBP1

Transcription factors targeting metastasis suppressor genes in MCF7 [Feng et al., 2019]

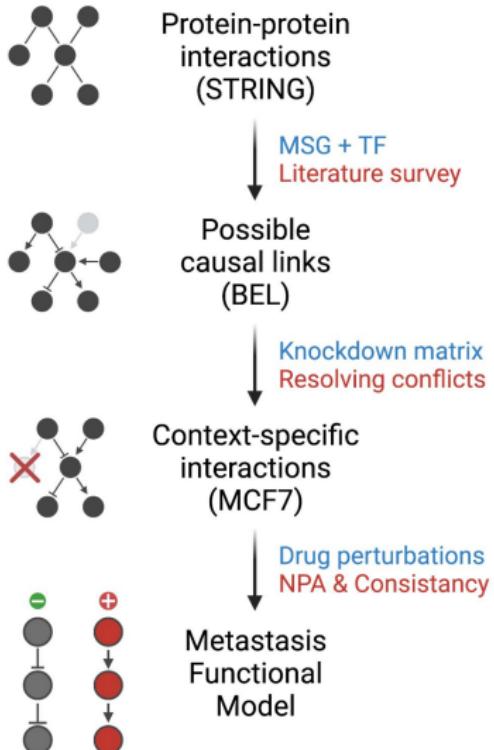
TF	Name	Dataset ID	Ref.
ESR1	Estrogen receptor 1	GSE10061	[Yau and Benz, 2008]
FOS	Fos Proto-Oncogene AP-1 Transcription Factor Subunit	GSE36586	[Dahlman-Wright et al., 2012]
FOXM1	Forkhead Box M1	GSE55204	[Bergamaschi et al., 2014]
GATA3	GATA Binding Protein 3	GSE39623	[Theodorou et al., 2013]
HIF1A	Hypoxia Inducible Factor 1 Subunit Alpha	GSE3188	[Elvidge et al., 2006]
NR5A2	Nuclear Receptor Subfamily 5 Group A Member 2	GSE47803	[Lai et al., 2013]
POLR3A	RNA Polymerase III Subunit A	GSE42239	[Lee et al., 2015]
RARA	Retinoic Acid Receptor Alpha	GSE26298	[Salazar et al., 2011]
SPDEF	SAM Pointed Domain Containing ETS Transcription Factor	GSE40985	[Buchwalter et al., 2013]
TFAP2C	Transcription Factor AP-2 Gamma	GSE26740	[Tan et al., 2011]
YBX1	Y-Box Binding Protein 1	GSE28433	[Lasham et al., 2012]
ZFX	Zinc Finger Protein X-Linked	ENCSR005AHI	[Dunham et al., 2012]

Drug perturbations in MCF7 cell line

[Koleti et al., 2018]



Building a network of the metastasis suppressors and their regulators



Identifying protein-protein interaction (PPI) based on STRING database

Version: 11.5

LOGIN | REGISTER | SURVEY

STRING

Search Download Help My Data

Welcome to STRING

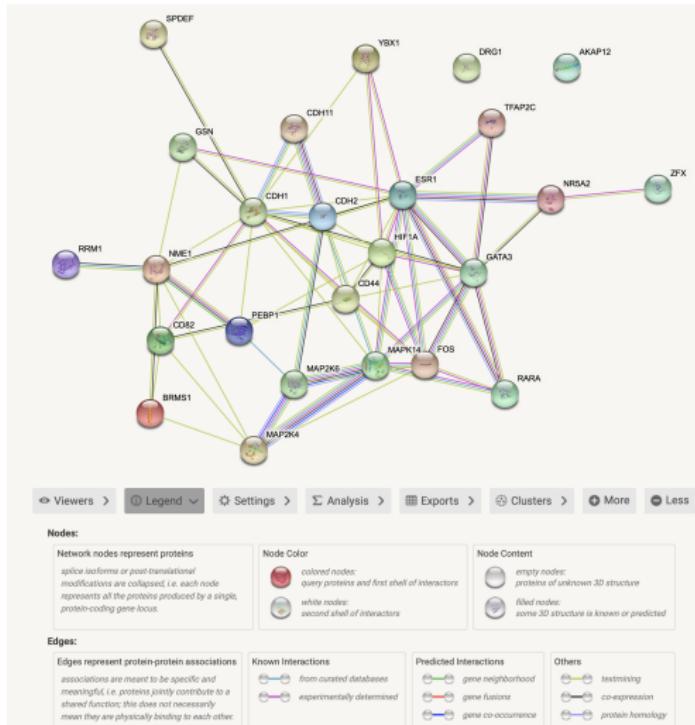
Protein-Protein Interaction Networks
Functional Enrichment Analysis

ORGANISMS | PROTEINS | INTERACTIONS

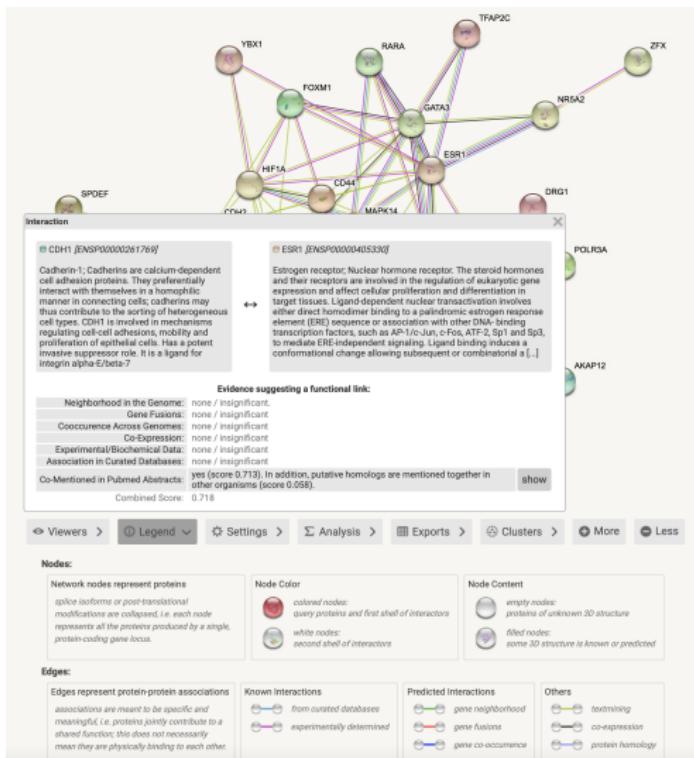
14094 | 67.6 mio | >20 bln

SEARCH

Metastasis suppressor proteins and their regulators on STRINGDB



Surveying literature search to establish causal relations between entities



Converting possible interactions of metastasis suppressors to Biological expression language (BEL)

TEXTMINING

Relevant publications mentioning your query species (*Homo sapiens*):

PMID:32210754 The role of WIF1 in breast cancer: clinical implications, biological effects and molecular mechanisms.
▶ [PubMed](#) ▶ [TextMining](#) ▶ [TF](#) ▶ [Ying,ZC,YL,Tan,XN,Jiang,J,Cong,T,OJ,WY](#)
Int J Biol Stat. 2018;14(2):1486-2323.

