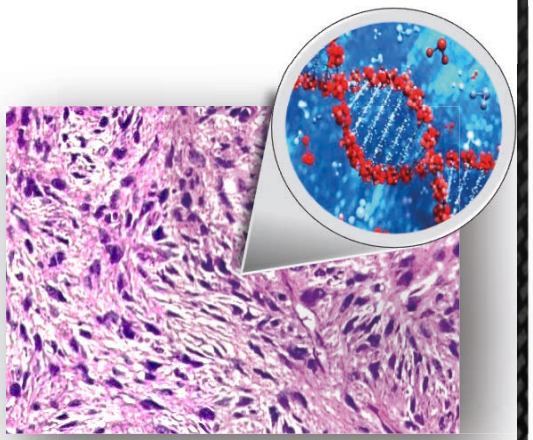

Biologie des sarcomes des tissus mous

Quoi de Neuf 2017-2018 ?

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ORIGINAL PAPER

Transcriptomic definition of molecular subgroups of small round cell sarcomas

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Abstract

Sarcoma represents a highly heterogeneous group of tumours. We report here the first unbiased and systematic search for gene fusions combined with unsupervised expression analysis of a series of 184 small round cell sarcomas. Fusion genes were detected in 59% of samples, with half of them being observed recurrently. We identified biologically homogeneous groups of tumours such as the *CIC*-fused (to *DUX4*, *FOXO4* or *NUTM1*) and *BCOR*-rearranged (*BCOR–CCNB3*, *BCOR–MAML3*, *ZC3H7B–BCOR*, and *BCOR* internal duplication) tumour groups. *VGLL2*-fused tumours represented a more biologically and pathologically heterogeneous group. This study also refined the characteristics of some entities such as *EWSR1–PATZ1* spindle cell sarcoma or *FUS–NFATC2* bone tumours that are different from *EWSR1–NFATC2* tumours and transcriptionally resemble *CIC*-fused tumour entities. We also describe a completely novel group of epithelioid and spindle-cell rhabdomyosarcomas characterized by *EWSR1*– or *FUS–TFCP2* fusions. Finally, expression data identified some potentially new therapeutic targets or pathways.

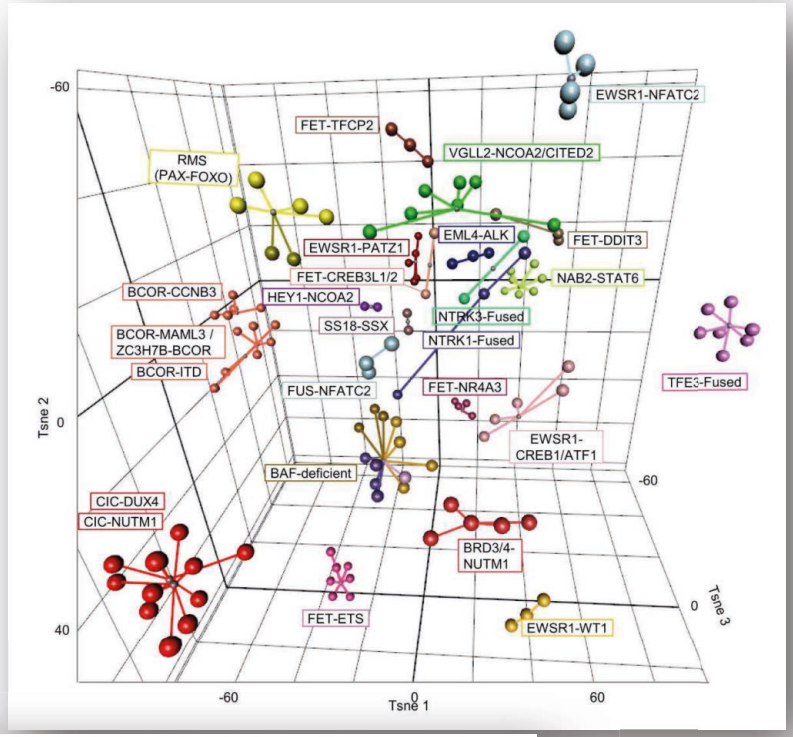
Keywords: sarcoma; fusion genes; *FET–TFCP2*; *FUS–NFATC2*; *EWSR1–PATZ1*; *VGLL2–NCOA2*; *BCOR*-rearranged; *CIC*-fused; RNAseq

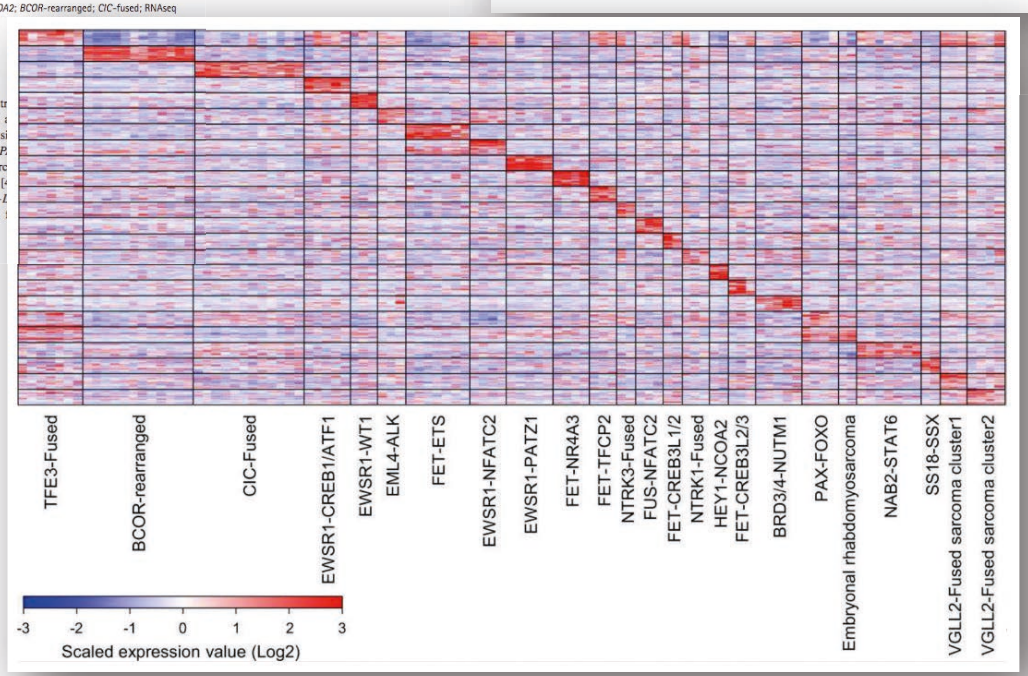
Received 12 December 2017; Revised 10 January 2018; Accepted 2 February 2018

No conflicts of interest were declared.

