Onsdag 4/9 8.30 – 10.00.
7:2 Tumörbiologi och behandlingsutvärdering

Tumörbiologi och nya cancerbehandlingar

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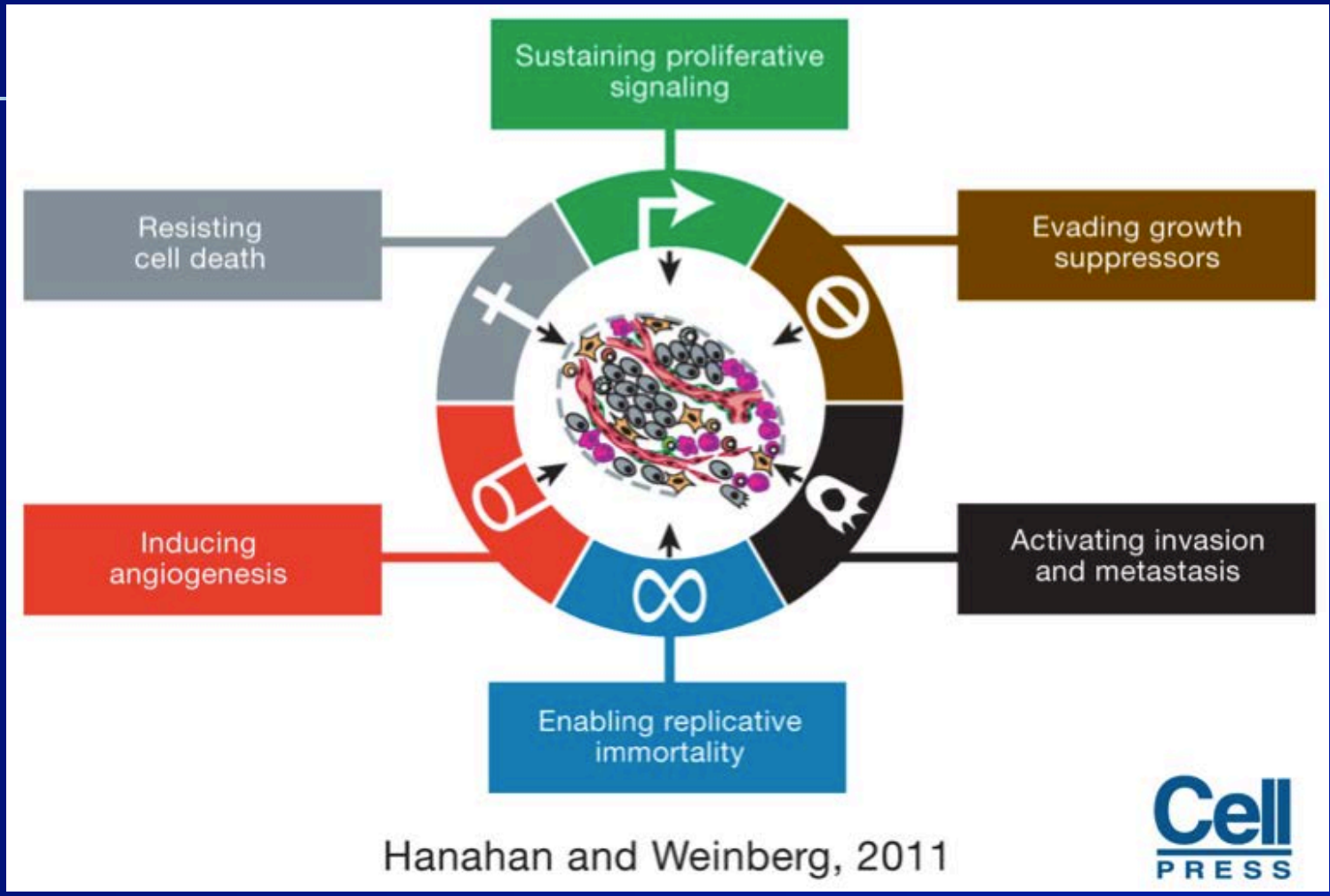
Tumörbiologi och nya cancerbehandlingar