Abstract:
Werner's Wilms' tumor gene (WT1) was first cloned and identified as a tumor suppressor gene in nephroblastoma, subsequent studies have demonstrated that it can also play an oncogenic role in leukemia and various solid tumors. WT1 exerts biological functions with high tissue- and cell-specificity. This article reviews the relationship between WT1 and breast cancer from two aspects: (1) clinical application of WT1, including the relationship between expression of WT1 and prognosis, the relationship between WT1 and tumor grade, and the relationship between WT1 and tumor stage; (2) the molecular mechanism of WT1 in the development and progression of breast cancer, including proliferation, apoptosis, invasion, and metastasis of breast cancer cells. **Excepted from full text:**
WT1 overexpression in tumor high WT1 mRNA expression was associated with high histological grade, **estrogen receptor (ER)** (ER)-negative status, basal-like subtype, and ERBB2 (erbB-2 receptor [,] (ESR+KTRb) did not effect p21 expression, but promoted EMT, which was demonstrated by membrane **E-cadherin (ECD)** translocation into the nucleus, and the developing mesenchymal cell-like ...

PMID:32190007 Vascularogenic mimicry in carcinogenesis and clinical applications.
▶ [PubMed](#) ▶ [TextMining](#) ▶ [TF](#) ▶ [Zhao,H,Zhu,H,Peng,Z,Liu,X,Li,B,Zhang,H,Shan,K,Zhang,C,Duan,C](#)
Int J Cancer. 2018;142(10):2281-2290.

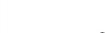
Abstract:
Different from classical tumor angiogenesis, vascularogenic mimicry (VM) provides a blood supply for tumor cells independent of endothelial cells. VM has two distinct types, namely tubular type and patterned matrix type. VM is associated with high tumor grade, tumor progression, invasion, metastasis, and poor prognosis in patients with malignant tumors. Hence, we discuss the recent studies on the role of VM in tumor progression and the diverse mechanisms and signaling pathways involved in the development of VM in tumors. Furthermore, we also summarize the latest findings of non-tumor VM, such as normal VM formation. In addition, we review the potential of vascularogenic mimicry in diagnosis of VM in malignant tumors. Emerging evidence suggests that VM is significantly associated with poor overall survival in patients with malignant tumors and could be a potential therapeutic target. **Excepted from full text:**
- breast cancer (TNBC) corresponds to the basal-like subtype of breast cancer that is negative for **estrogen receptor (ER)** (ER), progesterone receptor (PR), and human epidermal growth factor [,] by specific procedures, including reduction of expression of cell adhesion molecules (such as **E-cadherin (ECD)**) and some upregulated proteins (such as vE-cadherin/beta-catenin of VM, ...

PMID:32193024 CDK4/6 inhibition blocks cancer metastasis through a USP11-ZEB1-dependent deubiquitination mechanism.
▶ [PubMed](#) ▶ [TextMining](#) ▶ [TF](#) ▶ [Yang,Y,Wu,HY,Zheng,HJ,Zhong,YJ,Wang,Z,Wang,Q,Meng,H,Sun,H,Sun,H,Yu,CH](#)
Signal Transduct Target Ther. 2020;5:203.

▶ **Ecadherin** || **estrogen receptor** || ...

PMID:32290005 Heredit Active Ingredients: An Emerging Potential for the Prevention and Treatment of Papillary Thyroid Carcinoma.
▶ [PubMed](#) ▶ [TextMining](#) ▶ [TF](#) ▶ [Yang,Y,Chen,Q,Yu,HW,Zheng,HJ,Zhong,YJ,Wang,Z,Wang,Q,Meng,H,Sun,H,Sun,H,Yu,CH](#)
Biomater Pharmaco. 2018;14(20):30-20.

▶ **E-cadherin** || **estrogen receptor** || ...



Protein-protein
interactions
(STRING)



MSG + TF
Literature survey

Possible
causal links
(BEL)



Biological expression language (BEL)

What is BEL?

BEL is a language for representing scientific findings in the life sciences in a computable form. BEL is designed to represent scientific findings by capturing causal and correlative relationships in context, where context can include information about the biological and experimental system in which the relationships were observed, the supporting publications cited and the process of curation. [BEL.bio](https://bel.bio)

Why BEL?

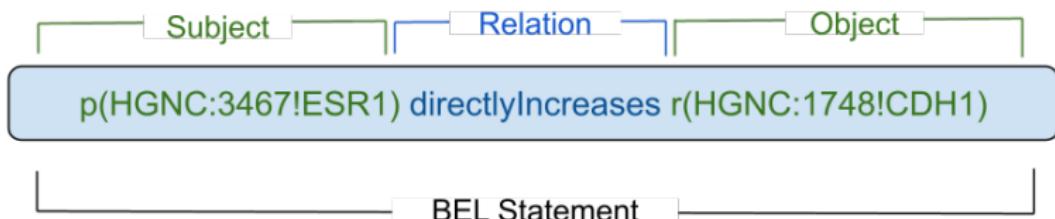
Open standard for communication and knowledge storage.