Introduction

Small round cell sarcoma is a heterogeneous group of tumours mostly affecting children and young adults and characterised by an overall poor prognosis [1]. They remain challenging for pathologists because those tumours share overlapping morphological and immunophenotypical features. The identification of specific fusion tr
their diagnosis a
by a specific fusi
SS18–SSX, and *P*
[2], synovial sarc
coma (ARMS) [4
described *CIC–D*
BCOR–CCNB3





Received: 12 October 2017 | Revised: 17 December 2017 | Accepted: 17 December 2017
DOI: 10.1002/gcc.22521

RESEARCH ARTICLE

WILEY

RREB1–MKL2 fusion in biphenotypic "oropharyngeal" sarcoma: New entity or part of the spectrum of biphenotypic sinonasal sarcomas?

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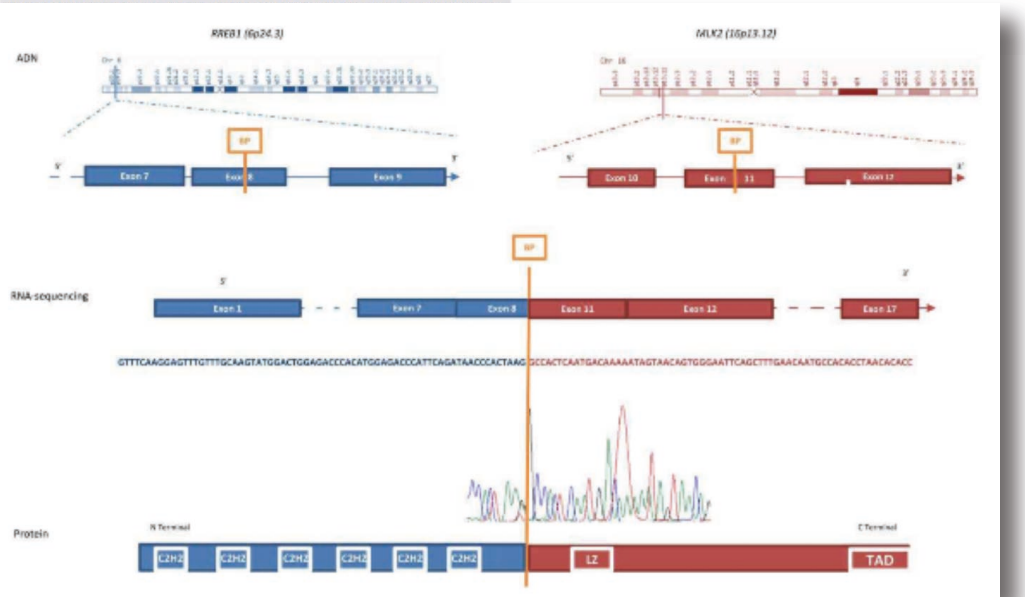
Abstract

An increasing number of sarcomas displaying a primitive, monomorphic spindle cell phenotype have been shown to harbor recurrent gene fusions, including biphenotypic sinonasal sarcoma (SNS).



1 | INTRODUCTION

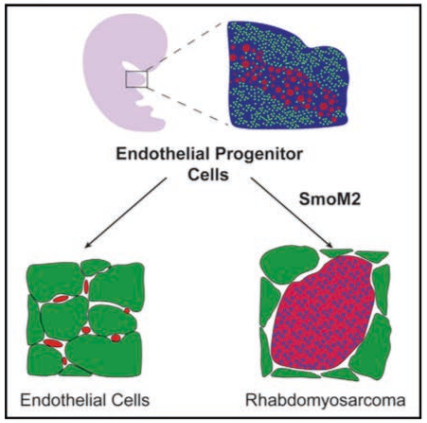
Biphenotypic sinonasal sarcoma (SNS) o
and myogenic features (SNS) is a recentl
tumor that occurs in the sinonasal are
Around 90% of SNS harbor rearrangemer
most frequent translocation partner is M
by *NCOA1*[5] and *FOXO1*.[6] The PAX3–M
factor encoded by this fusion gene indu
transcriptional program of dual neural a
Establishing the correct diagnosis of SNS
owing to their rarity but also because se

1 sarcome cellules fus de l'oropharynx
2 facteurs de transcriptions

Cancer Cell

Hedgehog Pathway Drives Fusion-Negative Rhabdomyosarcoma Initiated From Non-myogenic Endothelial Progenitors

Graphical Abstract



Authors

Catherine J. Drummond, Jason A. Hanna, Matthew R. Garcia, ..., David Finkelstein, Jerold E. Rehg, Mark E. Hatley