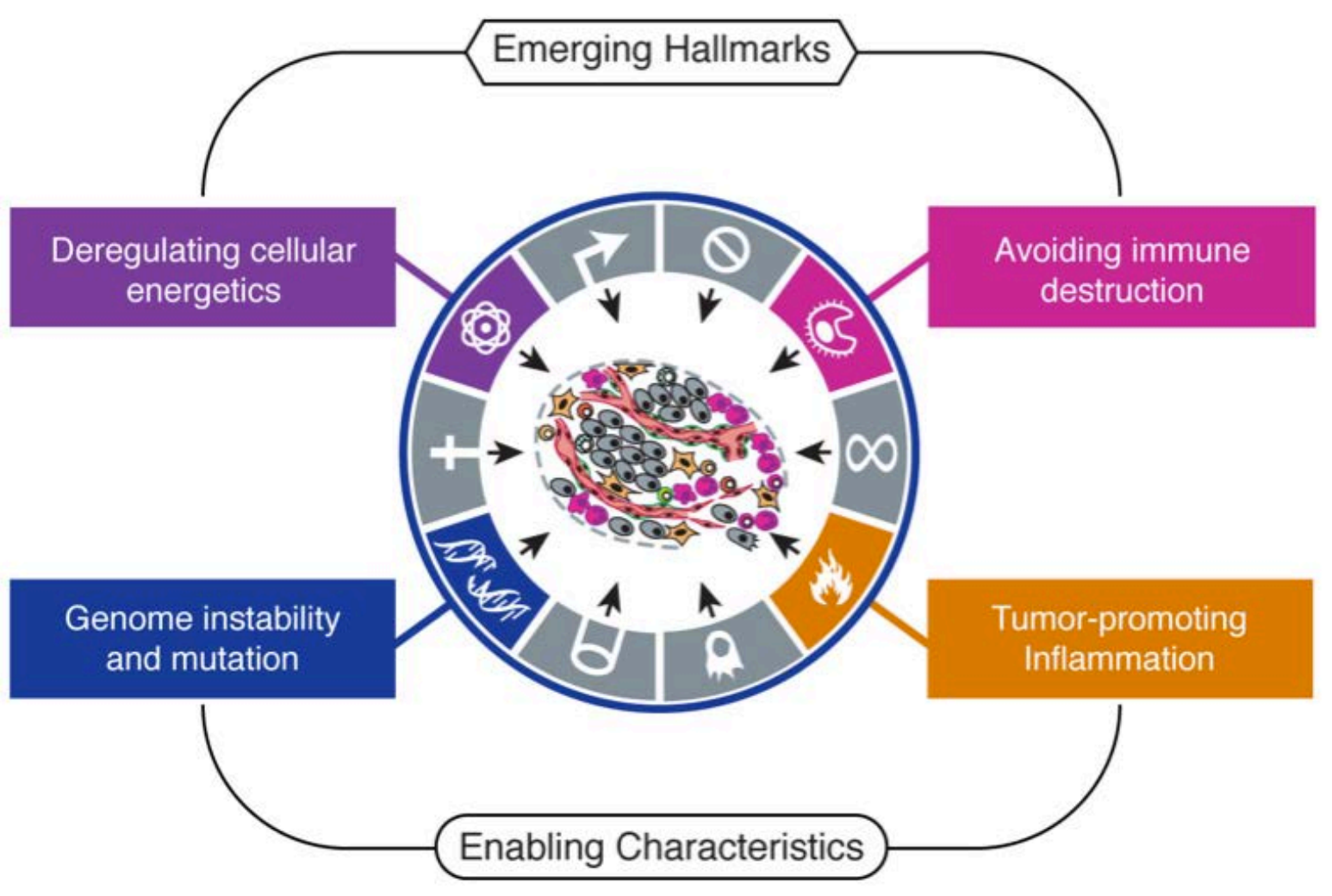
- Vilka biologiska egenskaper har cancer?
- Vilka nya behandlingar har kunnat utvecklas på basen av ny tumörbiologiskt kunskap?
- Vilka trender finns i försöken att förbättra cancerbehandlingen?
- Vad borde ”imaging” kunna bidra med?

Tumörcellernas egenskaper (1)

