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On Signaling Dysregulation in Cancer

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***Abstract*— The evolutionary dynamics of cancer underlie its near boundless potential for therapeutic resistance, representing the greatest challenge in the fight against cancer. These dynamics are driven by the evolving diversity of genetic and epigenetic alterations which translate into signaling dysregulations that underpin cancer hallmarks, including the evasion of growth suppression and the reprograming of metabolism. Pathway entropy is proposed as a measure that can differentiate between tumors and normal tissue as well as shed light on acquired therapeutic resistance. The potential utility of the proposed measure is discussed within the context of lung and colorectal cancers.**

Keywords—cancer, signaling, pathway, entropy, resistance.

I. INTRODUCTION

Cancer is a complex disease driven by genetic and epigenetic alterations co-evolving with the tumor microenvironment (TME), ultimately shaping the trajectory of disease progression and its response to therapeutic interventions [1]. The ever-expanding understanding of the genetic and epigenetic etiology of cancer has been priming the expectation that the development of more effective and targeted cancer therapies is at hand. This expectation is further fueled by the increasing affordability of whole genome sequencing and tumor omics profiling which provides a strong rational for the pursuit of personalized and precision cancer therapies based on patient genetic, epigenetic and metabolomics signatures [2]. Combination therapy has been explored as a promising approach to enhance clinical response and limit drug resistance, however more research is needed on how to rationalize treatment modalities that combine multiple cancer drugs [3-6]. On the other hand, the evolutionary perspective of cancer, first proposed by Nowell [7], suggests that there is an intrinsic barrier to achieving a lasting cure using therapeutic modalities aiming at killing as many cancer cells as possible [8]. According to this perspective, selection pressures of cancer therapies, many of which are genotoxic, eradicate sensitive cancer cells, leaving the resistant one to proceed and feed the recurrence of a potentially more malignant and therapeutically resistant cancer [9]. Recently, high accuracy DNA duplex sequencing of colorectal tumors revealed that there does not exist a single DNA base that is not mutated in at least one cancer cell [10]. Such hyper genetic diversity of tumors, asserted at diagnosis time, provides a substrate for cancer evolutionary dynamics, leading to a near infinite number of potential avenues for therapeutic resistance. Herein lies one of the most critical challenges in the fight against cancer.

Recent studies have revealed patterns of cancer evolutionary trajectories involving different sets of driver mutations and copy number alterations (CNA) affecting different chromosomes, depending on the stage of cancer progression [11-13]. In other words, at each stage of cancer evolution, different genetic alterations and hence corresponding signaling pathways are more at play as determinants of its progression dynamics. For instance, the evolutionary trajectory of colorectal adenocarcinoma involves early initiating genetic alterations which include driver mutations in APC, KRAS, PI3KCA, TP53 and FBXW7 as well as copy number alterations such as the deletion of chromosome arm 17p. This is followed in few years after diagnosis, by driver mutations in CTNNB1, PCBP1, ACVR2A, B2M, SOX9, TCF7L2, SMAD2, SMAD4, PTEN and CNA affecting multiple chromosomes [11]. CNA affecting additional chromosomes are also prevalent in the late stage of cancer evolutionary trajectory [11]. The dynamic landscape of dysregulated signaling resulting from the evolving genetic and epigenetic alterations, subject to the selective pressure of the TME will ultimately determine tumor progression and its response to treatment. Indeed, it is the confluence of signaling-pathway-integrated effects of genetic and epigenetic alterations that drives cell death evasion, reprogramed metabolism and sustained proliferation [14]. The characterization of signaling dysfunction in cancer would therefore be instrumental to the development of an actionable understanding of cancer evolutionary dynamics and to the design of therapeutic strategies that can thwart resistance. This will require either the measurement or estimation of the activation states of signaling pathways. In the absence of effective, high-throughput protein-based measurement methods, mRNA-based approaches of assessing pathway activity have been proposed to support targeted cancer therapies [15]. Although the consideration of signaling activity in precision oncology addresses epigenetic alterations [16], the selective focus on pathways targeted by the treatment would also benefit from the consideration of the role of signaling-metabolism coupling in determining cancer pathophysiology and therapeutic resistance. New approaches would be needed to characterize the dysfunctions of signaling networks in cancer cells and their effects on all cellular

