Computational Systems Biology: Biology X

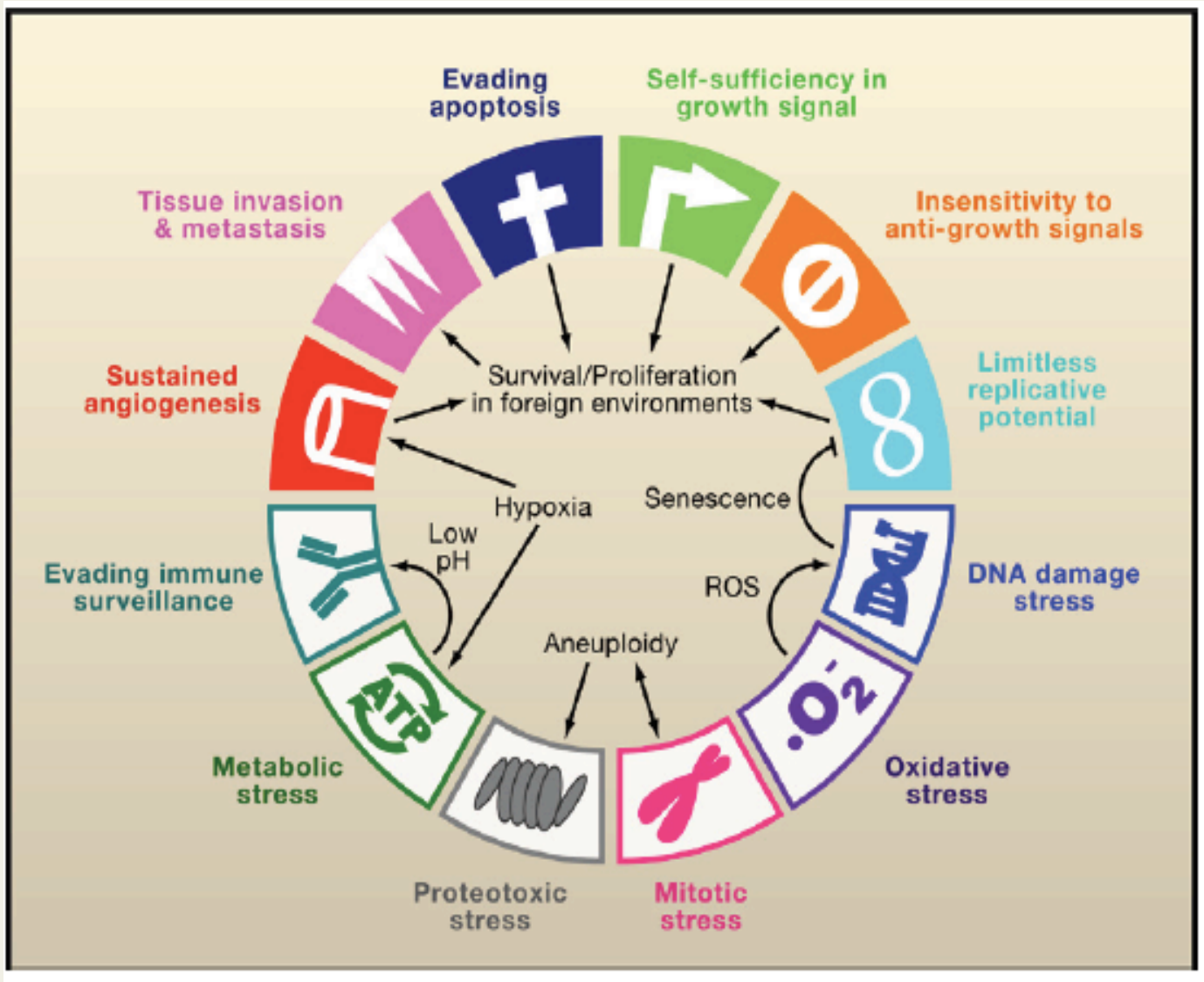
Bud Mishra

Room 1002, 715 Broadway, Courant Institute, NYU, New York, USA

L#12 (December-6-2010)

Cancer & Signals

Hallmarks of Cancer



Therapy

Anti-caner therapy must show **differential toxicity toward tumor cells** relative to normal cells.

Some unique properties of cancer cells not shared by normal cells, must be exploited

In principle, cancer can be treated by inducing cancer cells to undergo

Apoptosis

Necrosis

Senescence, or

Differentiation.