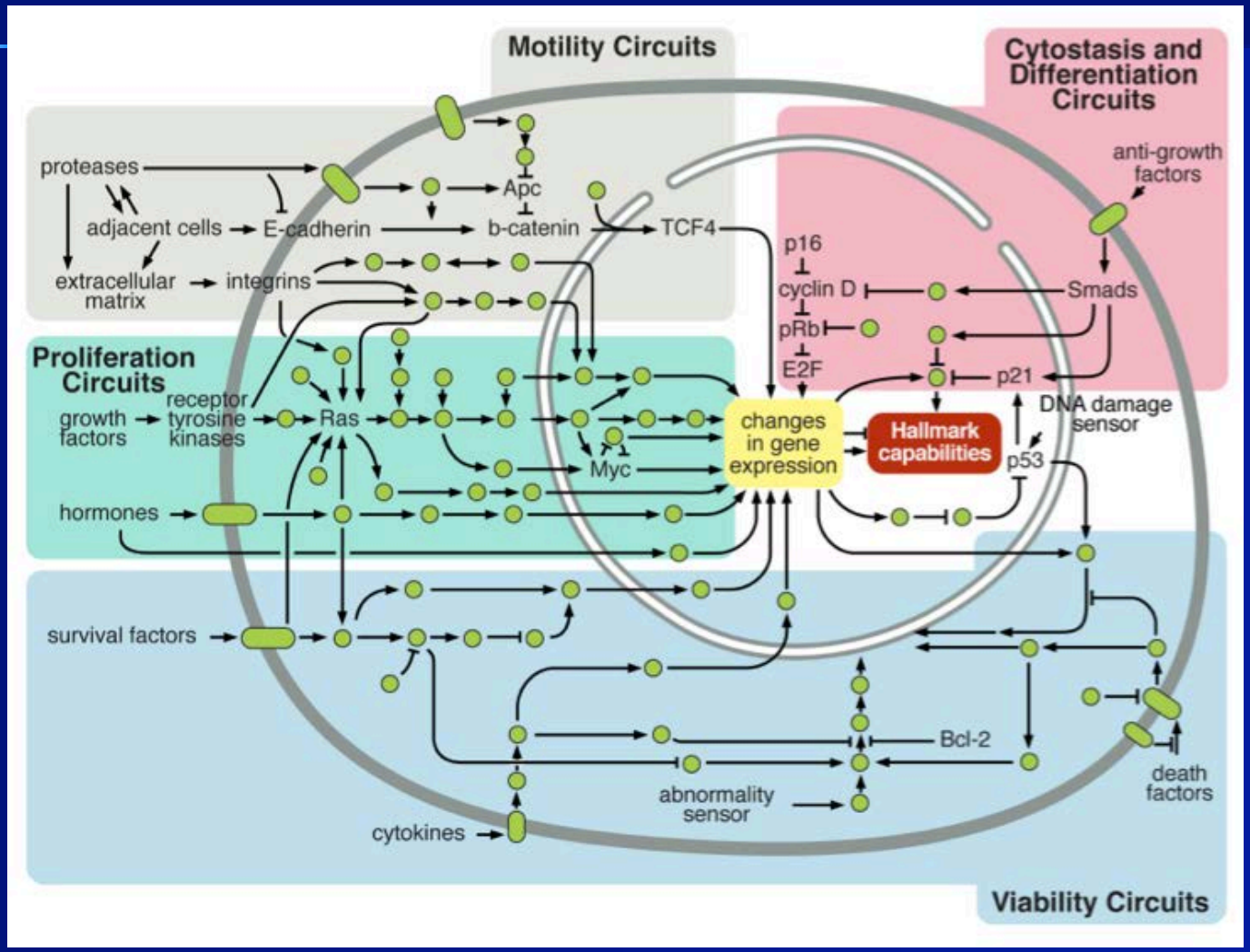


Hananhan & Weinberg, Cell 144; 646-674, 2011.”The Hallmarks of Cancer”

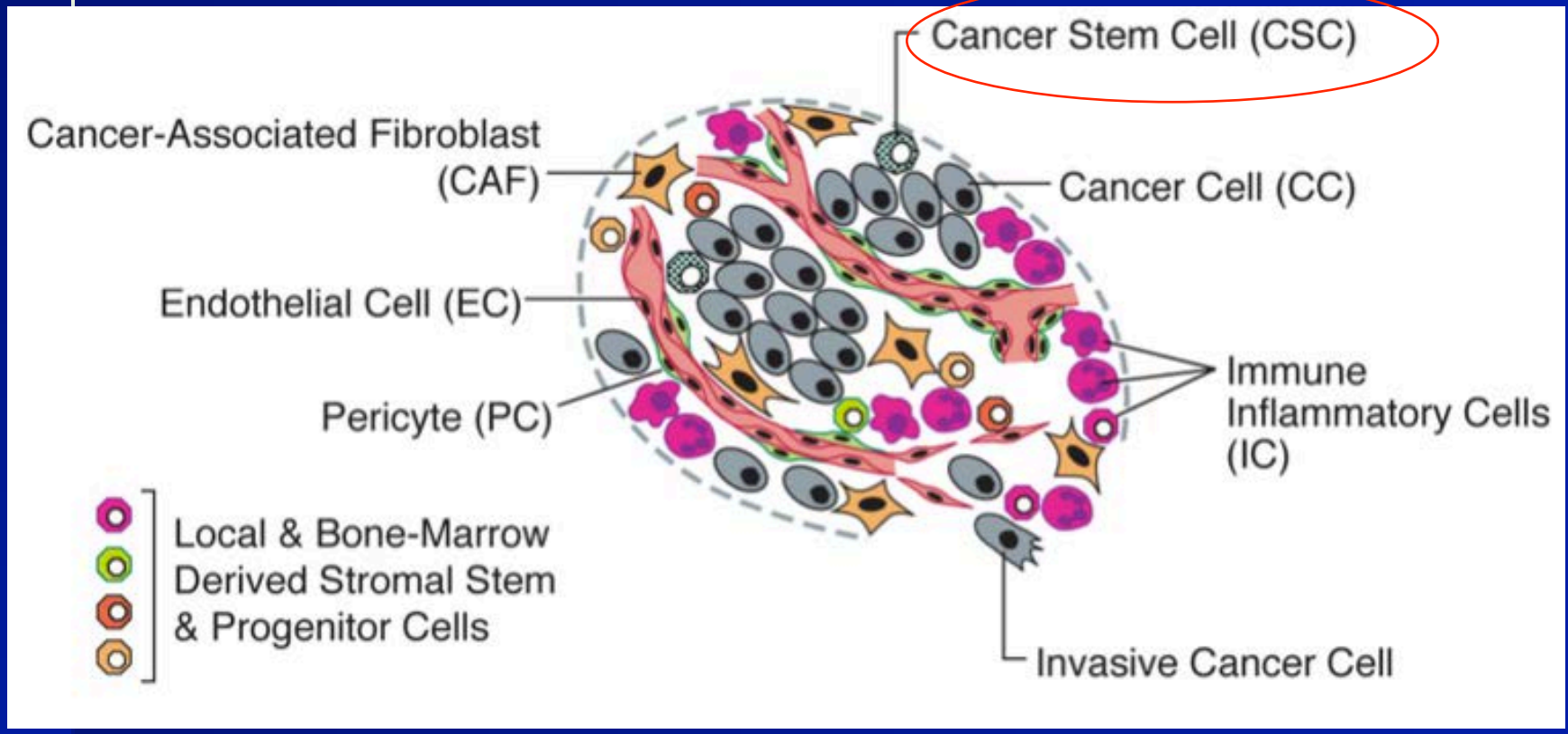
Tumörcellernas egenskaper (2)