processes, including metabolism. Network entropy has been previously used to characterize protein interaction networks. The robustness of networks such as protein-protein cell signaling networks was studied using the notion of network entropy [17], defined based on Kolmogorov–Sinai entropy [18]. Network entropy is defined on a graph, representing the network, with the stochastic probability transition matrix of an assumed Markov process generating information by visiting the graph nodes [17]. Network entropy was shown to be a measure of network robustness and a predictor of the evolution of the network's structure [17]. This is particularly relevant to cancer evolutionary dynamics where the rewiring of cell signaling pathways is a driver of cancer resilience manifested as therapeutic resistance. Network entropy was applied to signaling networks to discriminate cell differentiation state, where the stochastic matrix is estimated using the product of the expression levels of the interacting genes in the network, in accordance to the mass-action principle [19]. Local network entropy defined for signaling network nodes was also shown to be higher for tumors when compared to normal tissue [20], and predicts cancer drug sensitivity [21]. These and other works explored the notion of entropy as a measure with potential applications to the characterization of cancer progression and its therapeutic resistance. This article builds on and extend the results of these works with a pathway entropic measure that explicitly considers the paths of oncogenic signal transduction, providing hence a concrete model for the characterization of specific signaling pathways of interest, such as those considered for targeted therapy. The potential prognostic utility of the proposed measure is explored for lung and colorectal cancers using patient data sourced from The Cancer Genome Atlas (TCGA) project.

II. Dysregulation of Signaling Pathways in Cancer

The cell signaling network is represented using a directed graph D whose input nodes are receptors of stimuli such as growth factors and cytokines. An information or signal transduction path is defined as any directed path that connects two nodes in D. The dysregulation of the cell signaling network is manifested as an aberrant flow of information along the graph paths which serve as the backbone of signal transduction between cell stimuli nodes (e.g. growth factor receptors such as EGFR) and the major signaling hubs or end-effectors, such as AKT, RB, HIF, and AMPK, for the key cellular processes of growth, cell cycle, and metabolism. Signaling nodes such as RB and AMPK, are labelled as end-effectors due to their role as relays of effector actions at the interface between distinct cellular pathways such as is the case of AMPK which exert regulatory actions on metabolic enzymes such as GLUT and ACC [22]. A signaling pathway w_i is defined as the set of shortest directed paths on the graph D that link a stimuli node to a sink/end-effector node i. We will assume that at any point in time, only one among the $n_i > 0$ directed paths of w_i is an oncogenic driver of the signaling pathway w_i. In other words, w_i is assumed to take n_i states corresponding to the distinct possible paths through which dominant oncogenic signals are transduced from a stimuli node to the end-effector of the signaling pathway under consideration. Let π_j be the probability that path $j = 0, \dots n_i - 1$ is an oncogenic driver. Pathway entropy for w_i, normalized over the number of paths, is defined as follows:

$$H_i = -\frac{1}{1+\log(n_i)} \sum_{j=0}^{n_i-1} \pi_j \log \pi_j \qquad (1)$$

The defined entropy represents the uncertainty about the knowledge of the oncogenic driver path, reflecting hence the oncogenic promiscuity, i.e. rewiring capacity, of the signaling pathway w_i. The additional constant value of 1 is used in the normalization factor to avoid a zero value for the cases of a single shortest graph path in a pathway. The interpretation of the proposed signaling entropy is akin to that assumed in [19]. However, the proposed quantification of signaling dysregulation is instead based on the effect of pathway-integrated genetic and epigenetic alterations manifested through the perturbation in mRNA expression of the relevant signaling proteins. This particular formulation is motivated by the understanding that signaling dysregulation underpins the hallmarks of cancer [14], and is supported by the fact that the selected targeting of specific signaling pathways is the actual lever of therapeutic action in precision oncology. The probability π_j that a graph path j is an oncogenic driver is defined as follows:

$$\pi_j = \prod_{k \in L_j} p_k \qquad (2)$$

Where p_k is the probability that the kth edge of path j is dysregulated, where L_j is the set of graph edges, linking two nodes, in the jth path. The probability of interactions between two signaling proteins x and y can be approximated, based on the mass-action principle, by the product $E_x E_y$ of their respective mRNA expression levels E_x and E_y [19]. The dysregulation probability p_k for a tumor sample (i.e. a patient) can therefore be approximated by the change of $E_x E_y$, i.e. $\Delta(E_x E_y)$, relative to gene expression levels

in normal tissue, quantifying hence the likelihood of genetic/epigenetic caused altered interactions between the two signaling proteins of graph edge k, as follows:

$$p_k = \frac{E_x(E_y - \overline{E_{0y}}) + E_y(E_x - \overline{E_{0x}})}{E_x(E_y + \overline{E_{0y}}) + E_y(E_x + \overline{E_{0x}})} \qquad (3)$$

