Influence of the Tumor Microenvironment on Prostate Cellular Behavior

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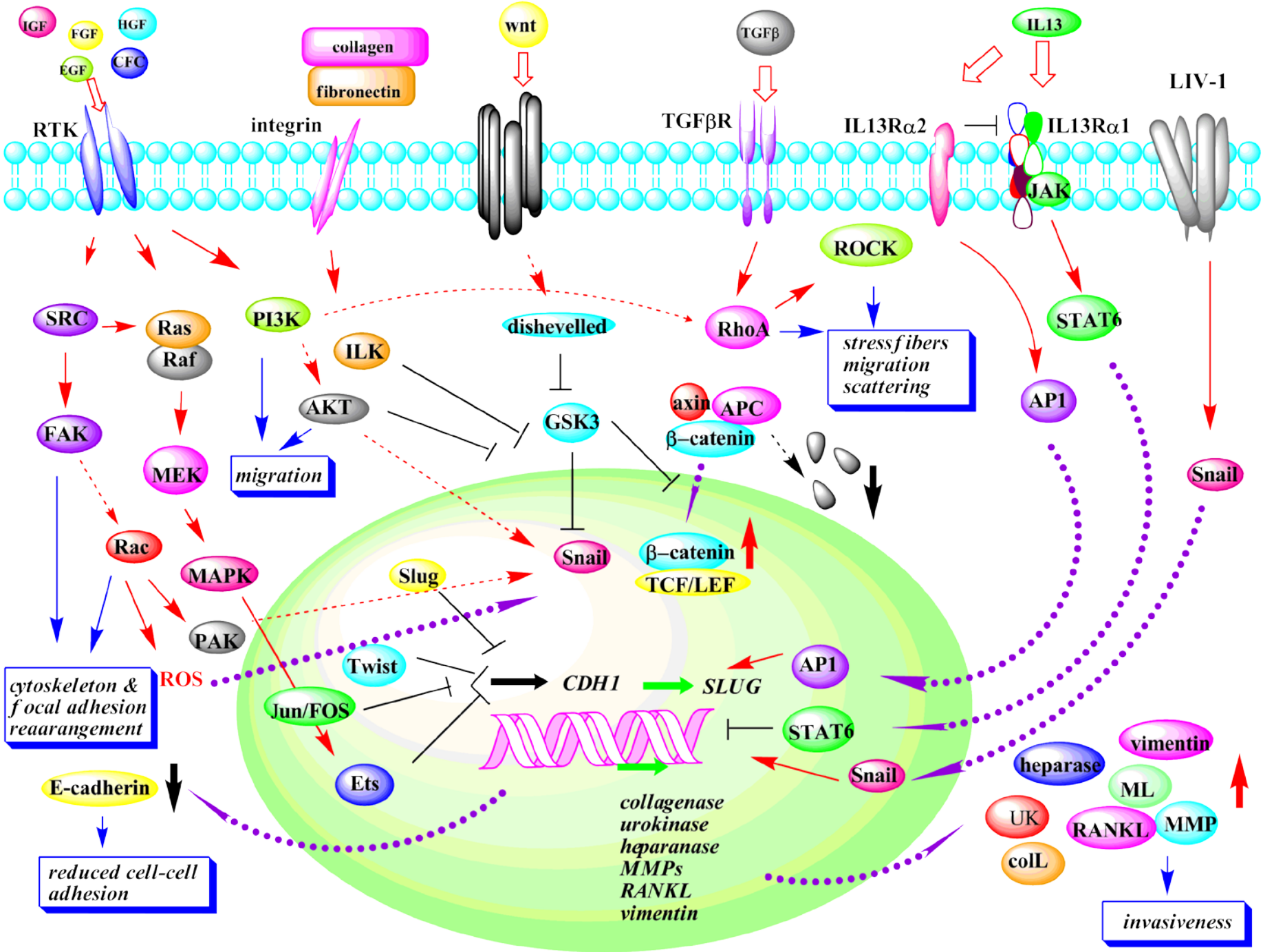
Discovery of EMT

- First observed and defined by Elizabeth Hay in late 1960's at Harvard
- First associated with early stages of embryonic development.
- Process is reversible

- EMT ⇔ MET ⇔ EMT

EMT

- Loss of E-cadherin
  - - Increase in translational repressors (Snail or Zeb1)
  - - Methylation promoter
- Secretion of proteolytic enzymes
- Gain of mesenchymal proteins
- Fibroblastic morphology
- Increased cell motility and invasion