Correspondence

mark.hatley@stjude.org

In Brief

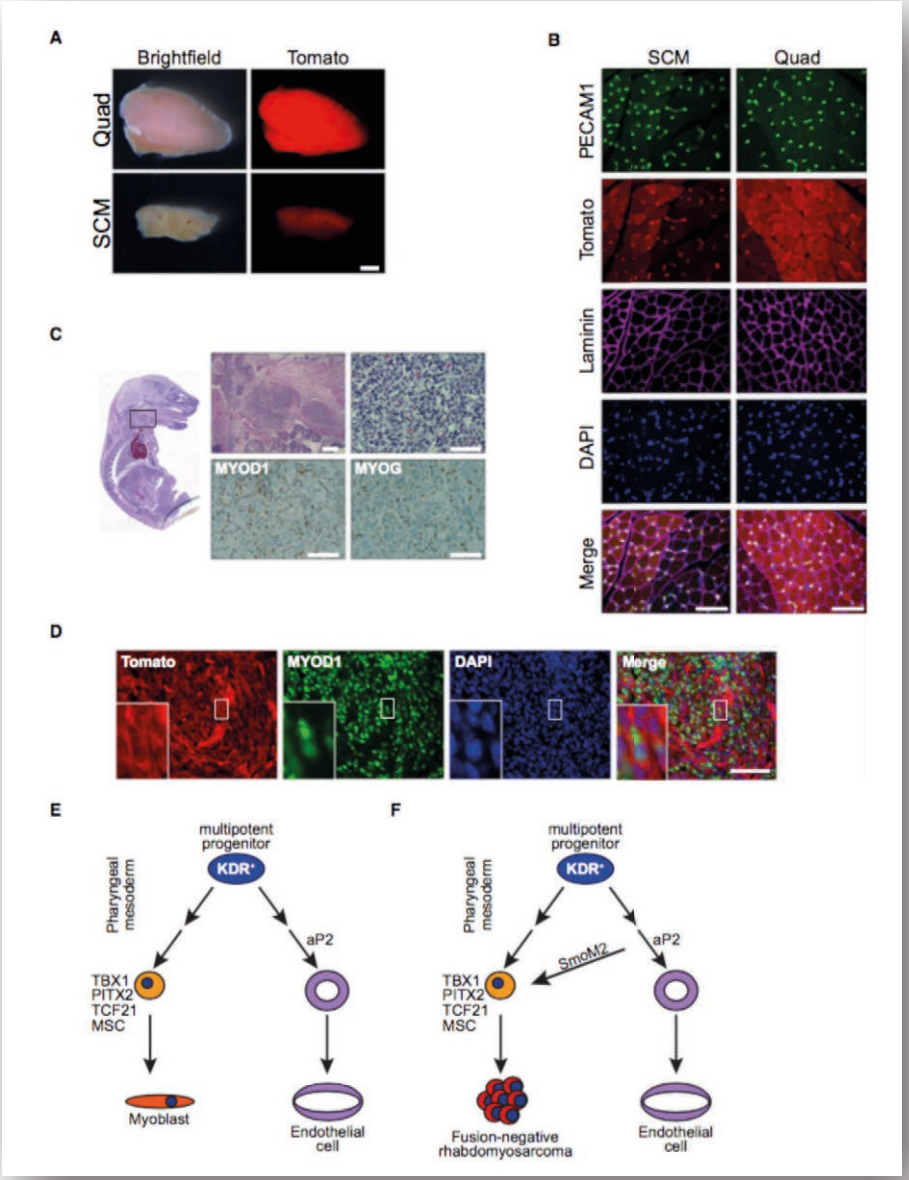
Using genetic fate mapping, Drummond et al. show that hedgehog pathway activation in endothelial progenitors results in aberrant expression of myogenic specification factors, myogenic transdifferentiation, and rhabdomyosarcoma (RMS). The finding may explain how RMS develops in sites devoid of skeletal muscle.

Highlights

- Committed endothelial progenitors can give rise to rhabdomyosarcoma (RMS)
- Aberrant activation of muscle development programs in non-myogenic cells drive RMS
- SmoM2 transdifferentiates endothelial progenitors resulting in RMS
- Cell of origin emerges as major determinant of RMS location

Drummond et al., 2018, Cancer Cell *33*, 108–124
January 8, 2018 © 2017 Elsevier Inc.
https://doi.org/10.1016/j.ccell.2017.12.001

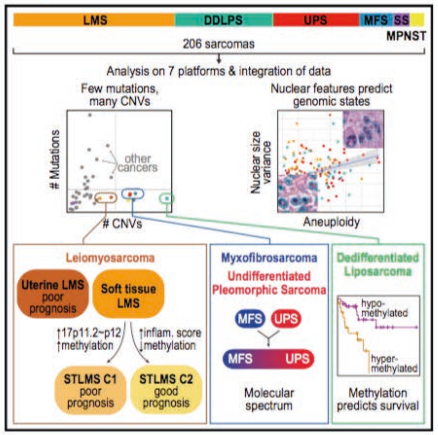
CellPress



Cell

Comprehensive and Integrated Genomic Characterization of Adult Soft Tissue Sarcomas

Graphical Abstract



Highlights

- Multiplatform genetic analysis of 206 sarcomas of 6 types shows their diversity
- Sarcomas harbor many more copy-number alterations than most other cancer types
- Inferred immune microenvironment associates with outcome in multiple sarcoma types
- Computed histologic nuclear pleomorphism correlates with aneuploidy estimates