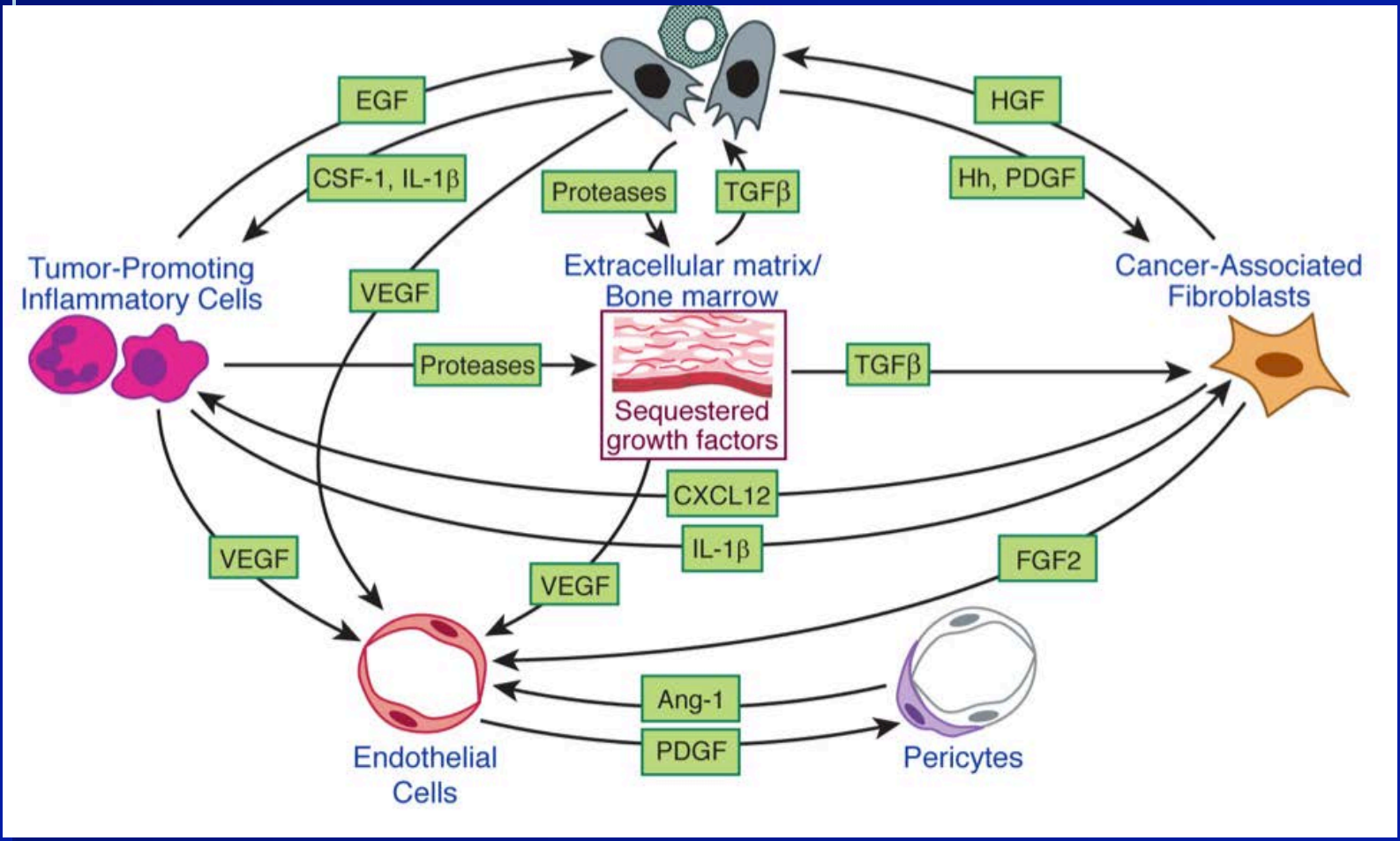
Signalsystemen är delvis kartlagda



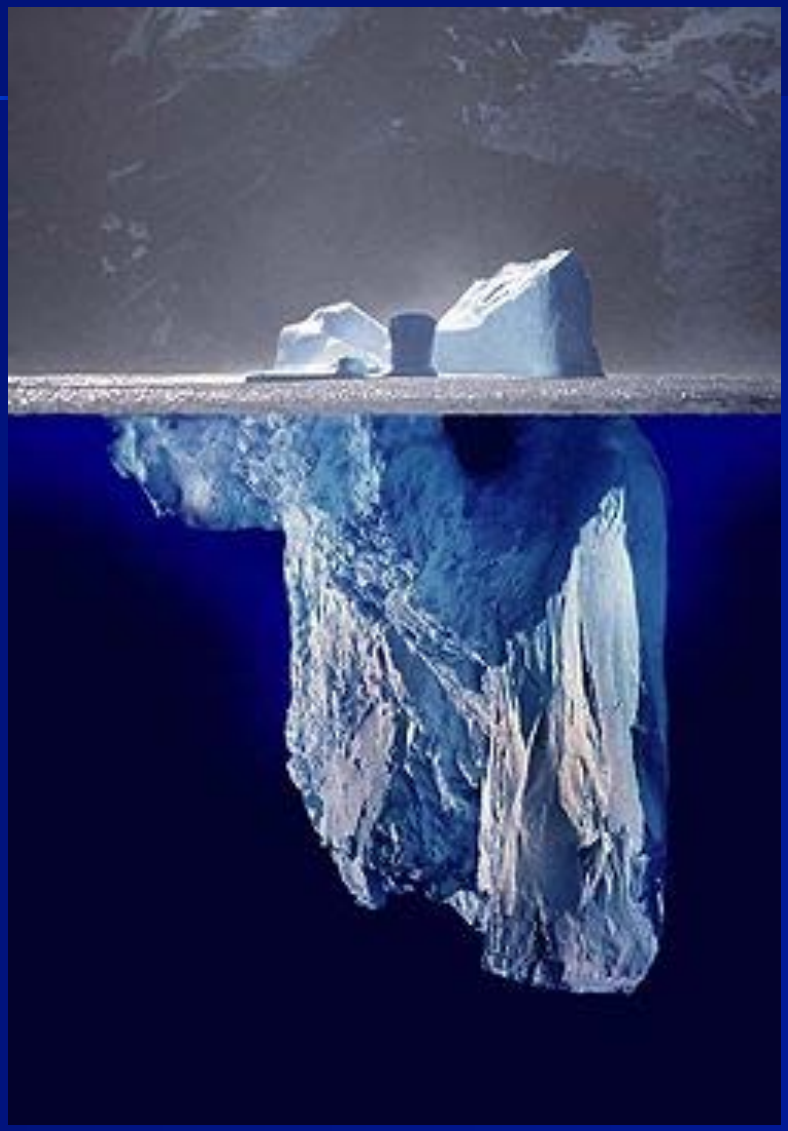
Cancer är mer än bara tumörceller!