Strategies

Disrupt cancer cell-autonomous processes, by …

- **Interfering** with autocrine/ paracrine **signaling** within tumors,
- **Blocking** heterotypic **signaling** between tumor cells and the surrounding stromal tissue or blood vessels
- **Enhancing** immune **surveillance** against cancer cells expressing novel antigens

Addictions in Cancer

- “Oncogene addiction” (OA)
- “Tumor suppressor gene hypersensitivity (TSGH)”
- “Non-oncogene addiction” (NOA)

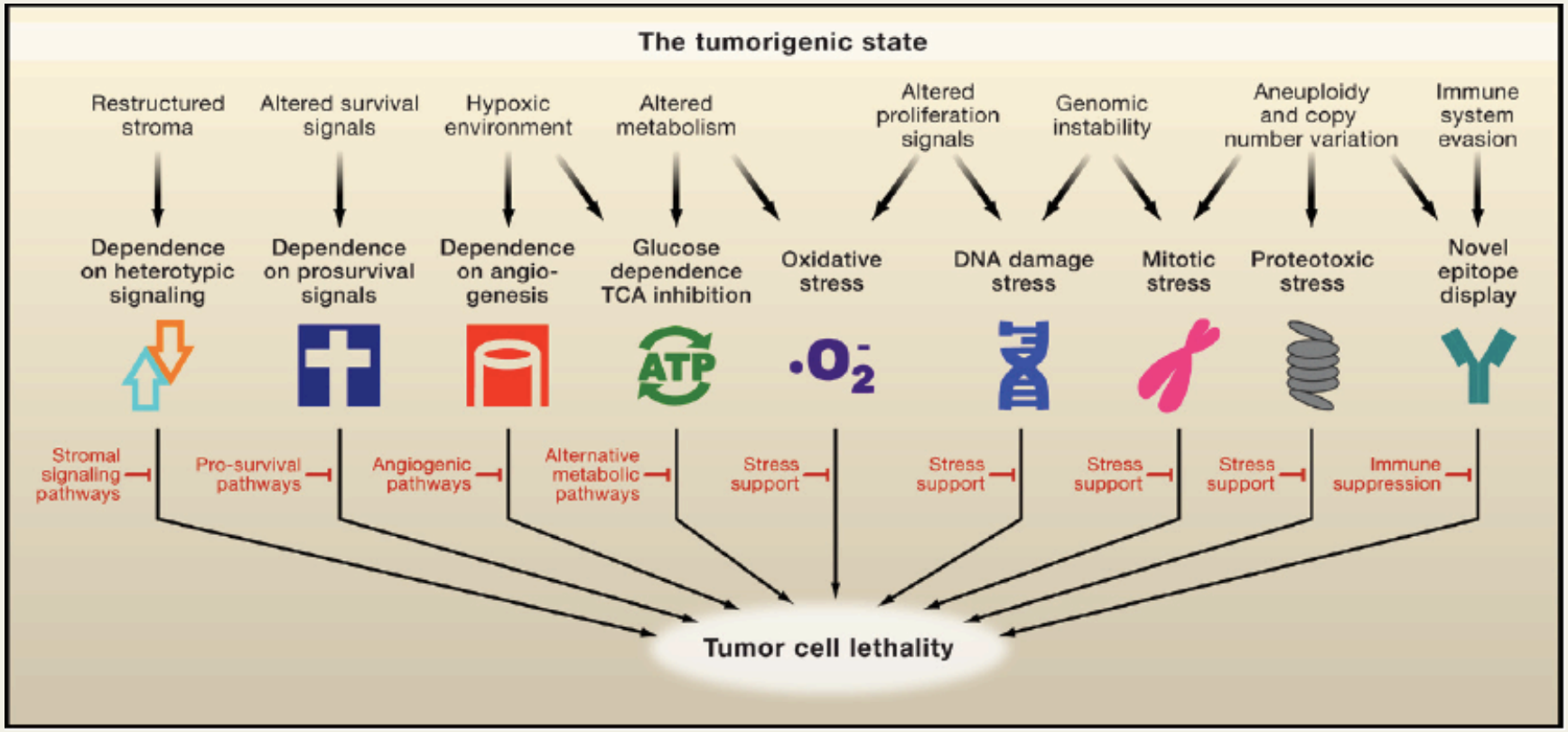
Theories of OA

- **Oncogene addiction**
  - *Oncogenes elicit strong, opposing prosurvival and proapoptotic signals in cancer cells*
  - *Acute inhibition of oncogenes tilts this balance toward cell death*
- To bring about their phenotypic manifestations, oncogenes rely on extensive adaptations in cellular processes that are themselves not oncogenic.
- In addition, cancer cells may also depend on the normal cellular functions of certain genes that act in oncogenic pathways but are not themselves classical oncogenes.
  - For example, mutations in many genes in a given oncogenic pathway are unable to directly promote tumor formation because, despite being required for their pathway, they cannot increase the overall activity of the pathway because they are not rate-limiting.