Authors

The Cancer Genome Atlas Research Network

Correspondence

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In Brief

Genetic
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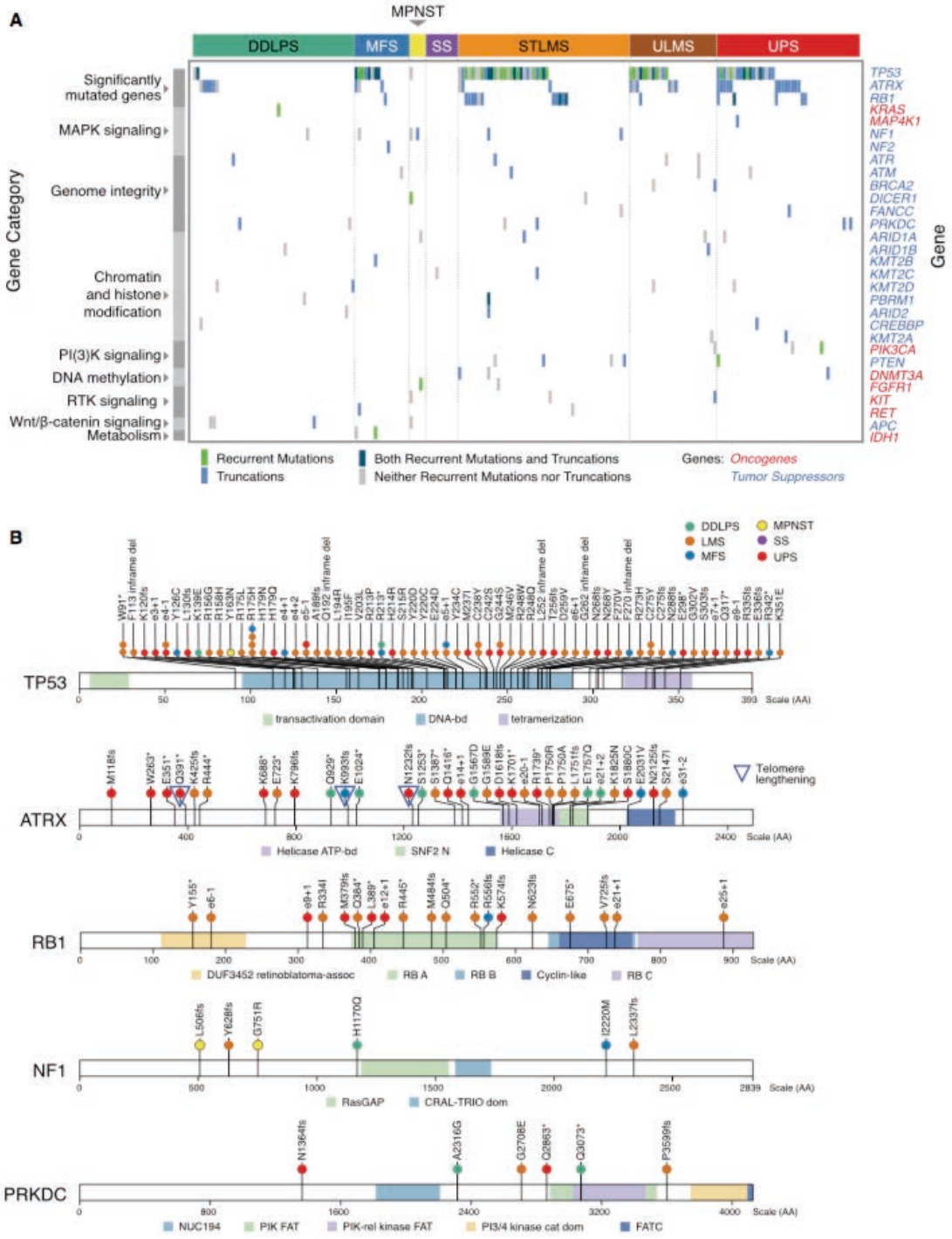
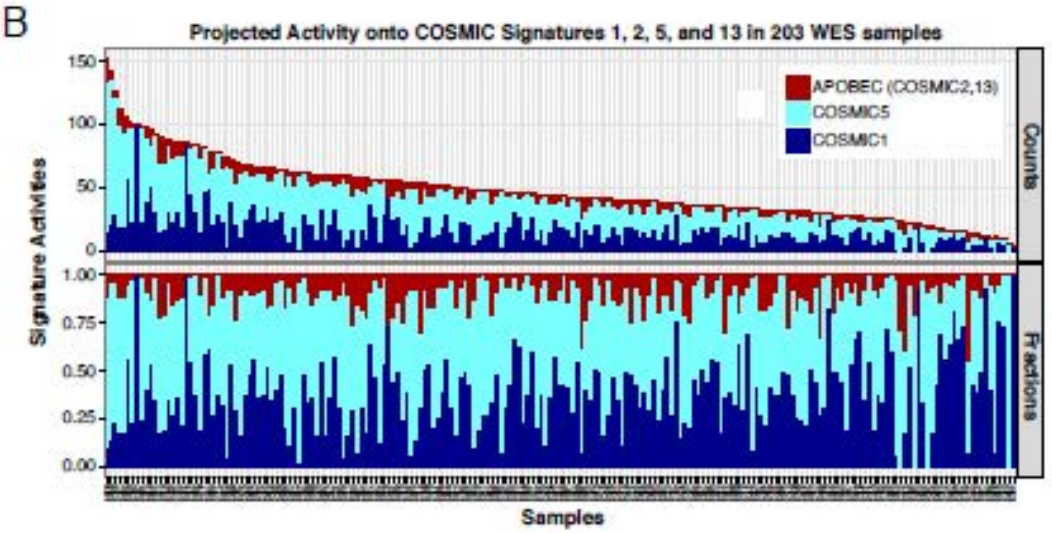
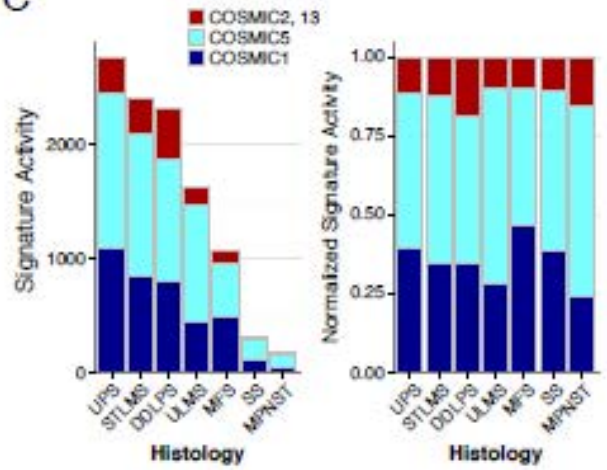
The Cancer Genome Atlas Research Network, 2017, Cell 171, 950–965
November 2, 2017 © 2017 The Authors. Published by Elsevier Inc.
https://doi.org/10.1016/j.cell.2017.10.014


A
MPNST
DDLPS
MFS
SS
STLMS
ULMS
UPS
Gene Category
Significantly mutated genes
MAPK signaling
Genome integrity
Chromatin and histone modification
PI(3)K signaling
DNA methylation
RTK signaling
Wnt/β-catenin signaling
Metabolism
Gene
TP53
ATRX
RB1
KRAS
MAP4K1
NF1
NF2
ATR
ATM
BRCA2
DICER1
FANCC
PRKDC
ARID1A
ARID1B
KMT2B
KMT2C
KMT2D
PBRM1
ARID2
CREBBP
KMT2A
PIK3CA
PTEN
DNMT3A
FGFR1
KIT
RET
APC
IDH1
Recurrent Mutations
Truncations
Both Recurrent Mutations and Truncations
Neither Recurrent Mutations nor Truncations
Genes: Oncogenes
Tumor Suppressors
B
DDLPS
LMS
MFS
MPNST
SS
UPS
TP53
transactivation domain
DNA-bd
tetramerization
Scale (AA)
ATRX
Helicase ATP-bd
SNF2 N
Helicase C
Telomere lengthening
RB1
DUF3452 retinoblatoma-assoc
RB A
RB B
Cyclin-like
RB C
NF1
RasGAP
CRAL-TRIO dom
PRKDC
NUC194
PIK FAT
PIK-rel kinase FAT
PI3/4 kinase cat dom
FATC