$\overline{E_{0x}}$ and $\overline{E_{0y}}$ are the mean mRNA expressions of gene x and y in normal tissue, respectively. The mRNA expression data available from the TCGA project often contain a small set of normal tissue samples, justifying the use of mean values for normal mRNA expressions. The probability p_k is estimated as the "partial" change of the product E_xE_y, normalized using $E_x(E_y + \overline{E_{0y}}) + E_y(E_x + \overline{E_{0x}})$ to ensure its interpretation as a probability measure. The estimation of p_k relies on the differential gene mRNA expression between tumor samples and normal tissue, reflecting hence the perturbation to protein-protein interaction caused by genetic alterations. Furthermore, with the consideration of the possible graph paths for the transduction of signals between stimuli and end-effector nodes of signaling pathways, the proposed entropic measure embodies a concrete reflection of the promiscuity of oncogenic signaling pathways and their rewiring potential in cancer.

III. Entropic Characterization of Cancer Signaling Dysregulation

Despite the multiplicity of intertwined dimensions of cancer adaptive complexity, all cancer types share the common phenotypes of robust proliferation and therapeutic resistance. In response to therapeutic interventions, tumors instantiate diverse adaptation strategies of resistance fueled by the evolving genetic diversity and epigenetic plasticity of cancer cells and the selection pressures of the co-evolving TME. The identification of potential biomarkers of resistance would inform the choice of treatment modalities to improve patient outcome and limit treatment toxicity. Given the driver role of dysregulated oncogenic pathways in the hallmarks of cancer, entropy is explored as a measure of signaling promiscuity using the cell signaling model of Fig. 1. The model includes a panel of genes (see Table I), selected for their contributions to major oncogenic pathways through their somatic mutations and/or copy number variations for different cancer types [23-25].

Table I. GENE PANEL

Cellular Pathways	Genes
AMPK	PRKAA2 (AMPK), STK11 (LKB1)
Cell Cycle	CCND1, CCNE1, CDKN1A, CDKN1B, CDKN2A, CDKN2B, RB1 (RB)
Genome Integrity	ATM, BRCA1, MDM2, TP53
Hippo	CDH1, YAP1
Hypoxia	HIF-1α (HIF), VHL
JAK/STAT	JAK1, STAT3
P38/JNK	MAPK14 (P38), MAPK8 (JNK)
NF-χB	CHUK, NFKB1, NFKBIA
PI3K/AKT/MTOR	AKT1 (AKT), PIK3CA (PI3K), PTEN, MTOR
RAS/ERK	KRAS, BRAF, MAP2K1 (MEK), MAPK1 (ERK), NFE2L2 (NRF2)
RTK	EGFR, ERBB2, FGFR1, KIT, ALK, MET
TGF-β	SMAD3, SMAD4,TGFBR2, ACVR2A
Wntb/β-Catenin	APC, CTNNB1, DVL2, GSK3B
Other	MYC, NOTCH1, AURKA, JUB, FBXW7, CREBBP, KEAP1, SOX9

The proposed exploration focuses on lung squamous cell carcinoma (LUSC) and colorectal adenocarcinoma (COADREAD) with the consideration of a select subset of driver genes relevant to the evolutionary histories of these cancers [11], and associated signaling interactions that are integral to pathways altered in cancer (see Fig. 1), including RTK [26, 27], RAS/ERK[28], P38/JNK [29, 30], Genome Integrity (P53-DNA repair) [31], PI3K/AKT [32], MTOR signaling [33], AMPK [34], NF-χB [35], Hippo [36], Wnt/β-Catenin [37, 38], TGF-β [39, 40], JAK/STAT [41], Hypoxia [42] and the cell cycle [43]. In particular, the signaling pathways listed in Table II are considered to explore the dysfunction of cell cycle regulation and altered metabolism in cancer. These pathways underpin cancer hallmarks of sustained proliferative signaling, evasion of growth suppression and the reprogramming of metabolism. Their consideration in this study stems from their relevance to current trends in targeted therapies [44, 45]. In addition, the regulation of the cell cycle is under the regulatory control of signaling pathways ending at the cell cycle genes and notably RB which is distinguished by its role as the end-effector in the decision for a cell to proliferate or enact apoptosis or senescence [46]. On the other hand the consideration of the transduction pathways involving the other selected genes such as APC, KRAS, ALK,

EGFR and MET is motivated by the known status of these genes as cancer drivers [23], many of which are targetable by tyrosine kinase inhibitors (TKIs) [44, 45]. For the reprogramming of metabolism, AMPK, MYC, HIF, and NFE2L2 are considered for their role as regulators of metabolic enzymes such as GLUT, LDH, PDK [22] and G6PD [47], respectively.