Non-Oncogene Addiction

- A reduction in the activity of many non-oncogenes in oncogenic pathway can become rate-limiting to the pathway in question, and thus, they represent potential drug targets.
  - By this rationale, cancer cells are addicted to both oncogenes and non-oncogenes.
- **Non-oncogene addiction, NOA**: The addiction of cancer cells to the functions of nononcogenes.
  - Although NOA genes, like oncogenes, are required for maintenance of the tumorigenic state, NOA genes do not undergo oncogenic mutations or functionally significant genomic alterations in tumors.

The Tumorigenic State



Drugs

Agent	Target	Addiction	Hallmarks	Potential mechanisms	References
17AAG (small molecule)	HSP90	NOA		A geldanamycin analog that binds to the ATP-binding pocket of HSP90 and inhibits its catalytic activity	Whitesell and Lindquist, 2005
1MT, MTH-Trp (small molecule)	IDO	NOA		Inhibits tryptophan catabolism in tumor microenvironment to allow T cell proliferation	Muller and Scherle, 2006
5-fluorouracil (small molecule)	DNA	NOA		Inhibits pyrimidine metabolism, incorporation in to DNA and RNA causes cell-cycle arrest	Longley et al., 2003
ABT-737, ABT-263 (small molecule)	BCL-XL, BCL-2	OA		Bind to the BH3 pocket of Bcl-XL and inhibit its antiapoptotic function	Stauffer, 2007
Alvocidib, PD 0332991 (small molecule)	CDKs	OA		Inhibit CDKs and induce cell-cycle arrest	Lee and Sicinski, 2006
AP 12009 (antisense oligo)	TGFβ 2	NOA		Inhibits tumor autocrine and paracrine signaling, reverses immune suppression in the tumor microenvironment	Muller and Scherle, 2006
AZD2281, AG014699 (small molecule)	PARP1	NOA		Inhibit base excision repair in homologous recombination repair-deficient cancer cells	Bryant et al., 2005; Farmer et al., 2005
Bevacizumab (antibody)	VEGF	NOA		Inhibits endothelial cell recruitment and tumor vasculature	Folkman, 2007
BEZ235 (small molecule)	PI3K	OA		Causes cell-cycle arrest in tumor cells and inhibits tumor angiogenesis	Maira et al., 2008
Bortezomib (small molecule)	Proteasome	NOA		Inhibits the catalytic activity of 26S proteasome and induces apoptosis	Roccaro et al., 2006

Contd.

Celecoxib (small molecule)	COX2	NOA		Reverses immune suppression in the tumor microenvironment, inhibits tumor autocrine and paracrine signaling	Muller and Scherle, 2006
Cisplatin and analogs (small molecule)	DNA	NOA		Induces DNA crosslinks	Siddik, 2003
Erlotinib, Gefitinib (small molecule)	EGFR	OA		Inhibit EGFR tyrosine kinase by competing with ATP binding	Sharma et al., 2007
GRN163L (modified oligo)	hTERT	OA		Mimics telomere sequence and inhibits the hTERT active site	Dikmen et al., 2005; Harley, 2008
GRNVAC1 (cell therapy)	hTERT	OA		Autologous dendritic cells transduced to express an hTERT-LAMP fusion protein to elicit T cell response to hTERT + tumor cells	Harley, 2008; Su et al., 2005
GV1001 (peptide)	hTERT	OA		A short immunogenic peptide from hTERT designed to elicit T cell response against hTERT + tumor cells	Harley, 2008; Nava-Parada and Emens, 2007
Imatinib, Dasatinib (small molecule)	BCR-ABL, c-Kit, Src, PDGFR, other TKs	OA		Tyrosine kinase inhibitor with multiple targets	Quintas-Cardama et al., 2007
Mapatumumab, Lexatumumab (antibody)	TRAIL receptor	NOA		Bind and activate TRAIL receptors to induce apoptosis	Carlo-Stella et al., 2007
Methotrexate (small molecule)	DHFR	NOA		Inhibits thymidine biosynthesis and induces replicative stress	McGuire, 2003

Contd.