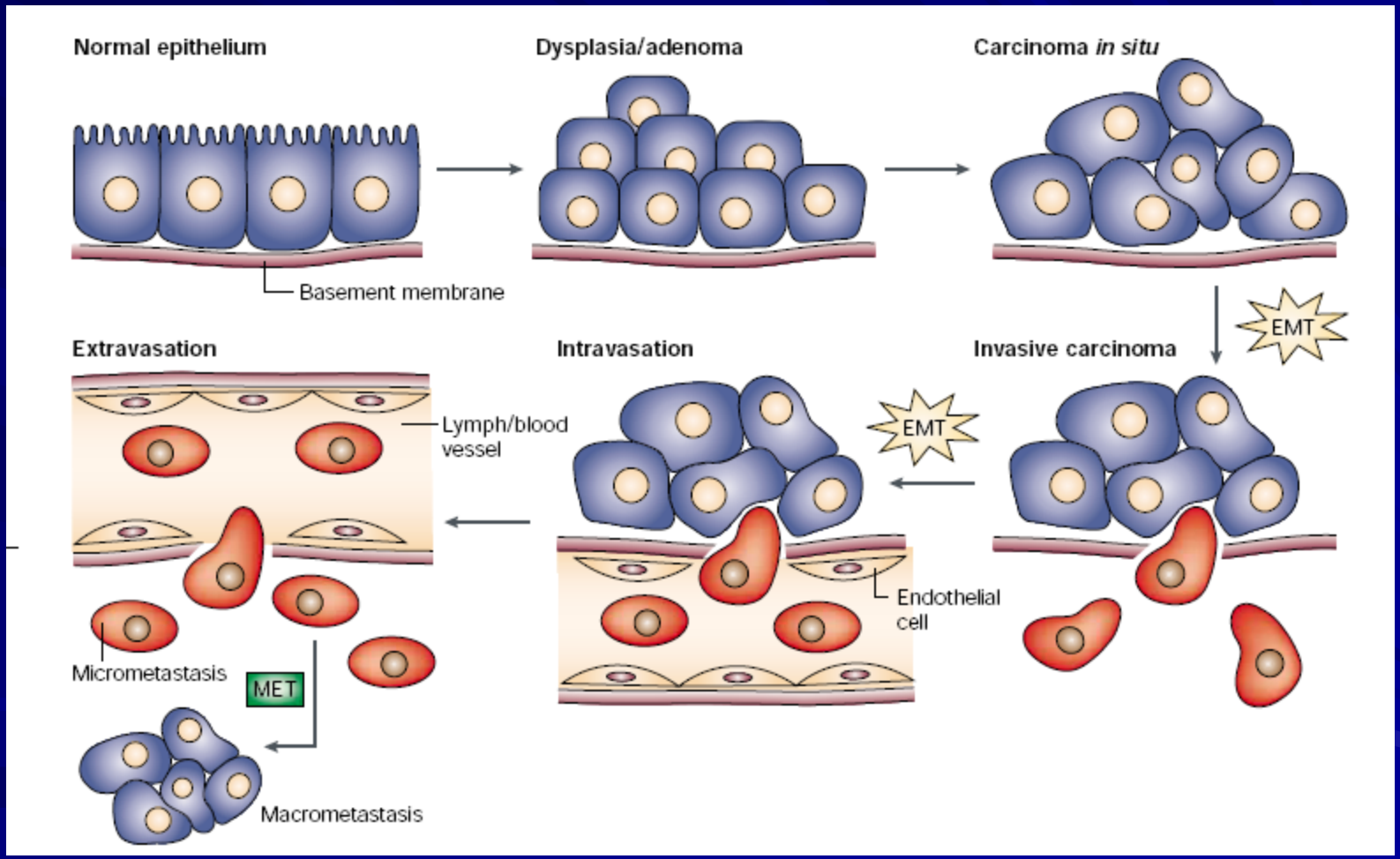

IGF
FGF
HGF
EGF
CFC
RTK
collagen
fibronectin
integrin
wnt
TGFβ
TGFβR
IL13
IL13Rα2
IL13Rα1
JAK
LIV-1
ROCK
SRC
Ras
Raf
PI3K
dishevelled
RhoA
stress fibers
migration
scattering
STAT6
ILK
AKT
GSK3
axin
APC
β–catenin
AP1
FAK
MEK
migration
Snail
Rac
MAPK
Snail
β–catenin
TCF/LEF
Slug
PAK
ROS
Twist
CDH1
SLUG
AP1
Jun/FOS
STAT6
Ets
Snail
cytoskeleton &
focal adhesion
reaarangement
E-cadherin
collagenase
urokinase
heparanase
MMPs
RANKL
vimentin
heparase
vimentin
ML
UK
RANKL
MMP
colL
reduced cell-cell
adhesion
invasiveness

Factors for metastatic progression

EMT ⟶ Dissemination ⟶ Micrometastasis ⟶ M-E-T

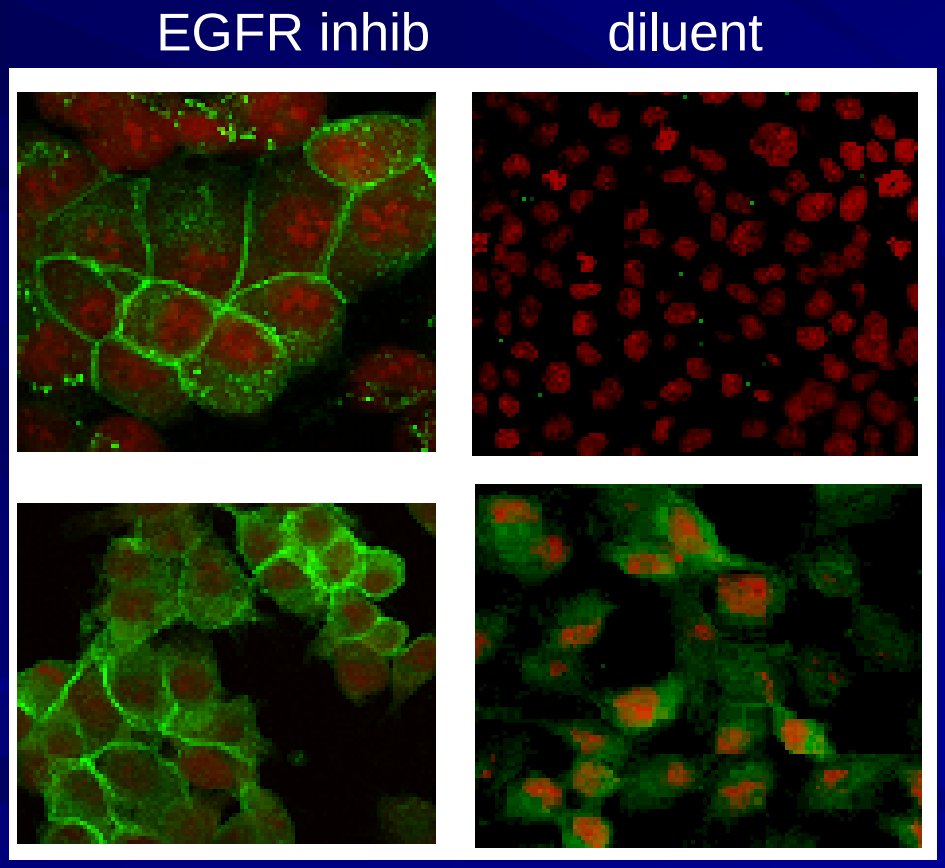
- Reversible (epigenetic)
- Environmental factors
- Location
  - – - bone marrow
  - – - liver (hepatocytes)