Example of a BEL statement

"ER α (ESR1) is bound to the E-cadherin (CDH1) promoter in both the presence and the complete absence of estrogen. Transfection of ER α , in the absence of ligands, was sufficient to restore E-cadherin transcription." (Pmid:19383788)



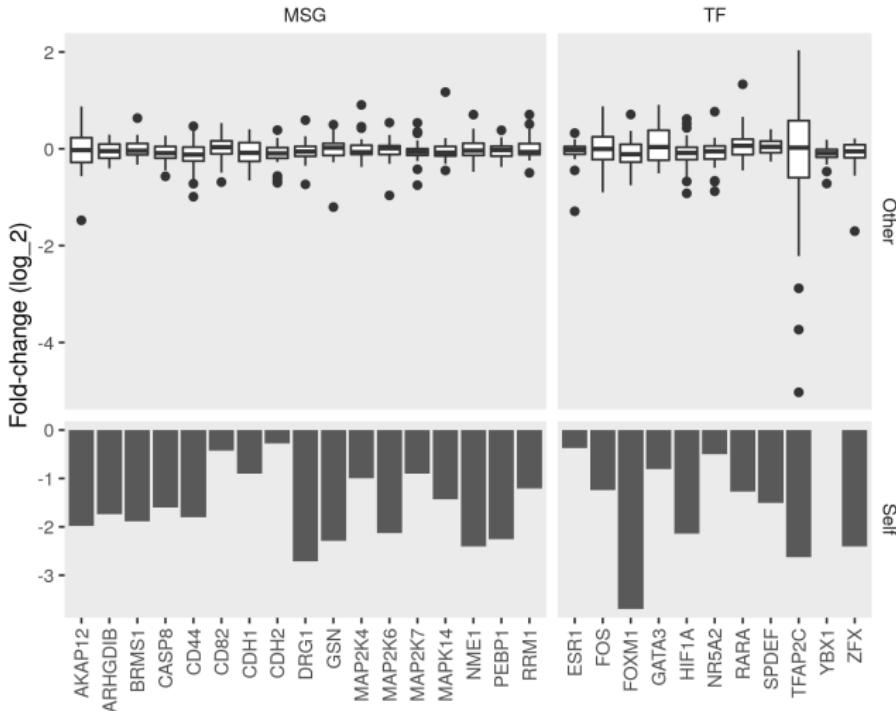
(Coding to BEL)



Examples of Interactions of metastasis suppressor genes and their transcription factor

Subject	Object	Ref.	Interaction
MAPK14	FOS	[Janknecht and Hunter, 1997]	act(p(HGNC:6876!MAPK14), p(HGNC:3796!FOS) ma(kin)) increases
MAP2K4	FOS	[Xue et al., 2018]	p(HGNC:6844!MAP2K4) increases p(HGNC:3796!FOS)
MAPK14	GATA3	[Wan, 2014]	p(HGNC:6876!MAPK14) increases act(p(HGNC:4172!GATA3))
RUNX2	HIF1A	[Lee et al., 2012]	p(HGNC:10472!RUNX2) act(p(HGNC:4910!HIF1A)) increases
PEBP1	MAP2K6	[Lai et al., 2017]	p(HGNC:8630!PEBP1) act(p(HGNC:6846!MAP2K6)) increases
PEBP1	MAP2K3	[Lai et al., 2017]	p(HGNC:8630!PEBP1) act(p(HGNC:6843!MAP2K3)) increases
MAPK14	RUNX2	[Hutchison, 2013]	p(HGNC:6876!MAPK14) r(HGNC:10472!RUNX2) increases
NME1	AKAP12	[McCorkle et al., 2014]	p(HGNC:7849!NME1) increases r(HGNC:370!AKAP12)
NME1	PEBP1	[Berger et al., 2005]	r(HGNC:7849!NME1) increases r(HGNC:8630!PEBP1)
PEBP1	MAPK14	[Lai et al., 2017]	p(HGNC:8630!PEBP1) act(p(HGNC:6876!MAPK14)) increases
TNFSF10	CASP8	[Mizamtsidi et al., 2018]	p(HGNC:11925!TNFSF10) p(HGNC:1509!CASP8) increases

Fold-change between control and knockdown of metastasis suppressors and transcription factors