Nutlin-3 (small molecule)	HDM2	OA		Binds to HDM2 and inhibits the binding and ubiquitination of p53	Vassilev, 2007
Oblimersen (antisense oligo)	BCL-2	OA		Inhibits the expression of BCL-2 by blocking translation of its mRNA	Moreira et al., 2006
Paclitaxel, Vinblastine (small molecule)	Mitotic spindle	NOA		Interfere with dynamics and stability of mitotic spindles, activate mitotic checkpoints, and induce chromosome mis-segregation	Weaver and Cleveland, 2005
PF-00477736 (small molecule)	Chk1	NOA		Prevents activation of the DNA damage response, leading to persistent DNA damage and replication stress	Ashwell and Zabludoff, 2008
PRIMA-1, MIRA-1 (small molecule)	Mutant p53	TSGH		Reactivate the function of mutant p53	Selivanova and Wiman, 2007
Rapamycin, RAD001, Temsirolimus (small molecule)	mTOR	NOA		Inhibit protein synthesis	Guertin and Sabatini, 2007
Retinoic acid (small molecule)	RAR, RXR	OA		Induces cellular differentiation	Spira and Carducci, 2003
SAHBs (stapled peptide)	BCL-XL, BCL-2	OA		Stapled BH3 domains that bind to BCL-2 family members and promote apoptosis	Verdine and Walensky, 2007
Sorafenib, Sunitinib (small molecule)	Multiple kinases (VEGFR, RAF, c-Kit, PDGFR)	NOA		Inhibit endothelial cell recruitment and tumor vasculature	Folkman, 2007
Topotecan, Irinotecan (small molecule)	Topo-isomerase I	NOA		Induce DNA breaks	Pommier, 2006
Trastuzumab (antibody)	ERBB2	OA		Inhibits ERBB2 activation and induces immune destruction of cancer cells	Hynes and Lane, 2005

Targets for Cancer Drug Development

- Only a subset of defective proteins may be effective target.
- “Small Molecules”… Low molecular weight organic compounds.
- Inhibit biochemical functions of
  - (i) TSGs (Tumor suppressor genes)/Gate-keepers
  - (ii) Repair Genes/ Care-takers
  - (iii) Oncogenes/ Developer

Oncoproteins

- Hyperactive oncoproteins have proven to be good targets:

Mutation	Drug
Anti-Erb8	Herceptin
Tyrosine-Kinase Inhibitor	ZD1839, 051-774
RAS Farnesyl-Transferase Inhinitor (FTI)	BMS 214622
RAF Inhibitor	BAY 43-9006
MEK Inhibitor	CI1040
mTOR Inhibitor	RAD 001

Biochemistry of Proteins

- Small Molecules:
  - (i) Easy to synthesize
  - (ii) Easy to penetrate into the interstices of a tumor
- Target Molecules:
  - Must have strong and specific interactions with small drug molecules

*Protein molecule is considered **druggable** if it carries out an identifiable enzymatic function, and a well-defined catalytic cleft for this purpose…*

DRUGGABILITY

- Transcriptional Factors
  - Considered highly undruggable as they lack catalytic clefts (Protein-DNA interaction)
- Ras
  - Druggability is problematic. It has a catalytic function (e.g., GTPase function), but it is a negative regulator of Ras signaling
  - Similar issues with Tyrosine phosphatase which reverses the effect of tyrosine kinase

Druggable targets in protein-protein interactions

- Insert a small molecule between the two docking proteins
  - E.g., Cyclin-Cdk pair
  - MDM-p53
  - BH3-BCL2/BCL-X
  - B-catenin-CBP

Kinases are attractive druggable targets

- As oncoproteins, responsible for driving neoplastic proliferation
- As enzyme processing proteins, possess catalytic clefts
- 518 protein coding genes in the human genome; out of which 90 encode tyrosine kinases