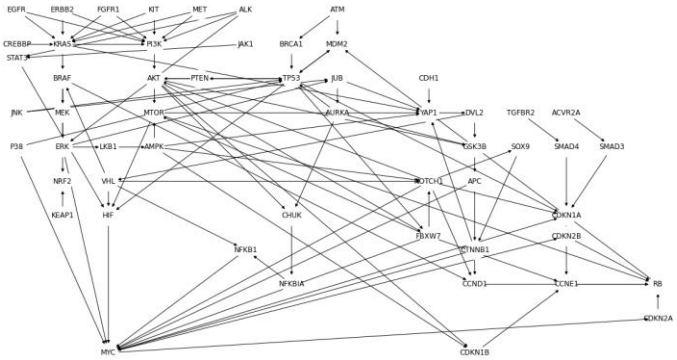

Figure 1. Cell signaling model

Table II. ONCOGENIC SIGNALING PATHWAYS

	Cell Cycle	**Metabolism**	**Proliferation**
COADREAD	APC → RB	ERK → AMPK	EGFR → AKT
	MTOR → RB	VHL → HIF	MET → AKT
	TGFBR2→ RB	ERK → HIF	ALK → AKT
LUSC	KRAS → RB	ERK → AMPK	EGFR →AKT
	MTOR→ RB	VHL→ HIF	MET → AKT
	TGFBR2 → RB	BRAF → NFE2L2	ALK → AKT

Pathway entropies where computed using the TCGA mRNA gene expression data, retrieved using the FireBrowse service [48]. The comparisons between pathway entropies of tumor and normal tissue samples are illustrated for LUSC and CODREAD using the Boxplots of Figs. 2-5. Signaling pathways are identified by source-sink pairs of signaling proteins separated by an arrow indicating the direction of signal flow. Tumor and normal tissue associated entropies are highlighted using the labels [C] and [N] respectively.

The illustrated results of pathway entropy computations, for the signaling pathways under consideration, show that the proposed measure differentiates between tumors and normal tissue. The increase in entropy for the pathways regulating the cell cycle and metabolism reflects a higher level of signaling promiscuity that underpin cancer evasion of growth suppression and the reprogramming of metabolism, which has been linked to therapeutic resistance [49]. The capacity of pathway entropy to assess the promiscuity of any select set of signaling pathways may help guide the design of combination therapies. Indeed, the entropic measure of signaling promiscuity may be interpreted as an estimation of the likelihood of pathway rewiring when evaluated for a patient following targeted therapy treatment such as EGFR inhibition.

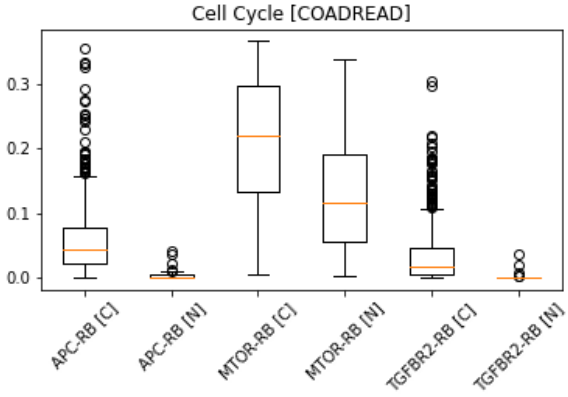

Figure 2. Entropies of signaling pathways regulating the cell cycle in colorectal cancer.