Interaktionen med omgivningen påverkar tumörens egenskaper



Isberget som metafor: det viktiga är dolt



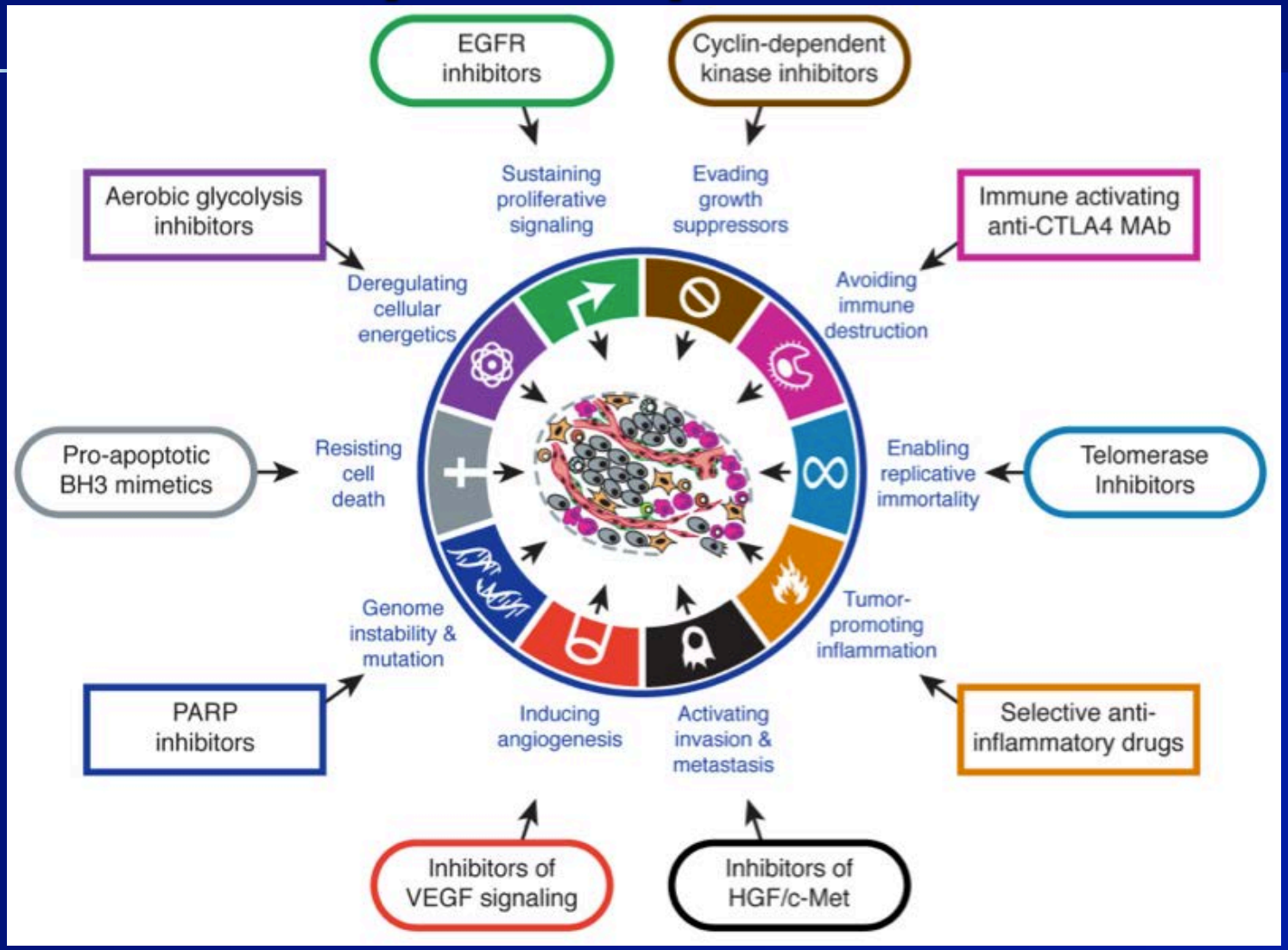
Under ytan:

mikrometastaser
cancerstamceller

Det tumörbiologiskt heta ur ett kliniskt perspektiv

- Kartläggning av signaleringsvägar
  - Nya ”targeted” drugs
- Individualiserad behandling
  - Diagnostik
  - Biomarkörer; genuttryck, proteinprofiler
- Heterogenitet
  - Försvårar individualiserad behandling
- Inte bara tumörceller….
  - Nya angreppspunkter
- Cancerstamceller
  - Recidiv trots komplett remission