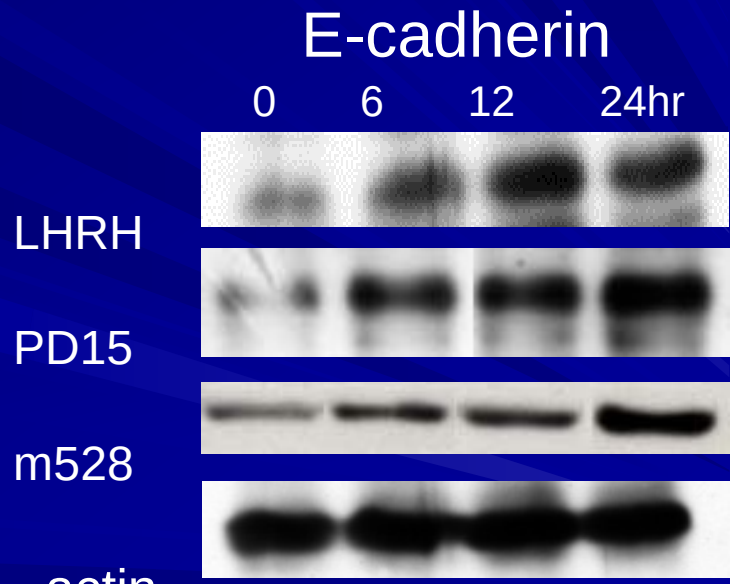
Molecular Events of Metastasis



Nature Reviews Cancer, 2002

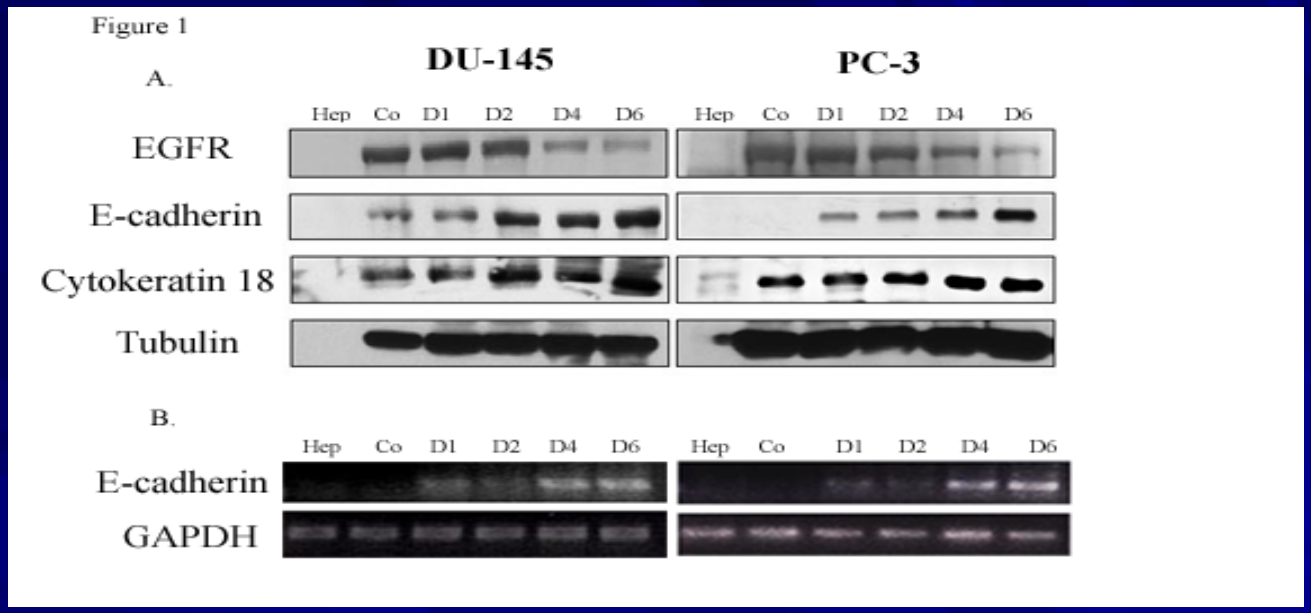
EGFR Modulates DU145 E-Cadherin Levels

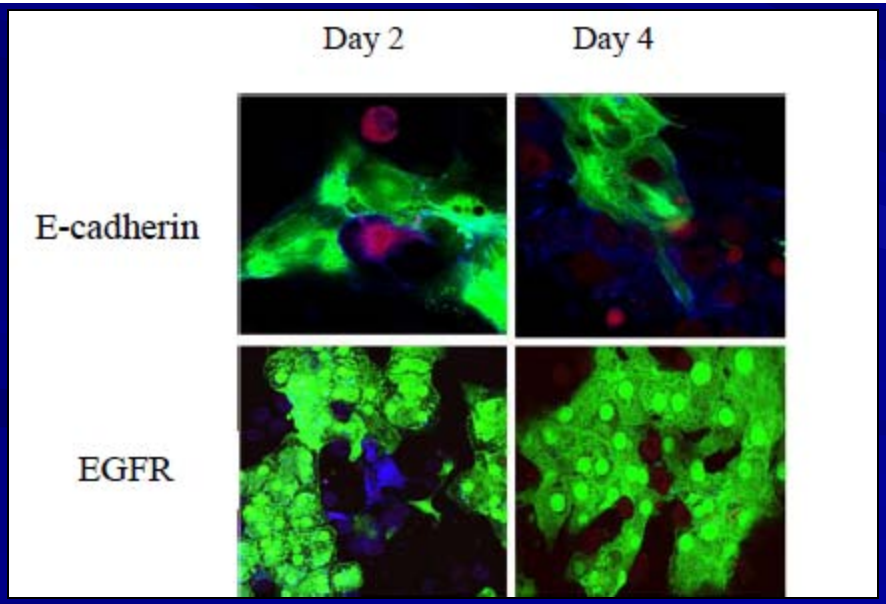




Yates et al 2005

E-cadherin/EGFR in Co-culture

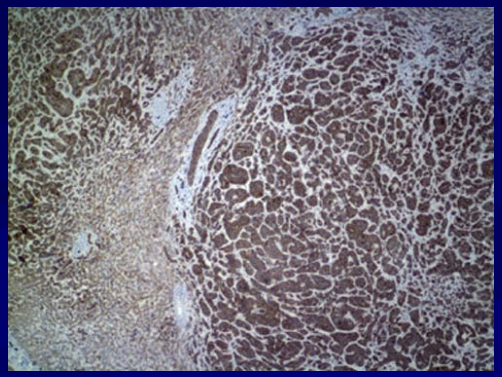




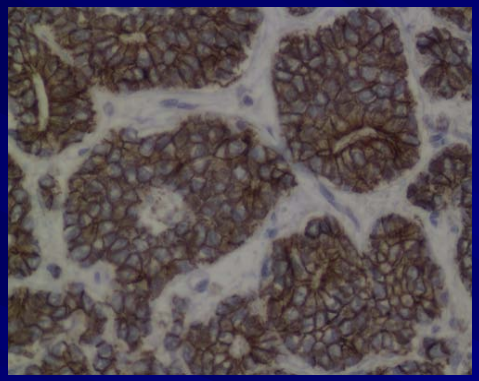
Green = Hepatocytes
Red= DU-145 prostate cancer
Blue = Anti-E-cadherin or EGFR staining