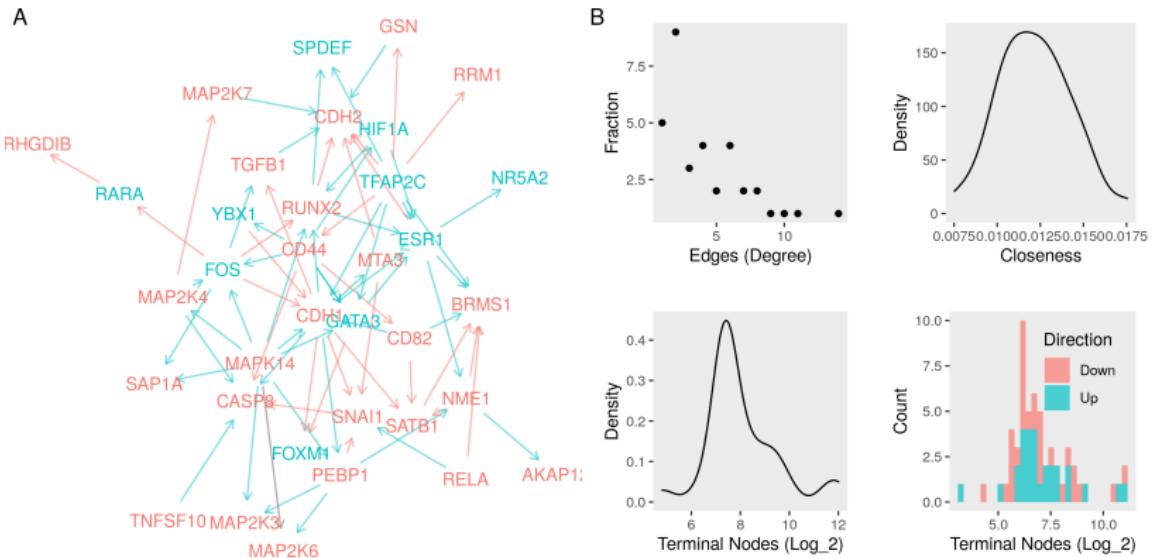


Resolving conflicts between possible interactions and fold-changes

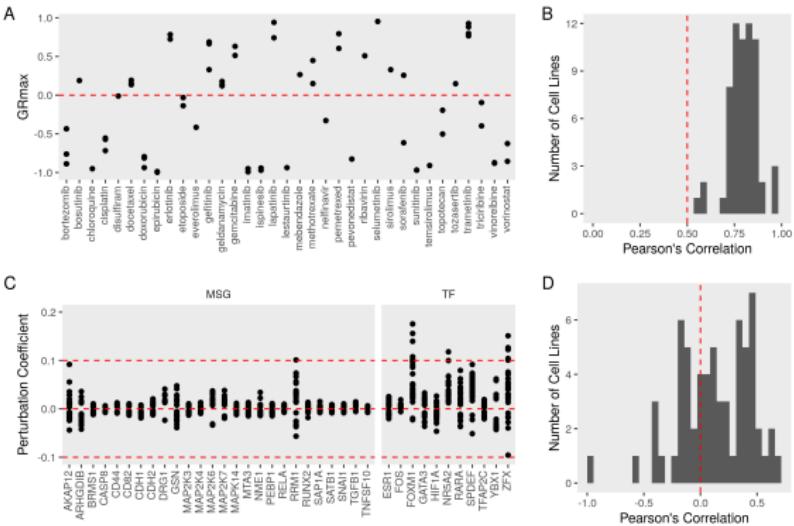
- No evidence to the contrary → Keep
- Significant change in the opposite direction → Remove
- Positive significant effects of the knockdown of one node on others as an interaction between the mRNA → Add

Conflicts			
	Possible Interaction	Observed Fold-change	Consensus
E1	↑	↑	✓
E2	↑		✗ Remove if weak evidence
E3		↓	✓ Add if big effect size

Network of interactions among metastasis suppressors and regulators



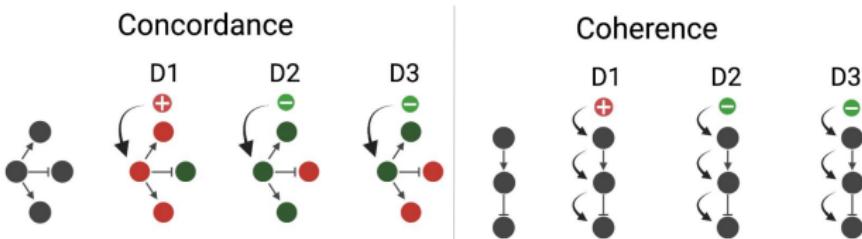
Evaluating the metastasis model using drug perturbation data



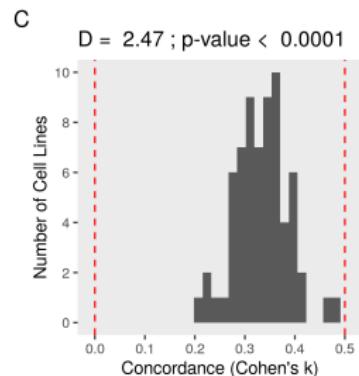
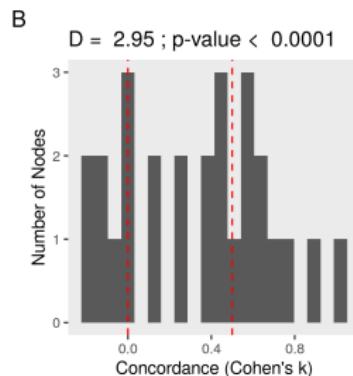
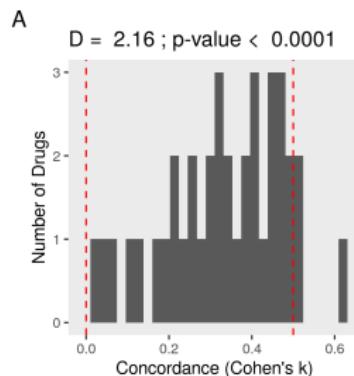
The agreement between expected and observed direction of change in the subnetworks and paths.

$$\frac{1}{n} \sum_{i=1}^n x_i - x = \begin{cases} 1, & \text{if } u.e = x' \\ 0, & \text{otherwise} \end{cases} \quad u = \begin{cases} 1, & \text{if } u \text{ is activated} \\ -1, & \text{if } u \text{ is repressed} \end{cases}$$

- Where x is the observed and x' is the expected effect on the nodes of the *subnetwork* downstream from u and connected to it by the edges e (**concordance**).
- Where x is the observed and x' is the expected effect on the nodes in a *path* connected by edges e and u is considered moving down the path (**coherence**).

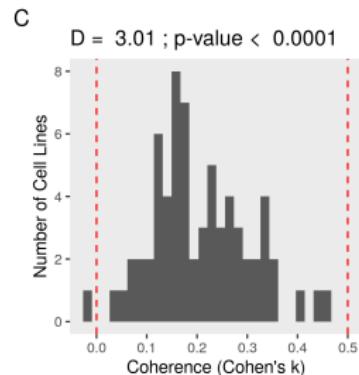
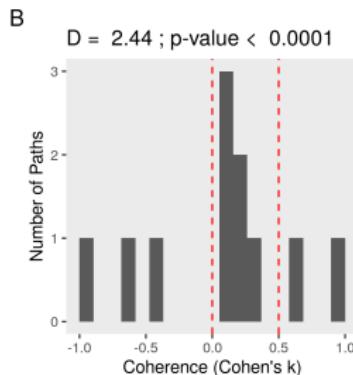
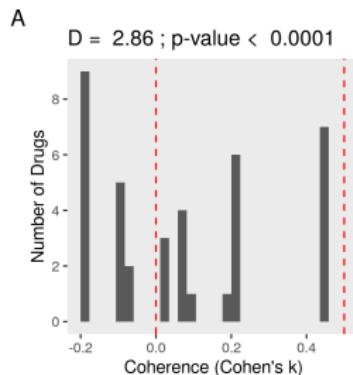


Concordance of expectation and observations in the subnetworks of the metastasis network