”Targeted drugs” har utvecklats på basen av ny kunskap

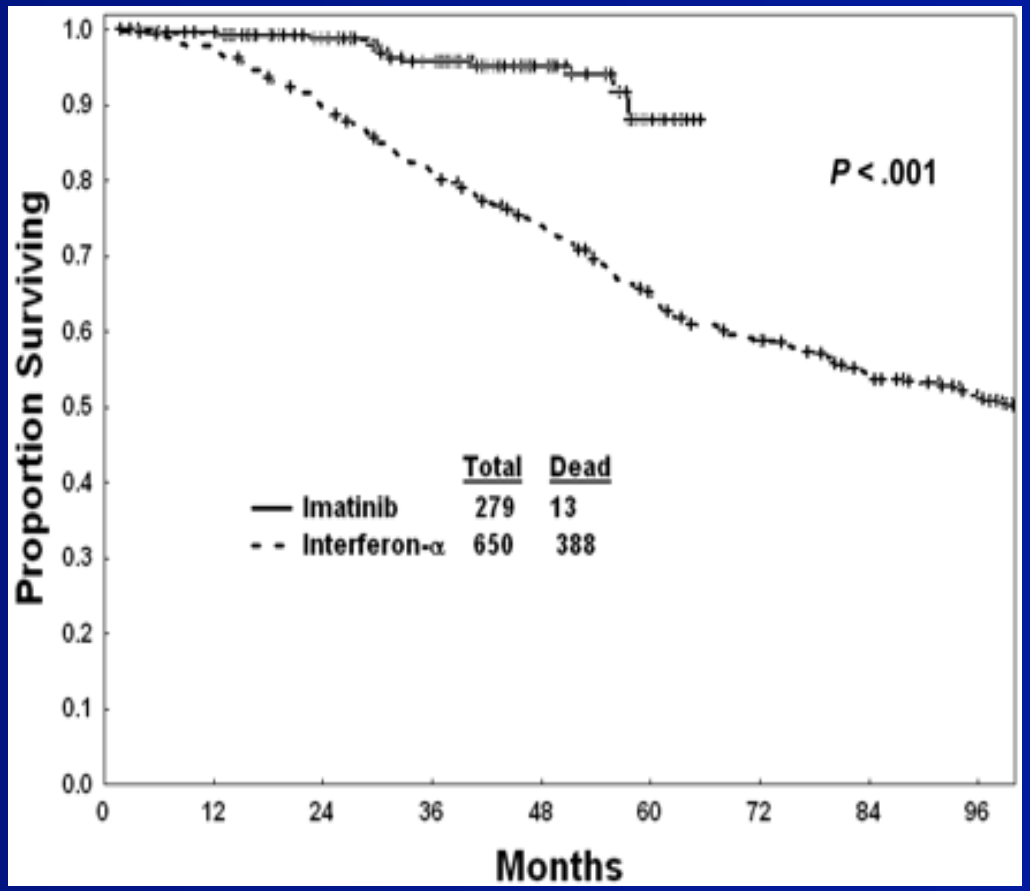


VILKA NYA ”MÅLINRIKTADE” CANCERLÄKEMEDEL FINNS IDAG?

- Antikroppar – signalhämning och immunologisk effekt
  - Herceptin (bröstcancer, magsäckscancer) – Her2
  - Mabthera, MabCampath, Zevalin, Arzera (lymfkörtelcancer, leukemi) – CD20
  - Avastin (tjock- och ändtarmscancer, lungcancer, bröstcancer, njurcancer) – VEGF
  - Erbitux (huvud/halscancer, tjock– och ändtarmscancer) - EGFR
  - Vectibix (tjock- och ändtarmscancer) – EGFR
  - Yervoy (melanom) – CTLA4/T-cellsaktivering

- Småmolekyler - signalhämning
  - Glivec (kronisk myeloisk leukemi, GIST) – Bcr/Abl TK
  - Tasigna (kronisk myeloisk leukemi) – Bcr/Abl TK
  - Sprycel (kronisk myeloisk leukemi) – Bcr/Abl TK
  - Tarceva (lungcancer, pancreascancer) – EGFR TK
  - Velcade (myelom) - Proteasomen
  - Nexavar (njurcancer, levercancer) – Bred TK hämmare
  - Sutent (njurcancer, GIST) – Bred TK hämmare
  - Torisel (njurcancer) – mTor hämning
  - Afinitor (njurcancer, EPT, bröstcancer) – mTor hämning
  - Votrient (njurcancer) – VEGF TK hämning
  - Tyverb (bröstcancer) – Erb/Her2 TKs

Framgångssagor finns….