Human PCa Mets to Liver

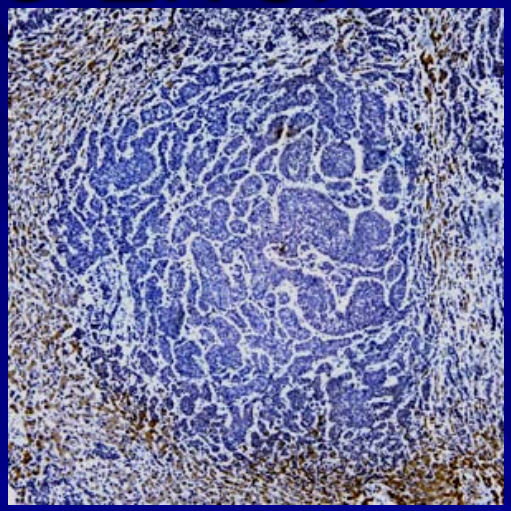
E-cadherin



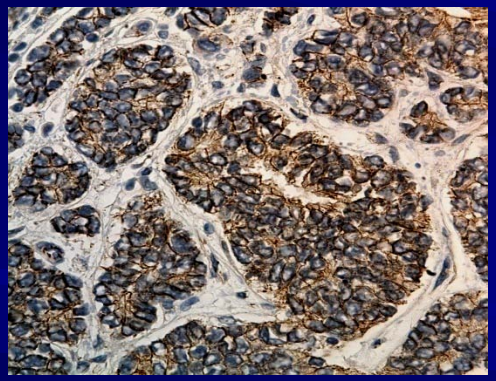
E-cadherin



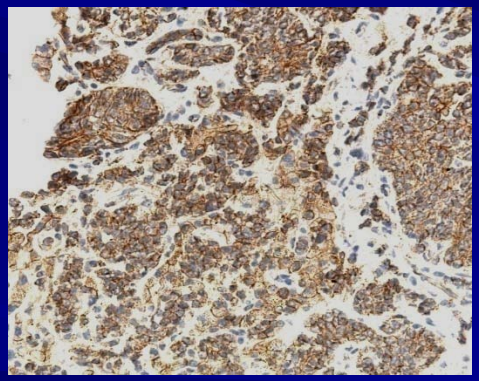
EGFR



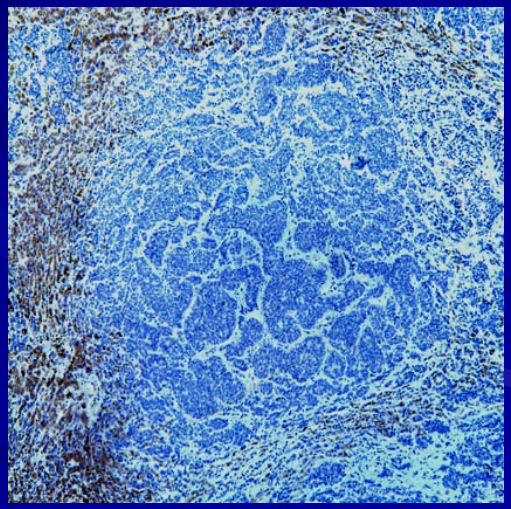
p120



B-catenin



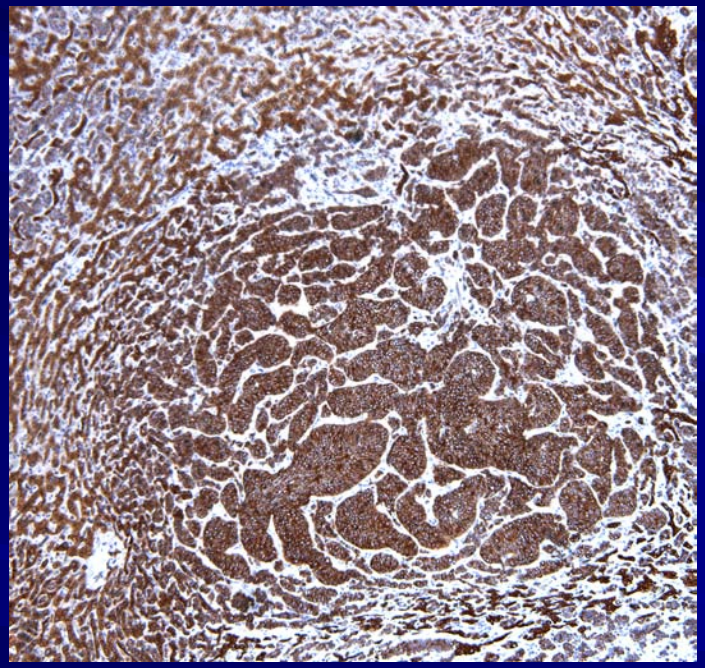
p-EGFR 1068



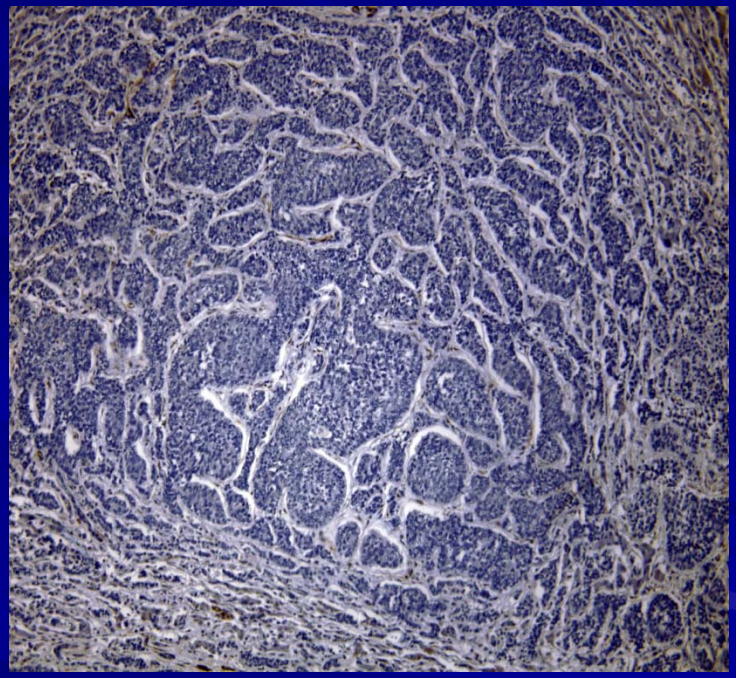
Top row = IHC with anti-E-cadherin, anti-β-catenin
Bottom row = anti-p120,