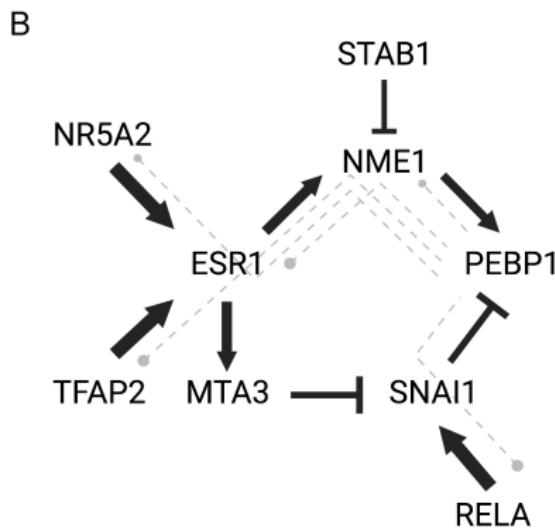
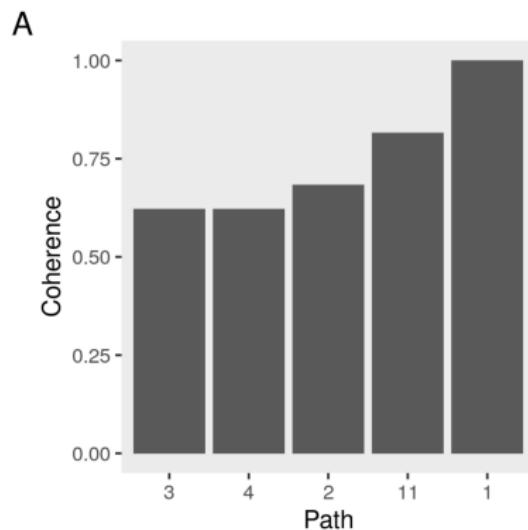
$$\kappa = (\text{observed agreement} - \text{expected agreement}) / (1 - \text{expected agreement})$$

Coherence of expectations and observations in the paths to RKIP.

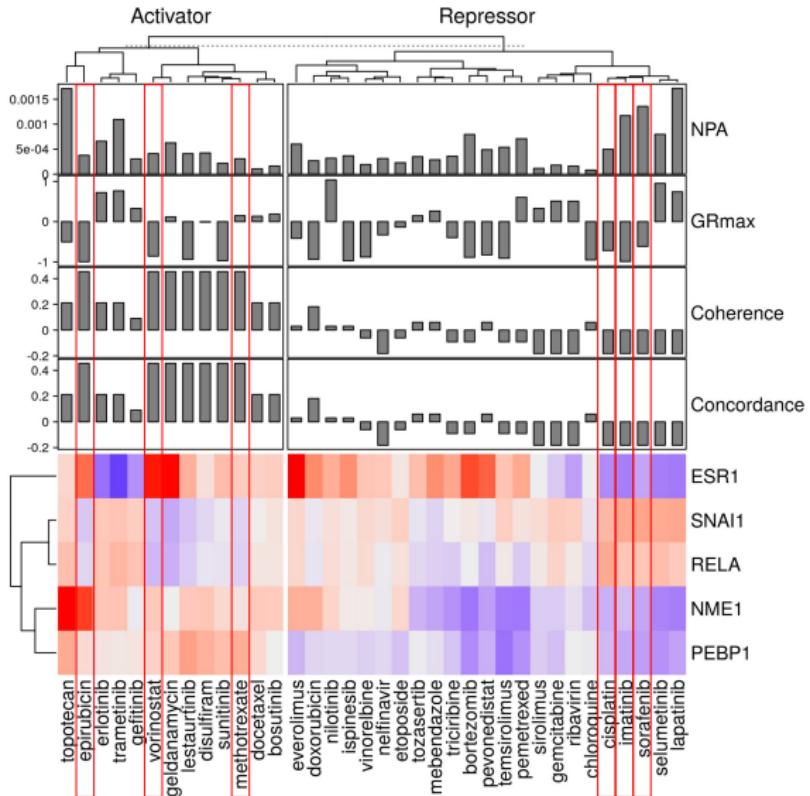


$$\kappa = (\text{observed agreement} - \text{expected agreement}) / (1 - \text{expected agreement})$$

Constructing a model of PEBP1 and its interaction with other metastasis suppressors

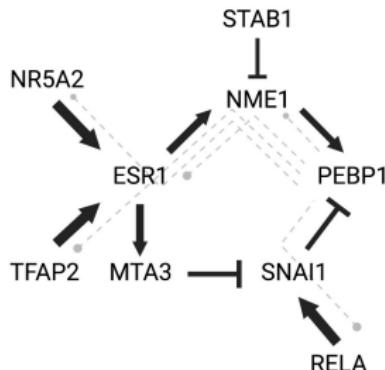


Drug profiles on the nodes of interest

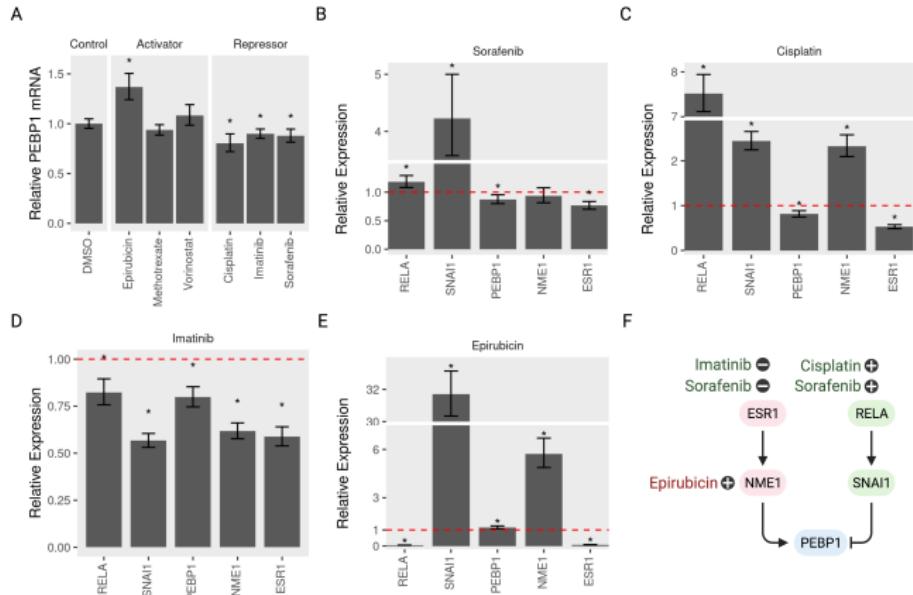


Validating the functional model of RKIP interactions with other metastasis suppressors and regulators

- **Goal:** Testing **gene expression** of related proteins under drug treatments.
- **Cell line:** MCF7- Breast cancer cell
- **Drugs:**
 - ▶ **Activators:** Epirubicin, Vorinostat, Methotrexate
 - ▶ **Repressors:** Cisplatin, Imatinib, Sorafenib
- **Assay:** RT-PCR
- **Target genes:** RKIP, RELA, SNAI, ESR1, NME1



Activation and repression of PEBP1/RKIP and its regulatory pathways.