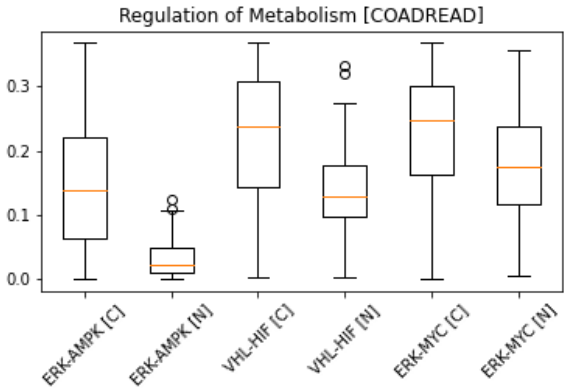

Figure 3. Entropies of signaling pathways regulating metabolism in colorectal cancer.

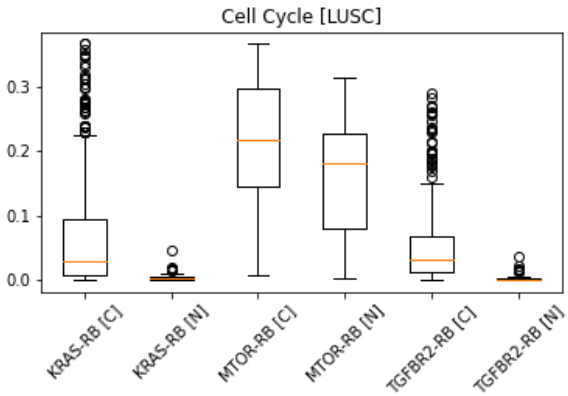

Figure 4. Entropies of signaling pathways regulating the cell cycle in lung cancer.

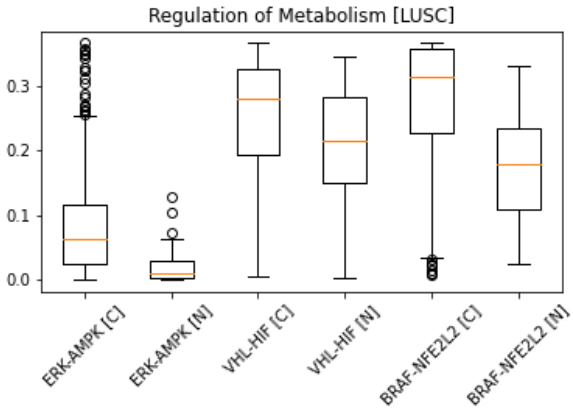

Figure 5. Entropies of signaling pathways regulating metabolism in lung cancer.

Predictive biomarkers for therapy response are available [50]. However, the use of the proposed pathway entropy as a measure of signaling promiscuity would shed light on pathway-integrated effects of genetic alterations and would hence supplement these biomarkers by identifying pathways with high entropy as potential drivers of therapeutic resistance. For instance, in the treatment of lung cancer, acquired resistance involves MET amplification in approximately 20% of NSCLC (Non-Small Cell Carcinoma) patients treated with EGFR TKIs [51]. Entropies of signaling pathways linking receptor tyrosine kinases (RTKs) and AKT, being a regulator of the cell cycle, proliferation and survival, may help identify patients that are more likely to benefit from the combination of TKIs such as EGFR and MET inhibitors. In particular, the wide interquartile ranges (IQRs) of EGFR-AKT, MET-AKT and ALK-ATK pathway entropies for lung tumor samples compared to those for normal tissue (see Fig. 6), could be suggestive of an inter-patient structural diversity of the oncogenic signaling network. This may be interpreted as an indicator of the potential for oncogenic pathway rewiring and hence acquired resistance under therapeutic targeting, which is indeed known to occur for NSCLC patients treated with EGFR, MET and ALK TKIs. On the other hand, somatic mutations, copy number variations (CNV), and mRNA expression profiles are often found to be prognostic factors, as is the case of MET amplification in NSCLC [51]. However, the proposed entropic measure quantifies the pathway-integrated effects of oncogenic alterations, and hence provides a pathway-level measure of oncogenic robustness that has a potential utility for treatment decision-making, especially in the selection of therapeutic modalities that involve targeting kinases engaged in crosstalk, as is believe to be the case for EGFR and MET[51].

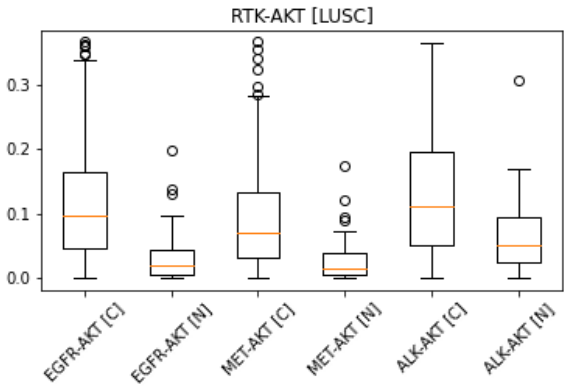

Figure 6. Entropies of select oncogenic signaling pathways targeted by TKIs for lung cancer.