Glivec-kronisk myeloisk leukemi

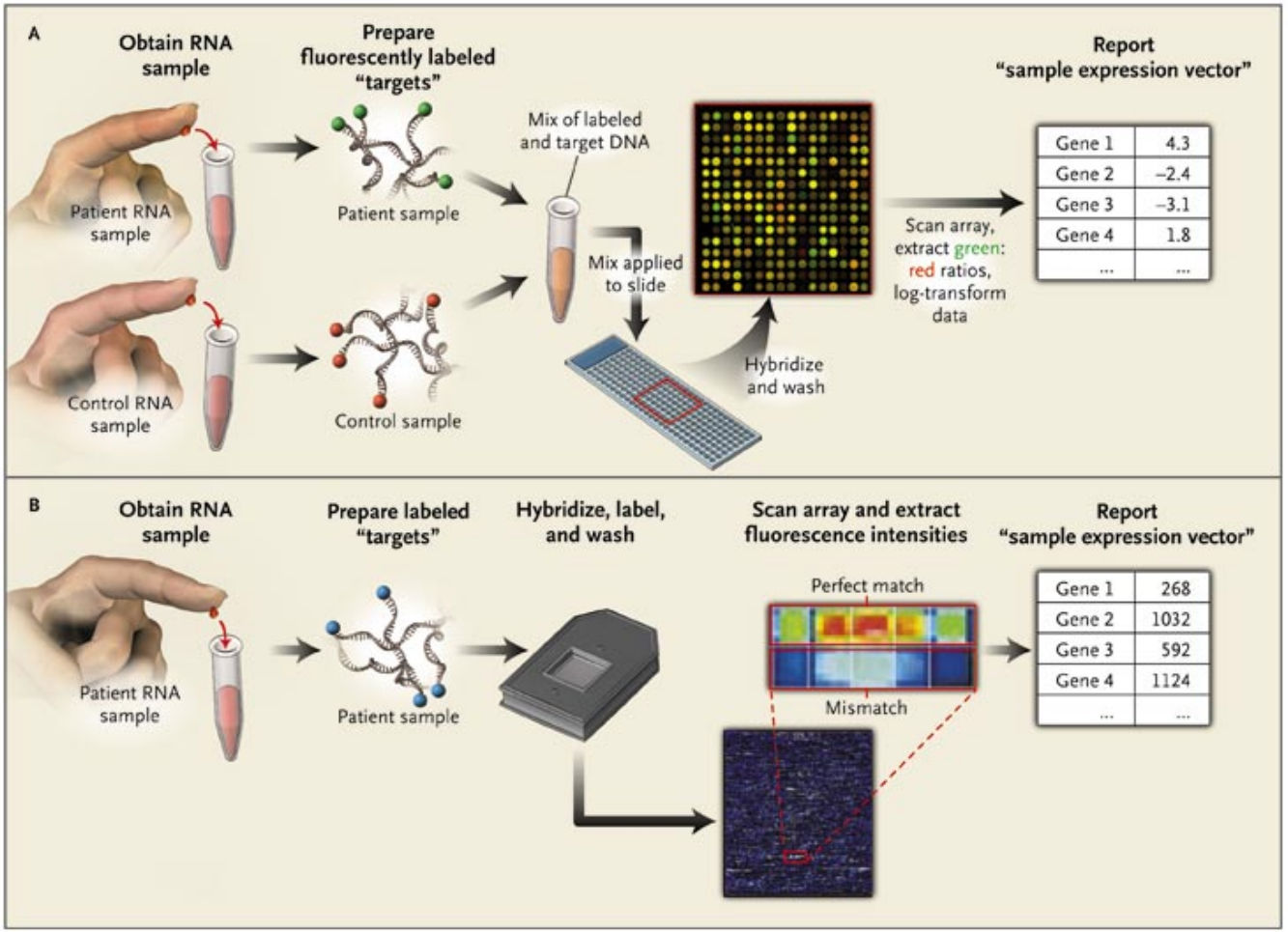
…men i de stora cancerdiagnoserna är förbättringarna modesta

Table 1. Selected Randomized Studies Supporting Drug Approval and/or Use in the United States

Drug	Mechanism	Disease	Random Assignment	No. of Patients	Survival (months)		*P*
					Median	Change	
Gemcitabine[3]	Cytotoxic	Pancreatic cancer	Gemcitabine *v* fluorouracil	126	5.65 *v* 4.41	6 weeks	.0025
Bevacizumab[4]	Anti-VEGF antibody	Colorectal cancer	Bevacizumab + FOLFOX4 *v* FOLFOX4	829	13.0 *v* 10.8	2.2	< .05
Erlotinib[5]	EGFR inhibitor	Pancreatic cancer	Erlotinib + gemcitabine *v* gemcitabine + placebo	569	6.24 *v* 5.91	11 days	.038
Bevacizumab[6]	Anti-VEGF antibody	Non–small-cell lung cancer	Bevacizumab/carboplatin/paclitaxel *v* carboplatin/paclitaxel	878	12.3 *v* 10.3	2	.013
Sorafenib[7]	VEGFR and Raf kinase inhibitor	Renal cancer	Sorafenib + supportive care *v* placebo + supportive care	902	4 *v* 2	2	< .001
Temozolomide[8]	Cytotoxic	Glioblastoma multiforme	Temozolomide + radiation therapy *v* radiotherapy alone	573	14.6 *v* 12.1	2.5	< .01
Docetaxel[9]	Cytotoxic	Prostate cancer	Docetaxel + prednisone *v* mitoxantrone + prednisone	1,005	18.9 *v* 16.5	2.4	.0094
Topotecan[10]	Cytotoxic	Cervical cancer	Topotecan + cisplatin *v* cisplatin	293	9.4 *v* 6.5	2.9	< .05
Cetuximab[11]	Anti-EGFR antibody	Colorectal cancer	Cetuximab + supportive care *v* supportive care	572	6.1 *v* 4.6	1.5	< .05

Stewart & Kurzrock, J Clin Oncol 27: 328, 2009

Individualiserad behandling: genomik



Quackenbush J. N Engl J Med 2006;354:2463-2472

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Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

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ABSTRACT

BACKGROUND

Intratumor heterogeneity may foster tumor evolution and adaptation and hinder personalized-medicine strategies that depend on results from single tumor-biopsy samples.

METHODS

To examine intratumor heterogeneity, we performed exome sequencing, chromosome aberration analysis, and ploidy profiling on multiple spatially separated samples obtained from primary renal carcinomas and associated metastatic sites. We characterized the consequences of intratumor heterogeneity using immunohistochemical analysis, mutation functional analysis, and profiling of messenger RNA expression.

RESULTS

Phylogenetic reconstruction revealed branched evolutionary tumor growth, with 63 to 69% of all somatic mutations not detectable across every tumor region. Intratumor heterogeneity was observed for a mutation within an autoinhibitory domain of the mammalian target of rapamycin (mTOR) kinase, correlating with S6 and 4EBP phosphorylation in vivo and constitutive activation of mTOR kinase activity in vitro. Mutational intratumor heterogeneity was seen for multiple tumor-suppressor genes converging on loss of function; *SETD2*, *PTEN*, and *KDM5C* underwent multiple distinct and spatially separated inactivating mutations within a single tumor, suggesting convergent phenotypic evolution. Gene-expression signatures of good and poor prognosis were detected in different regions of the same tumor. Allelic composition and ploidy profiling analysis revealed extensive intratumor heterogeneity, with 26 of 30 tumor samples from four tumors harboring divergent allelic-imbalance profiles and with ploidy heterogeneity in two of four tumors.