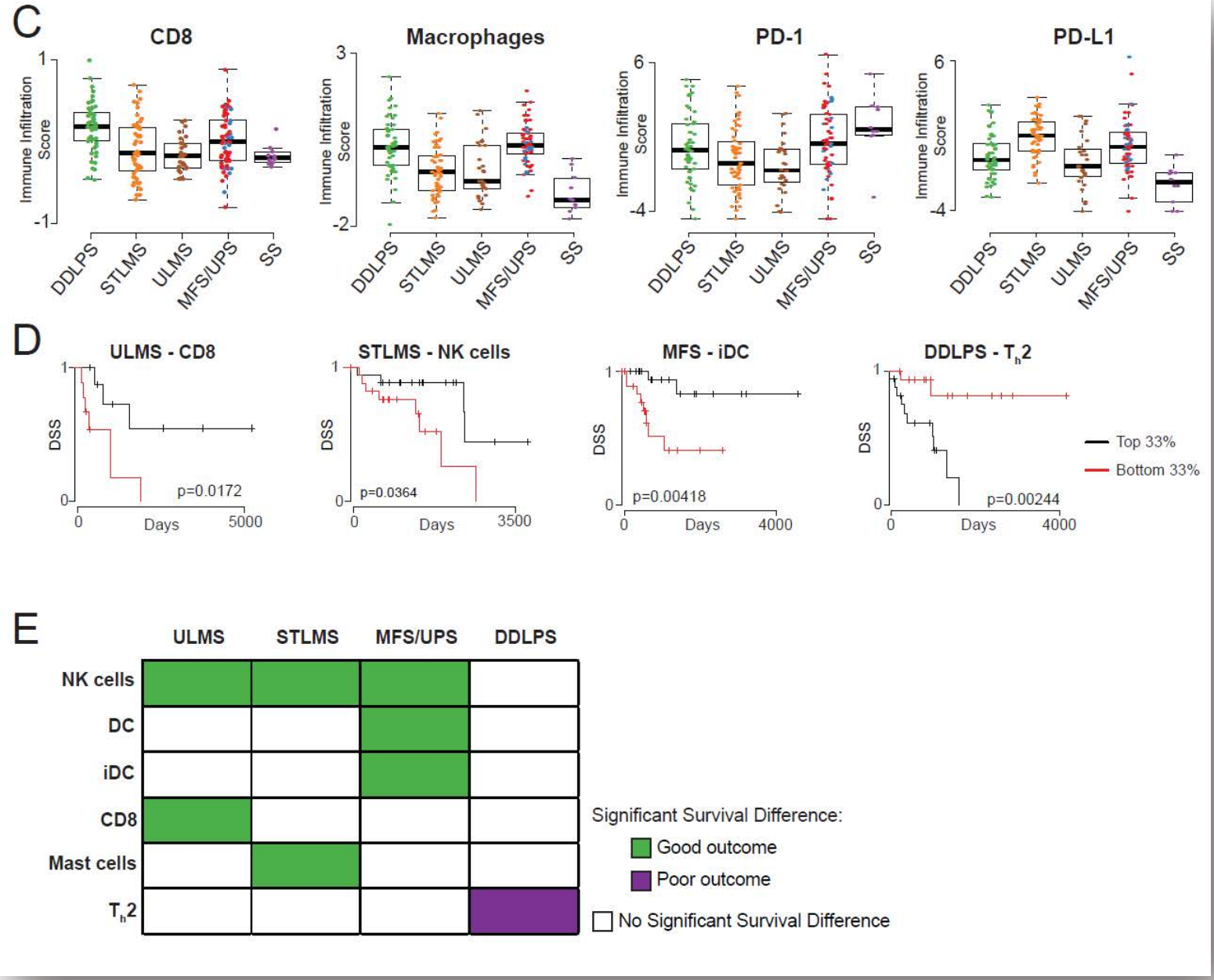
B


Projected Activity onto COSMIC Signatures 1, 2, 5, and 13 in 203 WES samples
APOBEC (COSMIC2,13)
COSMIC5
COSMIC1
Counts
Fractions
Signature Activities
Samples

C


COSMIC2, 13
COSMIC5
COSMIC1
Signature Activity
Normalized Signature Activity
UPS
STLMS
DDLPS
ULMS
MFS
SS
MPNST
Histology
Histology

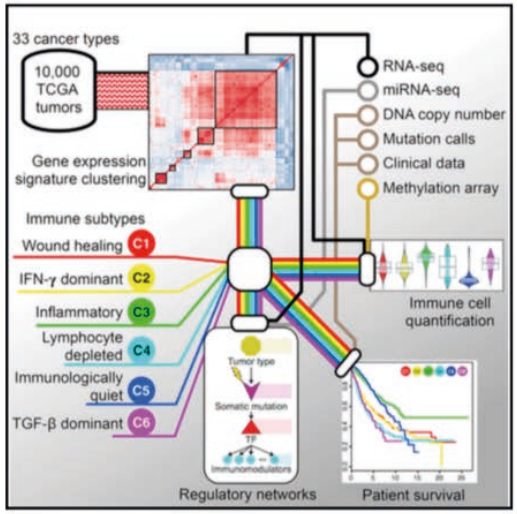
Immune Microenvironment



Immunity

The Immune Landscape of Cancer

Graphical Abstract



Highlights

- Six identified immune subtypes span cancer tissue types and molecular subtypes
- Immune subtypes differ by somatic aberrations, microenvironment, and survival
- Multiple control modalities of molecular networks affect tumor-immune interactions
- These analyses serve as a resource for exploring immunogenicity across cancer types

Authors

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Scott D. Brow
Benjamin G. V

Correspond

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(V.T.),
benjamin.vinc
(B.G.V.),
ilya.shmulevic
systemsbiolog

In Brief

Thorsson et al
analyses of m
identifying six
encompass m
hypothesized
patterns impa
provides a res
tumor-immun
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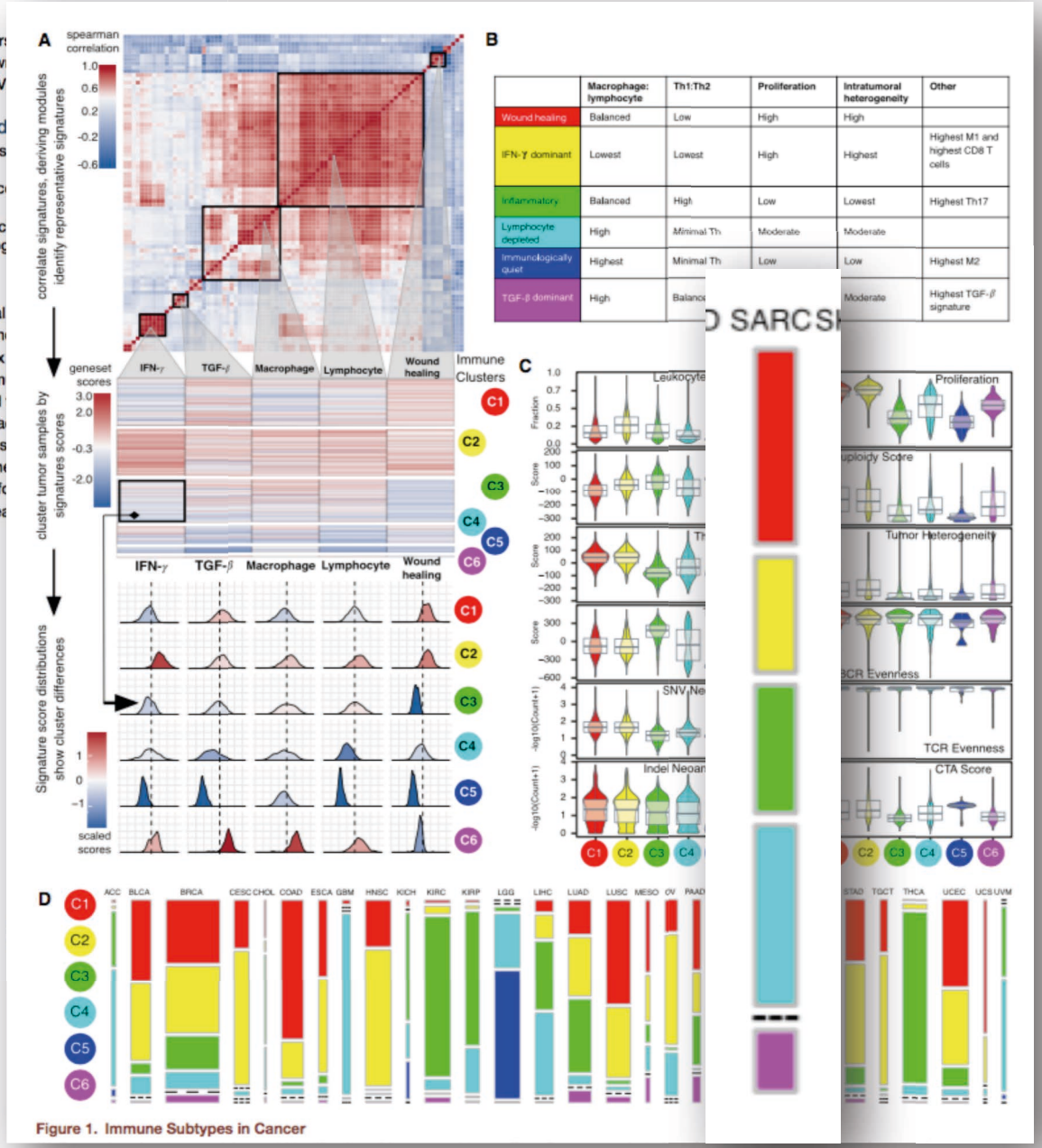