Summary

- We used text mining datasets and a manual literature search to extract evidence for *possible* interactions between several metastasis suppressors and their regulators.
- We then used the knockdown dataset to filter these interactions in the *context* of the breast cancer cell line MCF7.
- The resulting interactions were coded in the biological expression language (BEL) to build a functional metastasis *model*.
- A reverse causal reasoning approach was used to test and *prioritize* these interactions and extract pathways that are most consistent with drug treatments that inhibit cell growth.
- We suggested that the metastasis suppressor RKIP is on the receiving end of two key regulatory *pathways*. One involves P65 (RELA) and SNAI1, which were previously reported to inhibit RKIP, and the other involves the estrogen receptor (ESR1), which induces RKIP through the kinase NME1.

References I

-  Bergamaschi, A., Madak-Erdogan, Z., Kim, Y. J., Choi, Y.-L., Lu, H., and Katzenellenbogen, B. S. (2014). The forkhead transcription factor FOXM1 promotes endocrine resistance and invasiveness in estrogen receptor-positive breast cancer by expansion of stem-like cancer cells. *Breast cancer research : BCR*, 16(5):436.
-  Berger, J. C., Vander Griend, D. J., Robinson, V. L., Hickson, J. A., and Rinker-Schaeffer, C. W. (2005). Metastasis suppressor genes: From gene identification to protein function and regulation. *Cancer biology & therapy*, 4(8):805–812.
-  Buchwalter, G., Hickey, M. M., Cromer, A., Selfors, L. M., Gunawardane, R. N., Frishman, J., Jeselsohn, R., Lim, E., Chi, D., Fu, X., Schiff, R., Brown, M., and Brugge, J. S. (2013). PDEF promotes luminal differentiation and acts as a survival factor for ER-positive breast cancer cells. *Cancer cell*, 23(6):753–767.
-  Dahlman-Wright, K., Qiao, Y., Jonsson, P., Gustafsson, J.-A., Williams, C., and Zhao, C. (2012). Interplay between AP-1 and estrogen receptor $\{\$ \alpha \$\}$ in regulating gene expression and proliferation networks in breast cancer cells. *Carcinogenesis*, 33(9):1684–1691.
-  Dunham, I., Kundaje, A., Aldred, S. F., Collins, P. J., Davis, C. A., Doyle, F., Epstein, C. B., Frietze, S., Harrow, J., Kaul, R., Khatun, J., Lajoie, B. R., Landt, S. G., Lee, B. K., Pauli, F., Rosenbloom, K. R., Sabo, P., Safi, A., Sanyal, A., Shores, N., Simon, J. M., Song, L., Trinklein, N. D., Altshuler, R. C., Birney, E., Brown, J. B., Cheng, C., Djebali, S., Dong, X., Ernst, J., Furey, T. S., Gerstein, M., Giardine, B., Greven, M., Hardison, R. C., Harris, R. S., Herrero, J., Hoffman, M. M., Iyer, S., Kelis, M., Kheradpour, P., Lassmann, T., Li, Q., Lin, X., Marinov, G. K., Merkel, A., Mortazavi, A., Parker, S. C. J., Reddy, T. E., Rozowsky, J., Schlesinger, F., Thurman, R. E., Wang, J., Ward, L. D., Whitfield, T. W., Wilder, S. P., Wu, W., Xi, H. S., Yip, K. Y., Zhuang, J., Bernstein, B. E., Green, E. D., Gunter, C., Snyder, M., Pazin, M. J., Lowdon, R. F., Dillon, L. A. L., Adams, L. B., Kelly, C. J., Zhang, J., Wexler, J. R., Good, P. J., Feingold, E. A., Crawford, G. E., Dekker, J., Elnitski, L., Farnham, P. J., Giddings, M. C., Gingeras, T. R., Guigó, R., Hubbard, T. J., Kent, W. J., Lieb, J. D., Margulies, E. H., Myers, R. M., Stamatoyannopoulos, J. A., Tenenbaum, S. A., Weng, Z., White, K. P., Wold, B., Yu, Y., Wrobel, J., Risk, B. A., Gunawardena, H. P., Kuiper, H. C., Maier, C. W., Xie, L., Chen, X., Mikkelsen, T. S., Gillespie, S., Goren, A., Ram, O., Zhang, X., Wang, L., Issner, R., Coyne, M. J., Durham, T., Ku, M., Truong, T., Eaton, M. L., Dobin, A., Tanzer, A., Lagarde, J., Lin, W., Xue, C., Williams, B. A., Zaleski, C., Röder, M., Kokocinski, F., Abdelhamid, R. F., Alioto, T., Antoshechkin, I., Baer, M. T., Batut, P., Bell, I., Bell, K., Chakrabortty, S., Chrast, J., Curado, J., Derrien, T., Drenkow, J., Dumais, E., Dumais, J., Duttagupta, R.,