Reepithelialization of PCa Mets in the Liver

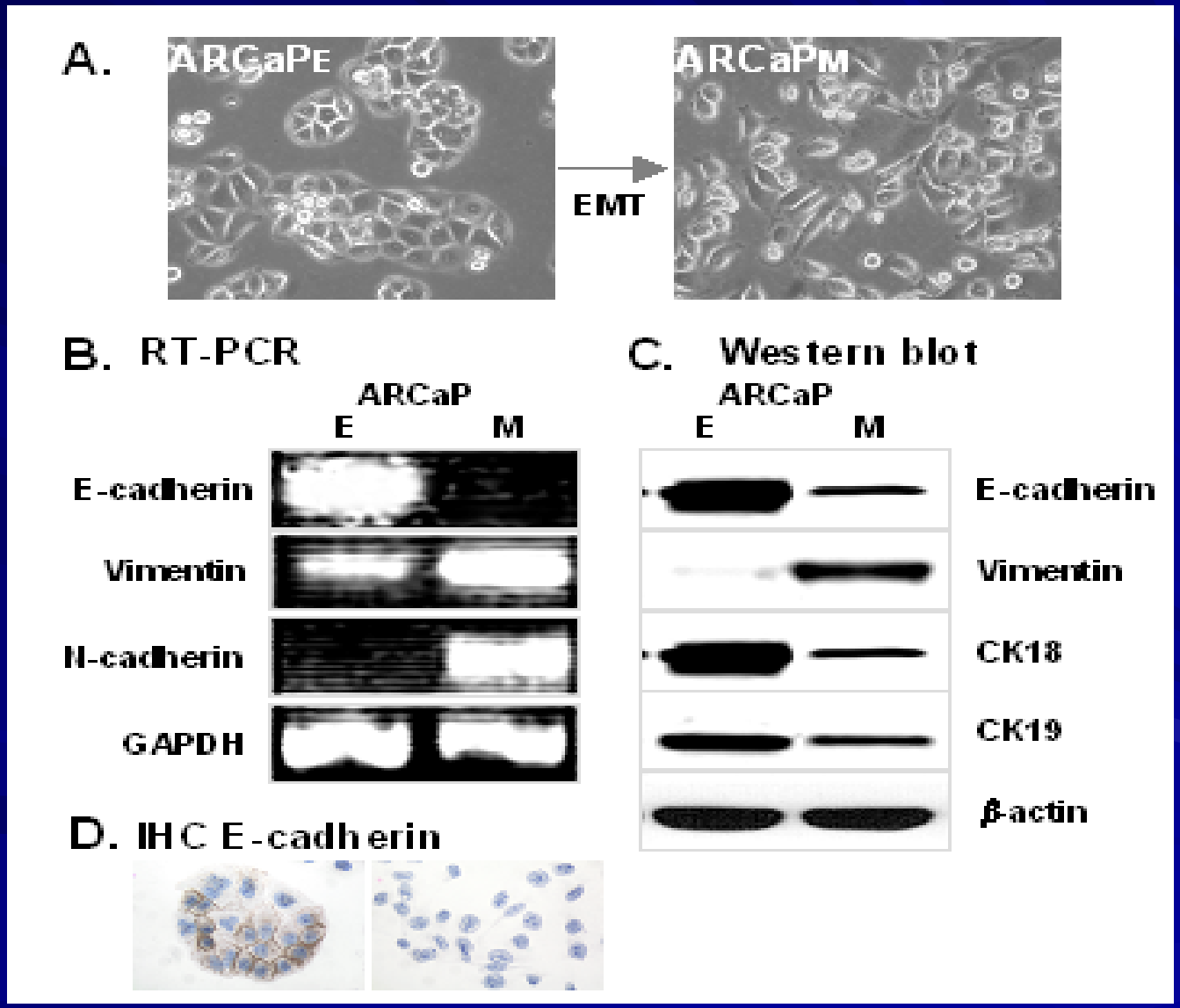
Cytokeratin 18



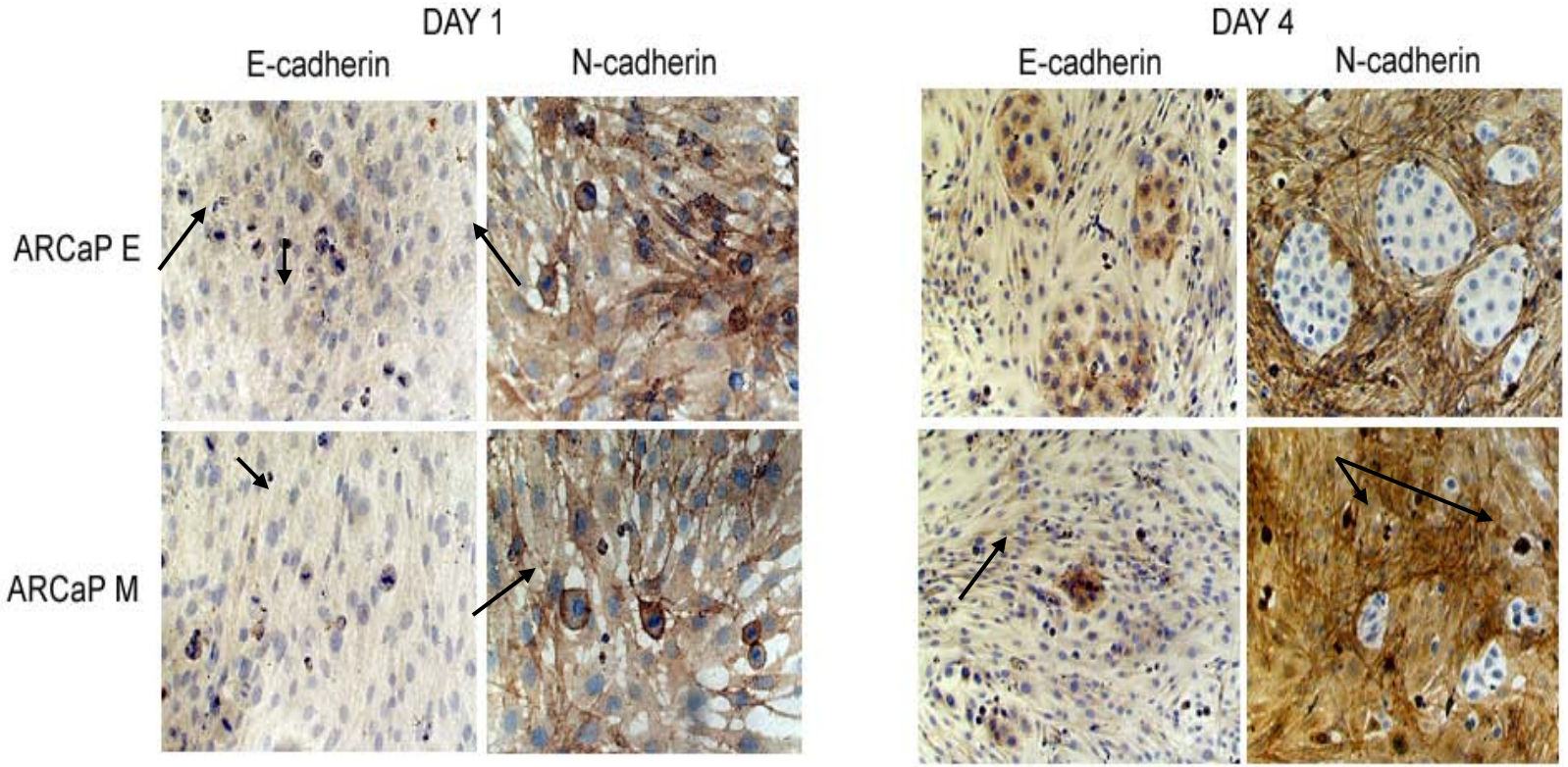
Vimentin



ARCaP: Classic EMT Model



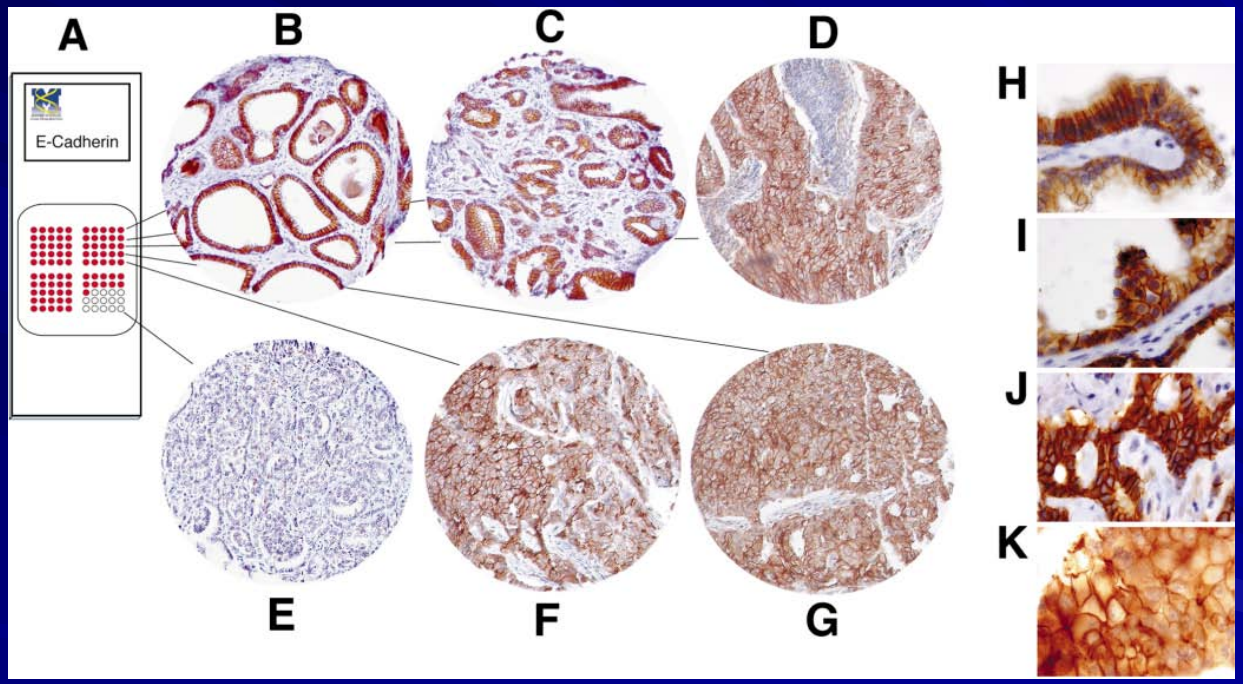
Prostate Cancer in Presence of Bone Stromal Cells



Josson et al 2010

E-Cadherin Expression in Prostate Cancer: A Broad Survey Using High-Density Tissue Microarray Technology