Figure 1. Immune Subtypes in Cancer

Thorsson et al., 2018, Immunity 48, 812–830
April 17, 2018 © 2018 The Authors. Published by Elsevier Inc.
https://doi.org/10.1016/j.immuni.2018.03.023

ARTICLE

doi:10.1038/nature25432

Chromosomal instability drives metastasis through a cytosolic DNA response

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Chromosomal instability is a hallmark of cancer that results from ongoing errors in chromosome segregation during mitosis. Although chromosomal instability is a major driver of tumour evolution, its role in metastasis has not been established. Here we show that chromosomal instability promotes metastasis by sustaining a tumour cell–autonomous response to cytosolic DNA. Errors in chromosome segregation create a preponderance of micronuclei whose rupture spills genomic DNA into the cytosol. This leads to the activation of the cGAS–STING (cyclic GMP–AMP synthase–stimulator of interferon genes) cytosolic DNA–sensing pathway and downstream noncanonical NF-κB signalling. Genetic suppression of chromosomal instability markedly delays metastasis even in highly aneuploid tumour models, whereas continuous chromosome segregation errors promote cellular invasion and metastasis in a STING–dependent manner. By subverting lethal epithelial responses to cytosolic DNA, chromosomally unstable tumour cells co-opt chronic activation of innate immune pathways to spread to distant organs.

Chromosomal instability (CIN) correlates with tumour metastasis[1,2], but it remains unclear whether it is a mere bystander or a driver of metastatic progression. Chromosomally unstable cells show evidence of chromosome missegregation during anaphase[3,4], offering an attractive bottleneck in which to target CIN and probe its selective contribution to metastasis. Destabilization of microtubule attachments to chromosomes at the kinetochores, through overexpression of the non-motile microtubule-depolymerizing kinesin-13 family proteins KIF2B or KIF2C (also known as MCAK), directly suppresses CIN in otherwise chromosomally unstable cells[5–7]. Cells overexpressing KIF2B or MCAK continue to propagate abnormal aneuploid karyotypes, albeit in a stable manner[7]. As such, this approach permits direct experimental interrogation of CIN, as defined by the rate of ongoing chromosome missegregation, independently of aneuploidy, which is defined as a state of abnormal chromosome numbers.

Increased CIN in human metastases

First, to determine whether CIN is associated with human metastases, we applied the weighted-genomic integrity index (wGII) as a proxy for CIN[8] to 79 matched pairs of primary tumour and brain metastasis from a published cohort[9]. Metastases showed higher wGII than primary tumours (Fig. 1a and Extended Data Fig. 1a, b).

Next, karyotype analysis of primary breast tumours and metastases archived in the Mitelman Database of chromosomal translocations[10] revealed a predilection for near-diploid ($2n$) karyotypes in primary tumours. Conversely, metastases were enriched for cells with near-triploid ($3n$) karyotypes and had twice as many structural or numerical chromosomal aberrations per clone as primary tumours. The number of chromosomal aberrations was highest in tumour samples with karyotypes ranging between the diploid and tetraploid ($4n$) range (Fig. 1b, c and Extended Data Fig. 1c, d).

Finally, histological analysis of primary tumours from patients with locally advanced head and neck squamous cell carcinoma[11] revealed a significant association ($P < 0.05$) between anaphase chromosome missegregation and the incidence of lymph node metastasis (Fig. 1d and Extended Data Fig. 1e).

CIN is a driver of metastasis

To determine whether CIN is causally involved in metastasis, we used transplantable metastatic tumour models of human (MDA-MB-231) or mouse (4T1) triple-negative breast cancer and human lung adenocarcinoma (H2030), in which 47%, 55%, and 67% of anaphase cells, respectively, show evidence of chromosome missegregation. Overexpression of KIF2B or MCAK suppressed chromosome missegregation, whereas overexpression of a dominant-negative MCAK mutant[12] (dnMCAK) led to a modest increase in chromosome missegregation in MDA-MB-231 cells. Overexpression of KIF2B or MCAK did not alter cellular proliferation or the number of centrosomes per cell (Fig. 2a, b and Extended Data Fig. 1f–i). As a control, we overexpressed KIF2A, a third member of the kinesin-13 family that lacks kinetochore and centromere localization domains[13]; although KIF2A showed microtubule-depolymerizing activity on interphase microtubules, it had no observable effect on CIN (Fig. 2b and Extended Data Fig. 1i–k). We ruled out a direct role for kinesin-13-mediated microtubule depolymerization in