The potential utility of pathway entropy to treatment decision making vis-à-vis therapeutic resistance would ultimately need to be clinically validated. This will require longitudinal mRNA expression data of patient tumors under treatments. Given the clinical unfeasibility of applying repeated biopsy procedures on patient tumors, circulating tumor cells (CTC) and circulating tumor-derived

components, such as mRNA, extracted from patient blood, using liquid biopsies [52], may provide a viable alternative for tumor gene expression measurements [53], enabling hence the monitoring of pathway entropies before, during and after treatments. Future works should also consider the use of signaling models that are dedicated to the specific cancer types based on the correspondingly relevant oncogenic pathways as asserted by genome wide studies.

IV. Conclusions

Pathway entropy is a measure of signaling pathway promiscuity estimated using mRNA expression data. It quantifies pathway-integrated effects of genetic alterations on signaling in cancer. Using the TCGA mRNA expression data for lung and colorectal cancers, pathway entropy is shown to differentiate between tumor and normal tissue samples. The potential prognostic value of the proposed measure vis-à-vis acquired resistance to targeted therapy is discussed in light of the quantification of signaling promiscuity for a set of signaling pathways whose dysregulation is implicated in the evasion of growth suppression and the reprogramming of metabolism in cancer. Future works are needed to investigate the clinical validity of pathway entropy as a prognostic factor of therapeutic resistance.