MARK A. RUBIN, MD, NEIL R. MUCCI, BS, JAY FIGURSKI, BS,
ALICE FECKO, BA, KENNETH J. PIENTA, MD, AND MARK L. DAY, PHD



A total of 1,220 prostate TMA samples were analyzed. High (normal) E-cadherin expression was seen in 87% of 757 benign, 80% of 41 high-grade PIN, 82% of 325 prostate carcinoma and 90% of hormone-refractory prostate carcinoma TMA samples.

Clinical implications of Repithelialization during Metastatic Seeding of Tumor Microenvironment

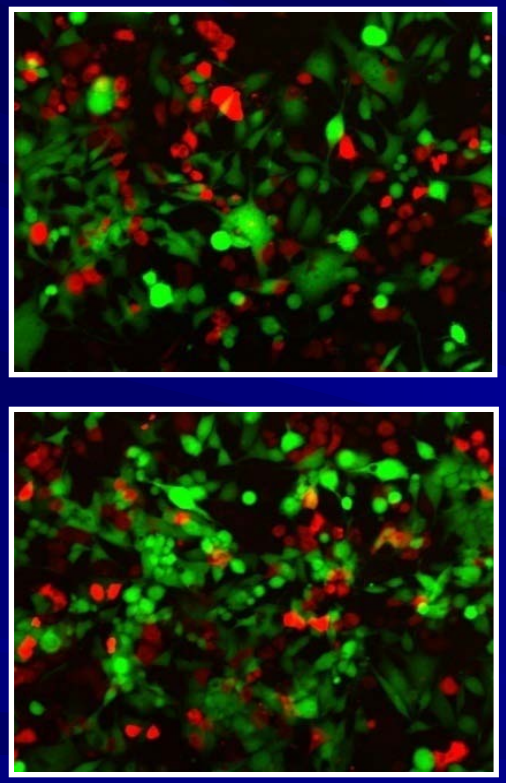
Metastatic Seeding within Tumor Microenvironment

A.

GFP- HS-27a

RFP-ARCaP$_E$

RFP-ARCaP$_M$



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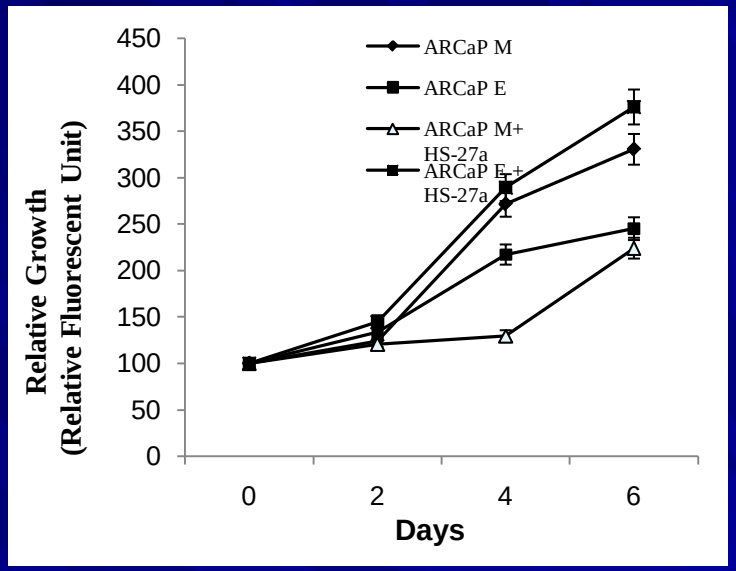