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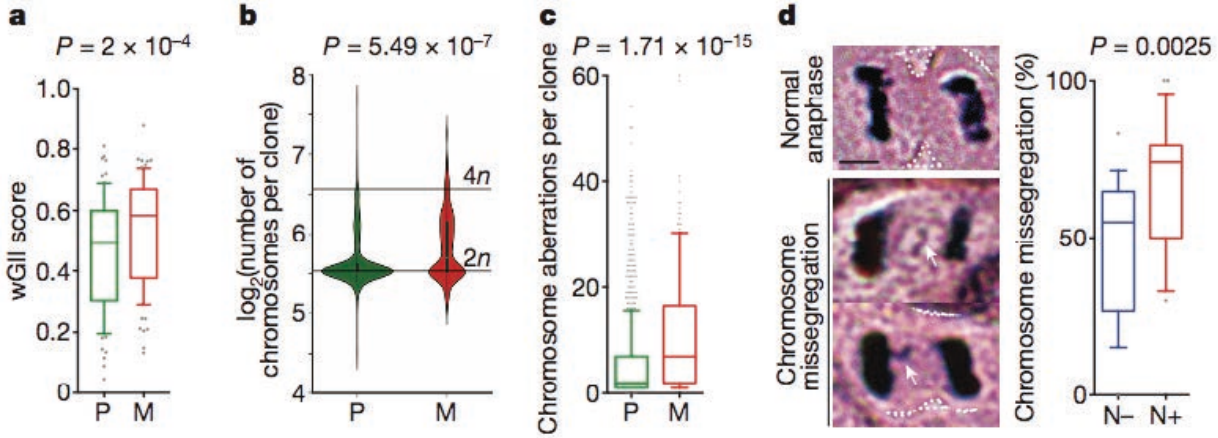
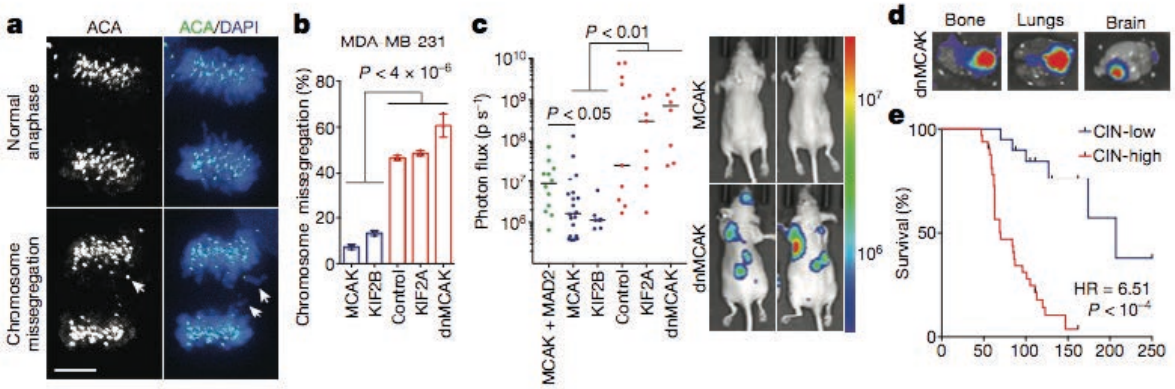
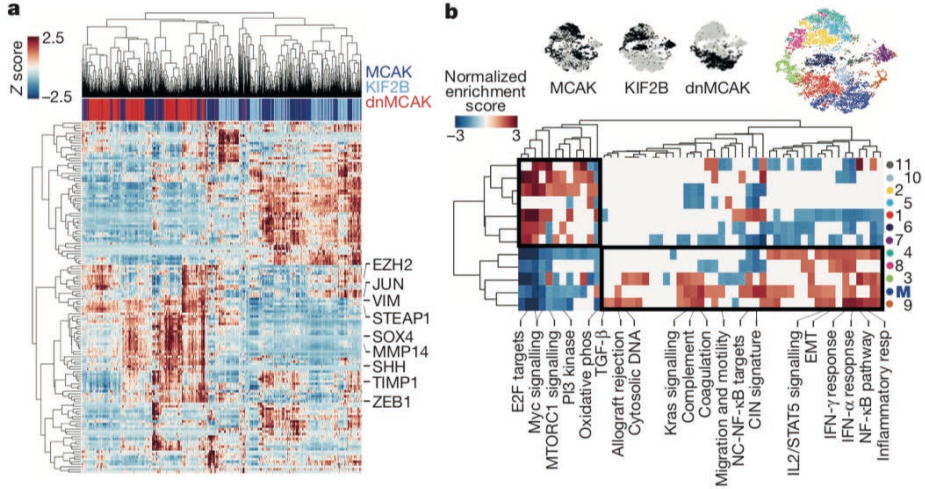
*These authors contributed equally to this work.

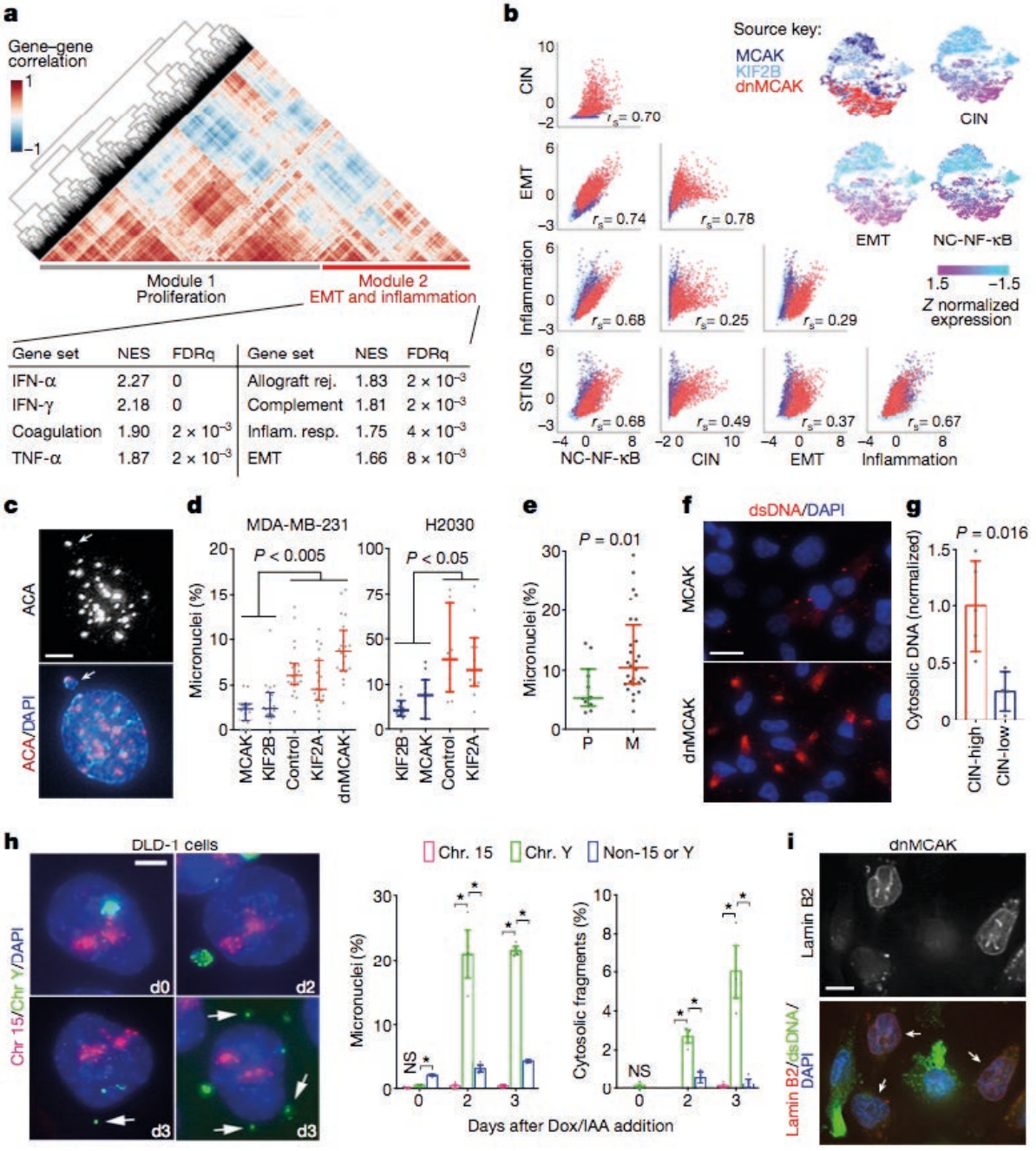
Instabilité génomique et évolution métastatique sont liés!