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References

[1] Y. Derbal, "The Adaptive Complexity of Cancer," *Biomed Res Int*, vol. 2018, p. 5837235, 2018.
[2] A. Re, C. Nardella, A. Quattrone, and A. Lunardi, Eds. "Precision Medicine in Oncology." Lausanne: Frontiers Media, 2019.
[3] "Rationalizing combination therapies," *Nature Medicine*, Editorial vol. 23, p. 1113, 10/06/online 2017.
[4] I. Bozic *et al.*, "Evolutionary dynamics of cancer in response to targeted combination therapy," *Elife*, vol. 2, p. e00747, Jun 25 2013.
[5] D. Day and L. L. Siu, "Approaches to modernize the combination drug development paradigm," *Genome Med*, vol. 8, no. 1, p. 115, Oct 28 2016.
[6] J. West *et al.*, "Towards Multidrug Adaptive Therapy," *Cancer Res*, vol. 80, no. 7, pp. 1578-1589, Apr 1 2020.
[7] P. C. Nowell, "The clonal evolution of tumor cell populations," *Science*, vol. 194, no. 4260, pp. 23-8, Oct 1 1976.
[8] P. M. Enriquez-Navas, J. W. Wojtkowiak, and R. A. Gatenby, "Application of Evolutionary Principles to Cancer Therapy," *Cancer Res*, vol. 75, no. 22, pp. 4675-80, Nov 15 2015.
[9] M. Greaves, "Evolutionary determinants of cancer," *Cancer Discov*, vol. 5, no. 8, pp. 806-20, Aug 2015.
[10] L. A. Loeb *et al.*, "Extensive subclonal mutational diversity in human colorectal cancer and its significance," *Proc Natl Acad Sci U S A*, Dec 5 2019.
[11] M. Gerstung *et al.*, "The evolutionary history of 2,658 cancers," *Nature*, vol. 578, no. 7793, pp. 122-128, Feb 2020.
[12] I. Martincorena *et al.*, "Universal Patterns of Selection in Cancer and Somatic Tissues," *Cell*, vol. 173, no. 7, p. 1823, Jun 14 2018.
[13] G. Caravagna *et al.*, "Detecting repeated cancer evolution from multi-region tumor sequencing data," *Nat Methods*, vol. 15, no. 9, pp. 707-714, Sep 2018.
[14] D. Hanahan and R. A. Weinberg, "Hallmarks of cancer: the next generation," *Cell*, vol. 144, no. 5, pp. 646-74, Mar 4 2011.
[15] W. Verhaegh *et al.*, "Selection of personalized patient therapy through the use of knowledge-based computational models that identify tumor-driving signal transduction pathways," *Cancer Res*, vol. 74, no. 11, pp. 2936-45, Jun 1 2014.
[16] V. L. Costa *et al.*, "Epigenetic regulation of Wnt signaling pathway in urological cancer," *Epigenetics*, vol. 5, no. 4, pp. 343-51, May 16 2010.
[17] L. Demetrius and T. Mankel, "Robustness and network evolution an entropic principle," *Physica A*, vol. 346, p. 15, 2005.
[18] P. Billingsley, *Ergodic theory and information* (Wiley series in probability and mathematical statistics). New York,: Wiley, 1965, pp. xiii, 193 p.
[19] C. R. Banerji *et al.*, "Cellular network entropy as the energy potential in Waddington's differentiation landscape," *Sci Rep*, vol. 3, p. 3039, Oct 24 2013.
[20] J. West, G. Bianconi, S. Severini, and A. E. Teschendorff, "Differential network entropy reveals cancer system hallmarks," *Sci Rep*, vol. 2, p. 802, 2012.
[21] A. E. Teschendorff, P. Sollich, and R. Kuehn, "Signalling entropy: A novel network-theoretical framework for systems analysis and interpretation of functional omic data," *Methods*, vol. 67, no. 3, pp. 282-93, Jun 1 2014.
[22] M. Sinkala, N. Mulder, and D. Patrick Martin, "Metabolic gene alterations impact the clinical aggressiveness and drug responses of 32 human cancers," *Commun Biol*, vol. 2, p. 414, 2019.
[23] I. T. P.-C. A. o. W. G. Consortium, "Pan-cancer analysis of whole genomes," *Nature*, vol. 578, no. 7793, pp. 82-93, Feb 2020.
[24] C. Kandoth *et al.*, "Mutational landscape and significance across 12 major cancer types," *Nature*, vol. 502, no. 7471, p. 333, 2013.
[25] G. Ciriello, M. L. Miller, B. A. Aksoy, Y. Senbabaoglu, N. Schultz, and C. Sander, "Emerging landscape of oncogenic signatures across human cancers," *Nat Genet*, vol. 45, no. 10, pp. 1127-33, Oct 2013.
[26] M. A. Lemmon and J. Schlessinger, "Cell signaling by receptor tyrosine kinases," *Cell*, vol. 141, no. 7, pp. 1117-34, Jun 25 2010.
[27] T. Regad, "Targeting RTK Signaling Pathways in Cancer," *Cancers (Basel)*, vol. 7, no. 3, pp. 1758-84, Sep 3 2015.
[28] A. De Luca, M. R. Maiello, A. D'Alessio, M. Pergameno, and N. Normanno, "The RAS/RAF/MEK/ERK and the PI3K/AKT signalling pathways: role in cancer pathogenesis and implications for therapeutic approaches," *Expert Opin Ther Targets*, vol. 16 Suppl 2, pp. S17-27, Apr 2012.