References II

- Fastuca, M., Fejes-Toth, K., Ferreira, P., Foissac, S., Fullwood, M. J., Gao, H., Gonzalez, D., Gordon, A., Howald, C., Jha, S., Johnson, R., Kapranov, P., King, B., Kingswood, C., Li, G., Luo, O. J., Park, E., Preall, J. B., Presaud, K., Ribeca, P., Robyr, D., Ruan, X., Sammeth, M., Sandhu, K. S., Schaeffer, L., See, L. H., Shahab, A., Skancke, J., Suzuki, A. M., Takahashi, H., Tilgner, H., Trout, D., Walters, N., Wang, H., Hayashizaki, Y., Reymond, A., Antonarakis, S. E., Hannon, G. J., Ruan, Y., Carninci, P., Sloan, C. A., Learned, K., Malladi, V. S., Wong, M. C., Barber, G. P., Cline, M. S., Dreszer, T. R., Heitner, S. G., Karolchik, D., Kirkup, V. M., Meyer, L. R., Long, J. C., Maddren, M., Raney, B. J., Grasfeder, L. L., Giresi, P. G., Battenhouse, A., Sheffield, N. C., Showers, K. A., London, D., Bhinge, A. A., Shestak, C., Schaner, M. R., Kim, S. K., Zhang, Z. Z., Mieczkowski, P. A., Mieczkowska, J. O., Liu, Z., McDaniell, R. M., Ni, Y., Rashid, N. U., Kim, M. J., Adar, S., Zhang, Z., Wang, T., Winter, D., Keefe, D., Iyer, V. R., Zheng, M., Wang, P., Gertz, J., Vielmetter, J., Partridge, E. C., Varley, K. E., Gasper, C., Bansal, A., Pepke, S., Jain, P., Amrhein, H., Bowling, K. M., Anaya, M., Cross, M. K., Muratet, M. A., Newberry, K. M., McCue, K., Nesmith, A. S., Fisher-Aylor, K. I., Pusey, B., DeSalvo, G., Parker, S. L., Balasubramanian, S., Davis, N. S., Meadows, S. K., Eggleston, T., Newberry, J. S., Levy, S. E., Absher, D. M., Wong, W. H., Blow, M. J., Visel, A., Pennachio, L. A., Petrykowska, H. M., Abyzov, A., Aken, B., Barrell, D., Barson, G., Berry, A., Bignell, A., Boychenko, V., Bussotti, G., Davidson, C., Despacio-Reyes, G., Diekhans, M., Ezkurdia, I., Frankish, A., Gilbert, J., Gonzalez, J. M., Griffiths, E., Harte, R., Hendrix, D. A., Hunt, T., Jungreis, I., Kay, M., Khurana, E., Leng, J., Lin, M. F., Loveland, J., Lu, Z., Manthravadi, D., Mariotti, M., Mudge, J., Mukherjee, G., Notre Dame, C., Pei, B., Rodriguez, J. M., Saunders, G., Sboner, A., Searle, S., Sisu, C., Snow, C., Steward, C., Tapanari, E., Tress, M. L., Van Baren, M. J., Washietl, S., Wilming, L., Zadissa, A., Zhang, Z., Brent, M., Haussler, D., Valencia, A., Addelman, N., Alexander, R. P., Auerbach, R. K., Balasubramanian, S., Bettinger, K., Bhardwaj, N., Boyle, A. P., Cao, A. R., Cayting, P., Charos, A., Cheng, Y., Eastman, C., Euskirchen, G., Fleming, J. D., Grubert, F., Habegger, L., Hariharan, M., Harmanci, A., Iyengar, S., Jin, V. X., Karczewski, K. J., Kasowski, M., Lacroute, P., Lam, H., Lamarre-Vincent, N., Lian, J., Lindahl-Allen, M., Min, R., Miotto, B., Monahan, H., Moqtaderi, Z., Mu, X. J., O'Geen, H., Ouyang, Z., Patacsil, D., Raha, D., Ramirez, L., Reed, B., Shi, M., Slifer, T., Witt, H., Wu, L., Xu, X., Yan, K. K., Yang, X., Struhl, K., Weissman, S. M., Penalva, L. O., Karmakar, S., Bhanvadia, R. R., Choudhury, A., Domanus, M., Ma, L., Moran, J., Victorsen, A., Auer, T., Centanin, L., Eichenlaub, M., Gruhl, F., Heermann, S., Hoeckendorf, B., Inoue, D., Kellner, T., Kirchmaier, S., Mueller, C., Reinhardt, R., Schertel, L., Schneider, S., Sinn, R., Wittbrodt, B., Wittbrodt, J., Jain, G., Balasundaram, G., Bates, D. L., Byron, R., Canfield, T. K., Diegel, M. J., Dunn, D., Ebersol, A. K., Frum, T., Garg, K., Gist, E., Hansen, R. S., Boatman, L., Haugen, E., Humbert, R., Johnson, A. K., Johnson, E. M., Kutyavin, T. V., Lee, K., Lotakis, D., Maurano, M. T., Neph, S. J., Neri, F. V., Nguyen, E. D., Qu, H., Reynolds, A. P., Roach, V., Rynes, E., Sanchez, M. E., Sandstrom, R. S., Shafer, A. O., Stergachis, A. B., Thomas, S., Vernot, B., Vierstra, J., Vong, S., Wang, H., Weaver, M. A., Yan, Y., Zhang, M., Akey, J. M., Bender, M., Dorschner, M. O., Groudine, M., MacCoss, M. J., Navas, P., Stamatoyannopoulos, G., Beal, K., Brazma, A., Fllice, P., Johnson, N., Lukk, M., Luscombe, N. M., Sobral, D., Vaquerizas, J. M., Batzoglou, S., Sidow, A., Hussami, N., Kyriazopoulou-Panagiotopoulou, S., Libbrecht, M. W., Schaub, M. A., Miller, W., Bickel, P. J., Banfafai, B., Boley, N. P., Huang, H., Li, J. J., Noble, W. S., Bilmes, J. A., Buske, O. J., Sahu, A. D., Kharchenko, P. V., Park, P. J., Baker, D., Taylor, J., and Lochovsky, L. (2012). An integrated encyclopedia of DNA elements in the human genome.

Nature, 489(7414).