CONCLUSIONS

Intratumor heterogeneity can lead to underestimation of the tumor genomics landscape portrayed from single tumor-biopsy samples and may present major challenges to personalized-medicine and biomarker development. Intratumor heterogeneity, associated with heterogeneous protein function, may foster tumor adaptation and therapeutic failure through Darwinian selection. (Funded by the Medical Research Council and others.)

From the Cancer Research UK London Research Institute (M. Gerlinger, A.J.R., S.H., D.E., E.G., P.M., N.M., A.S., B.P., S.B., N.Q.M., C.R.S., B.S.-D., G.C., G.S., J.D., C.S.), Royal Marsden Hospital Department of Medicine (J.L., M.N., L.P., G.S., M. Gore), Wellcome Trust Sanger Institute (P.T., I.V., A.B., D.J., K.R., C.L., P.A.F.), Barts Cancer Institute at the Barts and the London School of Medicine and Dentistry (M. Gerlinger), and the University College London Cancer Institute (C.S.) — all in London; the Technical University of Denmark, Lyngby (A.C.E., Z.S.); and Harvard Medical School, Boston (Z.S.). Address reprint requests to Dr. Swanton at the Cancer Research UK London Research Institute, Translational Cancer Therapeutics Laboratory, 44 Lincoln's Inn Fields, London WC2A 3LY, United Kingdom, or at charles.swanton@cancer.org.uk.

Drs. Gerlinger, Larkin, Gronroos, Martinez, and Swanton and Mr. Rowan, Mr. Horswell, Mr. Endesfelder, Mr. Matthews, and Mr. Stewart contributed equally to this article.

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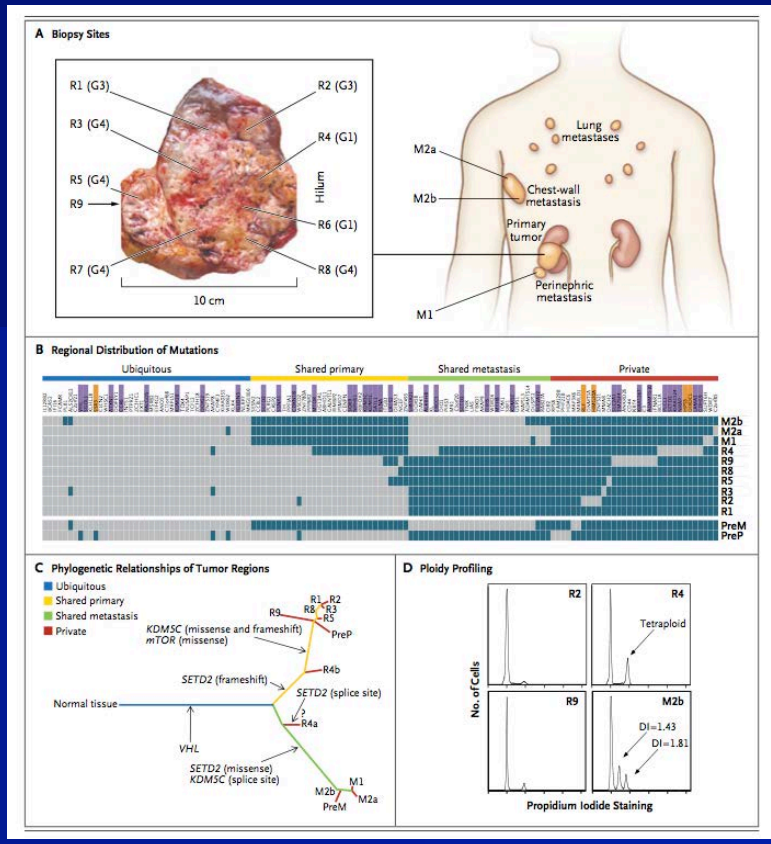

Genomics analyses from single tumor-biopsy specimens may underestimate the mutational burden of heterogeneous tumors. Intratumor heterogeneity may explain the difficulties encountered in the validation of oncology biomarkers owing to sampling bias,[29] contribute to Darwinian selection of preexisting drug-resistant clones,[12,30] and predict therapeutic resistance.[13] Reconstructing tumor clonal architectures and the identification of common mutations located in the trunk of the phylogenetic tree may contribute to more robust biomarkers and therapeutic approaches.

Imaging i dagens cancerbehandling

- Beskriver makroskopisk tumörutbredning
  - DT
  - MR
  - Ultraljud
  - FDG-PET
- Beskriver tumörrespons
  - DT/MR: volym
  - PET: metabolism
  - Klinisk relevans har minskat/är oklar

Imaging i morgondagens cancerbehandling

- Beskriva makroskopisk tumörutbredning
- Beskriva mikroskopisk tumörutbredning
- Beskriva tumörens egenskaper – generera biomarkörer som grund för terapival
  - Proliferationsgrad
  - Receptorer
  - Intratumoralt blodflöde/syrgastryck
  - Inflammation
  - Stamceller
  - Heterogenitet
  - Metabolism
- Beskriva behandlingseffekter utifrån tumörbiologi

Slutsatser

- Dramatisk ökning av tumörbiologisk kunskap
- Ännu inte fått dramatiskt genomslag i förbättrad cancerbehandling
- ”Tumörbiologi-imaging” behövs för att effektivt kunna omsätta den nya kunskapen i bättre behandling


Tack för uppmärksamheten!