Ouai, mais comment…?


a
P = 2 × 10−4
wGII score
P
M
b
P = 5.49 × 10−7
log2(number of chromosomes per clone)
4n
2n
c
P = 1.71 × 10−15
Chromosome aberrations per clone
d
Normal anaphase
Chromosome missegregation
P = 0.0025
Chromosome missegregation (%)
N–
N+


a
ACA
ACA/DAPI
Normal anaphase
Chromosome missegregation
b
MDA MB 231
P < 4 × 10−6
Chromosome missegregation (%)
MCAK
KIF2B
Control
KIF2A
dnMCAK
c
P < 0.01
P < 0.05
Photon flux (p s−1)
MCAK + MAD2
d
Bone
Lungs
Brain
e
CIN-low
CIN-high
Survival (%)
HR = 6.51
P < 10−4


a
Z score
MCAK
KIF2B
dnMCAK
EZH2
JUN
VIM
STEAP1
SOX4
MMP14
SHH
TIMP1
ZEB1
b
Normalized enrichment score
E2F targets
Myc signalling
MTORC1 signalling
PI3 kinase
Oxidative phos
TGF-β
Allograft rejection
Cytosolic DNA
Kras signalling
Complement
Coagulation
Migration and motility
NC-NF-κB targets
CIN signature
IL2/STAT5 signalling
EMT
IFN-γ response
IFN-α response
NF-κB pathway
Inflammatory resp



Gene set	NES	FDRq	Gene set	NES	FDRq
IFN-α	2.27	0	Allograft rej.	1.83	2×10^{-3}
IFN-γ	2.18	0	Complement	1.81	2×10^{-3}
Coagulation	1.90	2×10^{-3}	Inflam. resp.	1.75	4×10^{-3}
TNF-α	1.87	2×10^{-3}	EMT	1.66	8×10^{-3}

a
DAPI
cGAS
cGAS/DNA
cGAS –ve MN
cGAS +ve MN
b
P = 2 × 10−4
cGAS+ micronuclei (%)
dnMCAK
dnMCAK + LMNB2
c
MCAK
dnMCAK
STING
STING/DAPI
d
Cells with nuclear RelB (%)
MCAK + MAD2
MCAK + cGAMP
MCAK
KIF2B
Control
KIF2A
dnMCAK
Ctrl sh
STING
sh1
sh2
e
P = 6 × 10−8
NC-NF-κB signature
L
H
CIN-signature
f
Photon flux (10⁶)
P = 0.0007
P < 0.0001
sh
sh1
sh2
Ctrl
STING
dnMCAK
×10⁸
Ctrl shRNA
STING shRNA
g
Photon flux (10⁶)
P = 0.0003
P = 0.0021
P = 0.0008
P < 0.0001
sh
sh1
sh2
Ctrl
RelB
NFKB2

ANNALS OF ONCOLOGY

ACCEPTED MANUSCRIPT

Validation of the Complexity INdex in SARComas prognostic signature on formalin-fixed, paraffin-embedded, soft tissue sarcomas

S Le Guellec ✉, T Lesluyes, E Sarot, C Valle, T Filleron, P Rochaix, T Valentin, G Pérot, J-M Coindre, F Chibon

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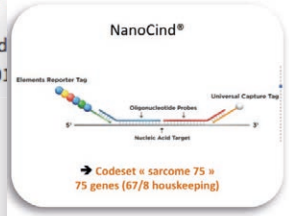
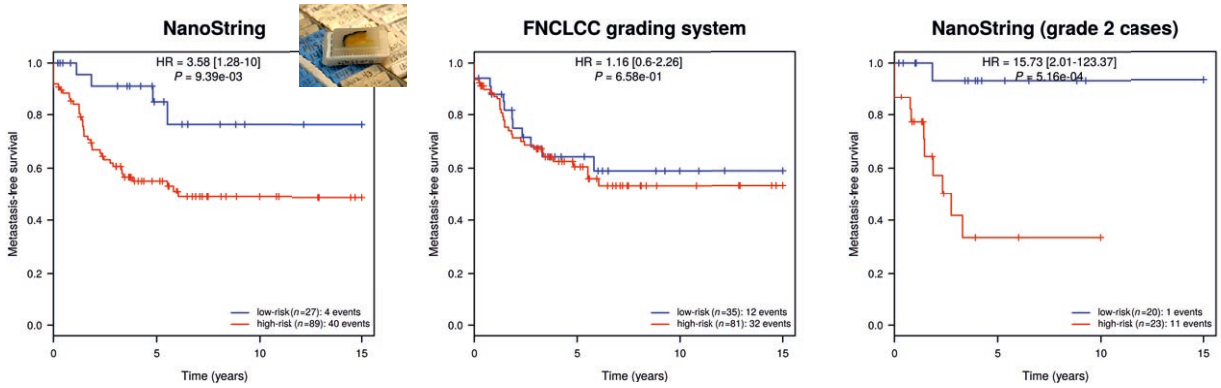


NanoCind vs FNCLCC grading….



Le Guellec et al, Ann Oncol; 2018