References III

-  Elvidge, G. P., Glenny, L., Appelhoff, R. J., Ratcliffe, P. J., Ragoussis, J., and Gleadle, J. M. (2006). Concordant regulation of gene expression by hypoxia and 2-oxoglutarate-dependent dioxygenase inhibition: the role of HIF-1alpha, HIF-2alpha, and other pathways. *The Journal of biological chemistry*, 281(22):15215–15226.
-  Feng, C., Song, C., Liu, Y., Qian, F., Gao, Y., Ning, Z., Wang, Q., Jiang, Y., Li, Y., Li, M., Chen, J., Zhang, J., and Li, C. (2019). KnockTF: a comprehensive human gene expression profile database with knockdown/knockout of transcription factors. *Nucleic acids research*.
-  Hutchison, M. R. (2013). Mice with a conditional deletion of the neurotrophin receptor TrkB are dwarfed, and are similar to mice with a MAPK14 deletion. *PloS one*, 8(6):e66206.
-  Janknecht, R. and Hunter, T. (1997). Convergence of MAP kinase pathways on the ternary complex factor Sap-1a. *The EMBO journal*, 16(7):1620–1627.
-  Koleti, A., Terryn, R., Stathias, V., Chung, C., Cooper, D. J., Turner, J. P., Vidović, D., Forlin, M., Kelley, T. T., D'Urso, A., Allen, B. K., Torre, D., Jagodnik, K. M., Wang, L., Jenkins, S. L., Mader, C., Niu, W., Fazel, M., Mahi, N., Pilarczyk, M., Clark, N., Shamsaei, B., Meller, J., Vasiliauskas, J., Reichard, J., Medvedovic, M., Ma'ayan, A., Pillai, A., and Schürer, S. C. (2018). Data Portal for the Library of Integrated Network-based Cellular Signatures (LINCS) program: Integrated access to diverse large-scale cellular perturbation response data. *Nucleic Acids Research*, 46(D1).
-  Lai, C.-F., Flach, K. D., Alexi, X., Fox, S. P., Ottaviani, S., Thiruchelvam, P. T. R., Kyle, F. J., Thomas, R. S., Launchbury, R., Hua, H., Callaghan, H. B., Carroll, J. S., Charles Coombes, R., Zwart, W., Buluwela, L., and Ali, S. (2013). Co-regulated gene expression by oestrogen receptor { $\$α\$$ } and liver receptor homolog-1 is a feature of the oestrogen response in breast cancer cells. *Nucleic acids research*, 41(22):10228–10240.

References IV

-  Lai, R., Gu, M., Jiang, W., Lin, W., Xu, P., Liu, Z., Huang, H., An, H., and Wang, X. (2017). Raf Kinase Inhibitor Protein Preferentially Promotes TLR3-Triggered Signaling and Inflammation. *Journal of immunology (Baltimore, Md. : 1950)*, 198(10):4086–4095.
-  Lasham, A., Samuel, W., Cao, H., Patel, R., Mehta, R., Stern, J. L., Reid, G., Woolley, A. G., Miller, L. D., Black, M. A., Shelling, A. N., Print, C. G., and Braithwaite, A. W. (2012). YB-1, the E2F pathway, and regulation of tumor cell growth. *Journal of the National Cancer Institute*, 104(2):133–146.
-  Lee, S.-H., Che, X., Jeong, J.-H., Choi, J.-Y., Lee, Y.-J., Lee, Y.-H., Bae, S.-C., and Lee, Y.-M. (2012). Runx2 protein stabilizes hypoxia-inducible factor-1 $\{\$ \alpha \$\}$ through competition with von Hippel-Lindau protein (pVHL) and stimulates angiogenesis in growth plate hypertrophic chondrocytes. *The Journal of biological chemistry*, 287(18):14760–14771.
-  Lee, Y.-L., Li, Y.-C., Su, C.-H., Chiao, C.-H., Lin, I.-H., and Hsu, M.-T. (2015). MAF1 represses CDKN1A through a Pol III-dependent mechanism. *eLife*, 4:e06283.
-  Marino, N., Collins, J. W., Shen, C., Caplen, N. J., Merchant, A. S., Gökmen-Polar, Y., Goswami, C. P., Hoshino, T., Qian, Y., Sledge, G. W., and Steeg, P. S. (2014). Identification and validation of genes with expression patterns inverse to multiple metastasis suppressor genes in breast cancer cell lines. *Clinical & Experimental Metastasis*, 31(7):771–786.
-  McCorkle, J. R., Leonard, M. K., Kraner, S. D., Blalock, E. M., Ma, D., Zimmer, S. G., and Kaetzel, D. M. (2014). The metastasis suppressor NME1 regulates expression of genes linked to metastasis and patient outcome in melanoma and breast carcinoma. *Cancer genomics & proteomics*, 11(4):175–194.
-  Mizamtsidi, M., Nastos, C., Mastorakos, G., Dina, R., Vassiliou, I., Gazouli, M., and Palazzo, F. (2018). Diagnosis, management, histology and genetics of sporadic primary hyperparathyroidism: old knowledge with new tricks. *Endocrine connections*, 7(2):R56–R68.

References V

-  Salazar, M. D., Ratnam, M., Patki, M., Kisovic, I., Trumbly, R., Iman, M., and Ratnam, M. (2011). During hormone depletion or tamoxifen treatment of breast cancer cells the estrogen receptor apoprotein supports cell cycling through the retinoic acid receptor $\{\alpha\}$ 1 apoprotein. *Breast cancer research : BCR*, 13(1):R18.
-  Smith, S. C. and Theodorescu, D. (2009). Learning therapeutic lessons from metastasis suppressor proteins. *Nature Reviews Cancer*, 9(4):253–264.
-  Tan, S. K., Lin, Z. H., Chang, C. W., Varang, V., Chng, K. R., Pan, Y. F., Yong, E. L., Sung, W. K., Sung, W. K., and Cheung, E. (2011). AP-2 $\{\gamma\}$ regulates oestrogen receptor-mediated long-range chromatin interaction and gene transcription. *The EMBO journal*, 30(13):2569–2581.
-  Theodorou, V., Stark, R., Menon, S., and Carroll, J. S. (2013). GATA3 acts upstream of FOXA1 in mediating ESR1 binding by shaping enhancer accessibility. *Genome research*, 23(1):12–22.
-  Wan, Y. Y. (2014). GATA3: a master of many trades in immune regulation. *Trends in immunology*, 35(6):233–242.
-  Xue, Z., Vis, D. J., Bruna, A., Sustic, T., van Wageningen, S., Batra, A. S., Rueda, O. M., Bosdriesz, E., Caldas, C., Wessels, L. F. A., and Bernards, R. (2018). MAP3K1 and MAP2K4 mutations are associated with sensitivity to MEK inhibitors in multiple cancer models. *Cell research*, 28(7):719–729.
-  Yau, C. and Benz, C. C. (2008). Genes responsive to both oxidant stress and loss of estrogen receptor function identify a poor prognosis group of estrogen receptor positive primary breast cancers. *Breast cancer research : BCR*, 10(4):R61.