[29] E. F. Wagner and A. R. Nebreda, "Signal integration by JNK and p38 MAPK pathways in cancer development," *Nat Rev Cancer*, vol. 9, no. 8, pp. 537-49, Aug 2009.
[30] G. Sabio and R. J. Davis, "TNF and MAP kinase signalling pathways," *Semin Immunol*, vol. 26, no. 3, pp. 237-45, Jun 2014.
[31] N. J. Curtin, "DNA repair dysregulation from cancer driver to therapeutic target," *Nat Rev Cancer*, vol. 12, no. 12, pp. 801-17, Dec 2012.
[32] M. C. Mendoza, E. E. Er, and J. Blenis, "The Ras-ERK and PI3K-mTOR pathways: cross-talk and compensation," *Trends Biochem Sci*, vol. 36, no. 6, pp. 320-8, Jun 2011.
[33] M. Laplante and D. M. Sabatini, "mTOR signaling in growth control and disease," *Cell*, vol. 149, no. 2, pp. 274-93, Apr 13 2012.
[34] M. M. Mihaylova and R. J. Shaw, "The AMPK signalling pathway coordinates cell growth, autophagy and metabolism," *Nat Cell Biol*, vol. 13, no. 9, pp. 1016-23, Sep 2 2011.
[35] A. Richmond, "Nf-kappa B, chemokine gene transcription and tumour growth," *Nat Rev Immunol*, vol. 2, no. 9, pp. 664-74, Sep 2002.
[36] K. F. Harvey, X. Zhang, and D. M. Thomas, "The Hippo pathway and human cancer," *Nat Rev Cancer*, vol. 13, no. 4, pp. 246-57, Apr 2013.
[37] Y. S. Jung and J. I. Park, "Wnt signaling in cancer: therapeutic targeting of Wnt signaling beyond beta-catenin and the destruction complex," *Exp Mol Med*, vol. 52, no. 2, pp. 183-191, Feb 2020.
[38] F. Ma *et al.*, "SOX9 drives WNT pathway activation in prostate cancer," *J Clin Invest*, vol. 126, no. 5, pp. 1745-58, May 2 2016.
[39] Y. Zhang, P. B. Alexander, and X. F. Wang, "TGF-beta Family Signaling in the Control of Cell Proliferation and Survival," *Cold Spring Harb Perspect Biol*, vol. 9, no. 4, Apr 3 2017.
[40] J. Massague, "TGFbeta signalling in context," *Nat Rev Mol Cell Biol*, vol. 13, no. 10, pp. 616-30, Oct 2012.
[41] S. J. Thomas, J. A. Snowden, M. P. Zeidler, and S. J. Danson, "The role of JAK/STAT signalling in the pathogenesis, prognosis and treatment of solid tumours," *Br J Cancer*, vol. 113, no. 3, pp. 365-71, Jul 28 2015.
[42] J. Zhang and Q. Zhang, "VHL and Hypoxia Signaling: Beyond HIF in Cancer," *Biomedicines*, vol. 6, no. 1, Mar 19 2018.
[43] T. Otto and P. Sicinski, "Cell cycle proteins as promising targets in cancer therapy," *Nat Rev Cancer*, vol. 17, no. 2, pp. 93-115, Jan 27 2017.
[44] Y. H. Xie, Y. X. Chen, and J. Y. Fang, "Comprehensive review of targeted therapy for colorectal cancer," *Signal Transduct Target Ther*, vol. 5, no. 1, p. 22, Mar 20 2020.
[45] M. Yuan, L. L. Huang, J. H. Chen, J. Wu, and Q. Xu, "The emerging treatment landscape of targeted therapy in non-small-cell lung cancer," *Signal Transduct Target Ther*, vol. 4, p. 61, 2019.
[46] S. Duggal, N. Jailkhani, M. K. Midha, N. Agrawal, K. V. S. Rao, and A. Kumar, "Defining the Akt1 interactome and its role in regulating the cell cycle," *Sci Rep*, vol. 8, no. 1, p. 1303, Jan 22 2018.
[47] K. Smolkova, E. Miko, T. Kovacs, A. Leguina-Ruzzi, A. Sipos, and P. Bai, "Nuclear Factor Erythroid 2-Related Factor 2 in Regulating Cancer Metabolism," *Antioxid Redox Signal*, vol. 33, no. 13, pp. 966-997, Nov 1 2020.
[48] M. Deng, J. Bragelmann, I. Kryukov, N. Saraiva-Agostinho, and S. Perner, "FirebrowseR: an R client to the Broad Institute's Firehose Pipeline," *Database (Oxford)*, vol. 2017, 2017.
[49] A. Morandi and S. Indraccolo, "Linking metabolic reprogramming to therapy resistance in cancer," *Biochim Biophys Acta Rev Cancer*, vol. 1868, no. 1, pp. 1-6, Aug 2017.
[50] A. Toss, M. Venturelli, C. Peterle, F. Piacentini, S. Cascinu, and L. Cortesi, "Molecular Biomarkers for Prediction of Targeted Therapy Response in Metastatic Breast Cancer: Trick or Treat?," *Int J Mol Sci*, vol. 18, no. 1, Jan 4 2017.
[51] J. Fu *et al.*, "HGF/c-MET pathway in cancer: from molecular characterization to clinical evidence," *Oncogene*, vol. 40, no. 28, pp. 4625-4651, Jul 2021.
[52] I. Martins *et al.*, "Liquid Biopsies: Applications for Cancer Diagnosis and Monitoring," *Genes (Basel)*, vol. 12, no. 3, Feb 27 2021.
[53] T. B. Porras, P. Kaur, A. Ring, N. Schechter, and J. E. Lang, "Challenges in using liquid biopsies for gene expression profiling," *Oncotarget*, vol. 9, no. 6, pp. 7036-7053, Jan 23 2018.