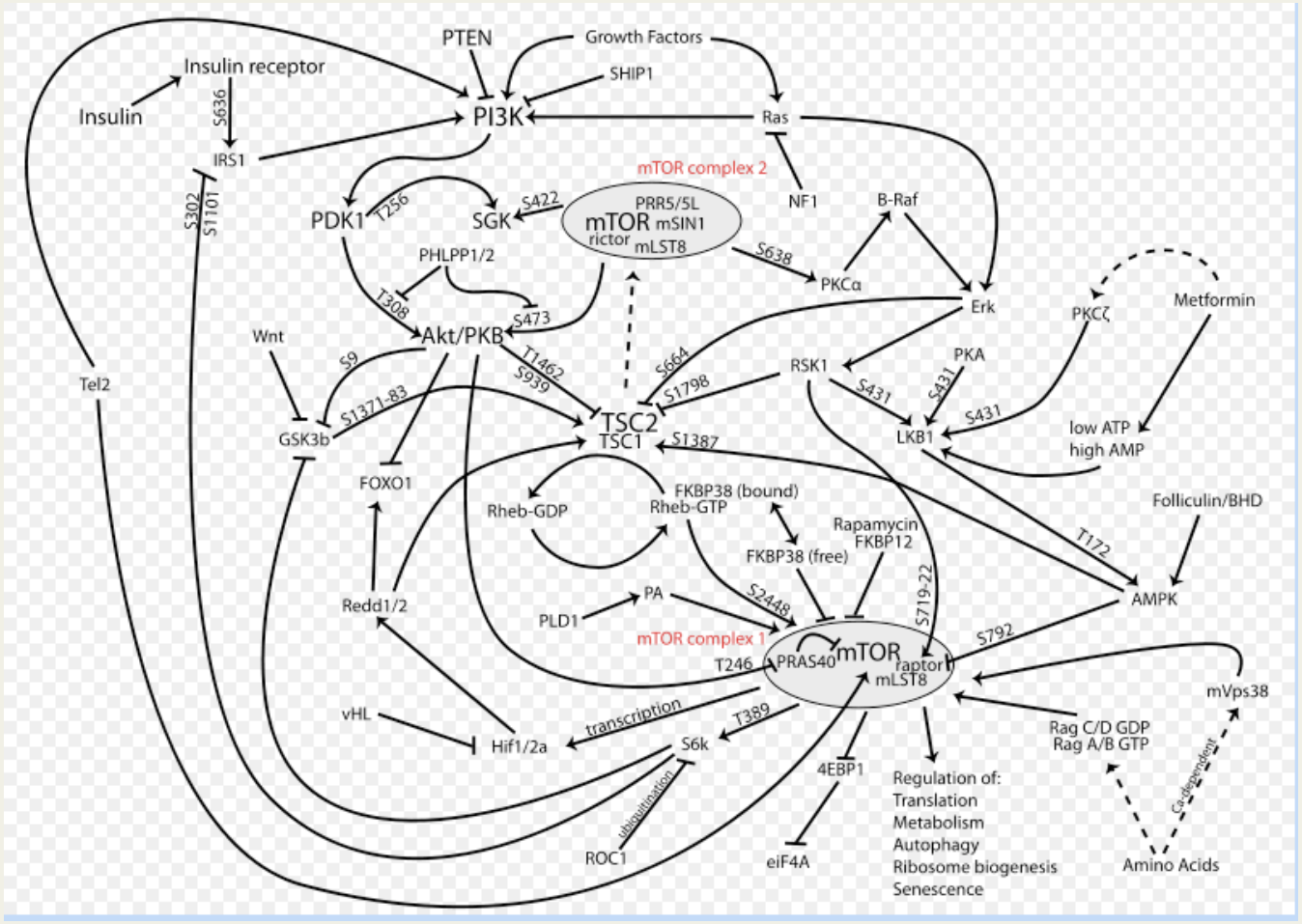
Two approaches

- Rational Drug Design
- High Throughput Screening (HTS)
  - Relative effect of the drug on its intended target, compared to its off-target effect…
  - Herceptin
  - Gleevec
  - Iressa/Tarceva

Rapamycin

- mTOR = mammalian Target of Rapamycin – regulating circuit
  - Rapamycin binds directly to FKBP12; the dimer/ complex associate with mTOR protein
  - mTOR normally phosphorylates two key governers of translation (p7056 kinase (S6K1) 4EBP1 & S6 proteins of the small ribosomal units
  - mTOR is also a key upstream activator of Akt/PKB (regulates apoptosis and proliferation)

mTOR


PTEN
Growth Factors
SHIP1
Insulin receptor
Insulin
S636
PI3K
Ras
IRS1
mTOR complex 2
S302
S1101
PDK1
T256
SGK
S422
PRR5/5L
mTOR mSIN1
rictor mLST8
NF1
B-Raf
PHLPP1/2
S638
PKCα
T308
S473
Akt/PKB
Erk
PKCζ
Metformin
Wnt
S9
T1462
S939
S664
S1798
RSK1
PKA
S431
S431
S431
Tel2
S1371-83
GSK3b
TSC2
TSC1
S1387
LKB1
low ATP
high AMP
FOXO1
FKBP38 (bound)
Rheb-GDP
Rheb-GTP
Rapamycin
FKBP12
FKBP38 (free)
Folliculin/BHD
T172
Redd1/2
PA
PLD1
S2448
S719-22
AMPK
mTOR complex 1
S792
T246
PRAS40
mTOR
raptor
mLST8
mVps38
vHL
transcription
T389
Hif1/2a
S6k
Rag C/D GDP
Rag A/B GTP
4EBP1
Regulation of:
Translation
Metabolism
Autophagy
Ribosome biogenesis
Senescence
ubiquitination
ROC1
eiF4A
Co-dependent
Amino Acids

[End of Lecture #12]