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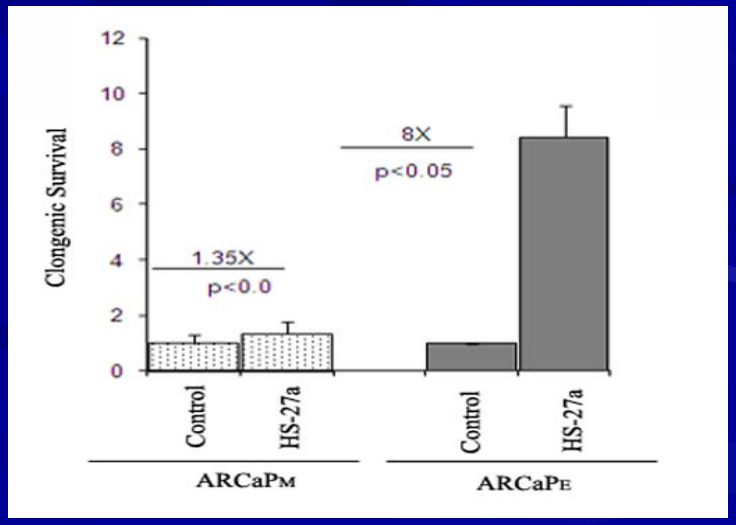

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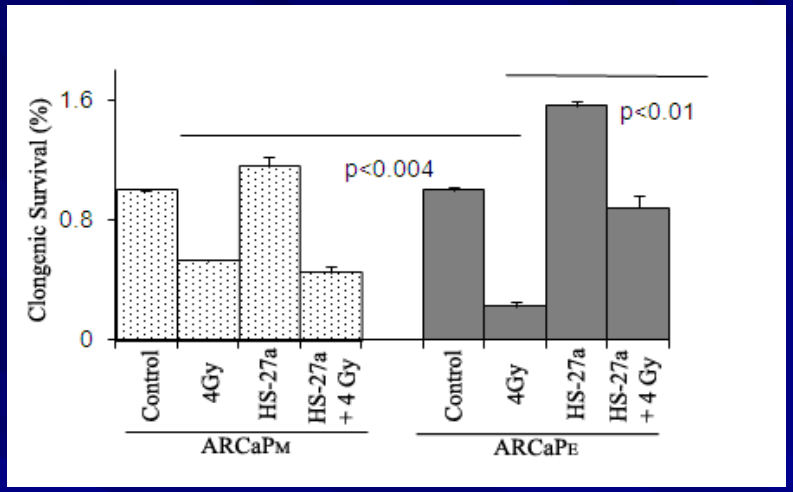
Prostate/Bone stromal cells decrease Radiation Sensitivity

A.



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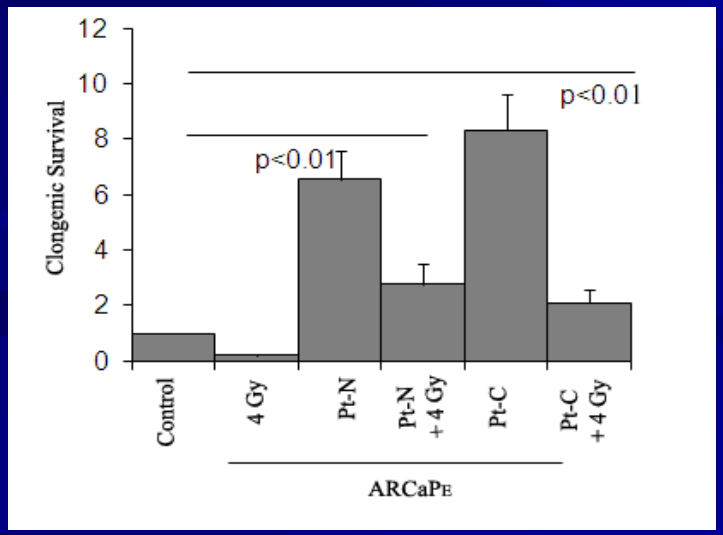

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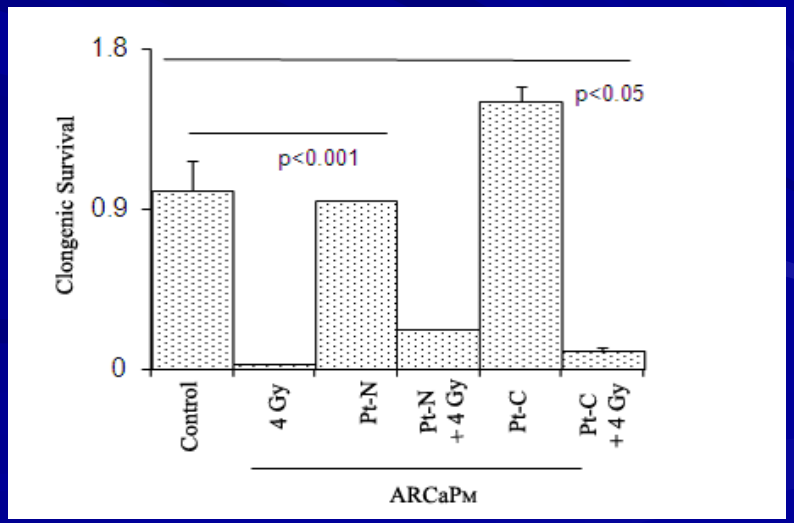

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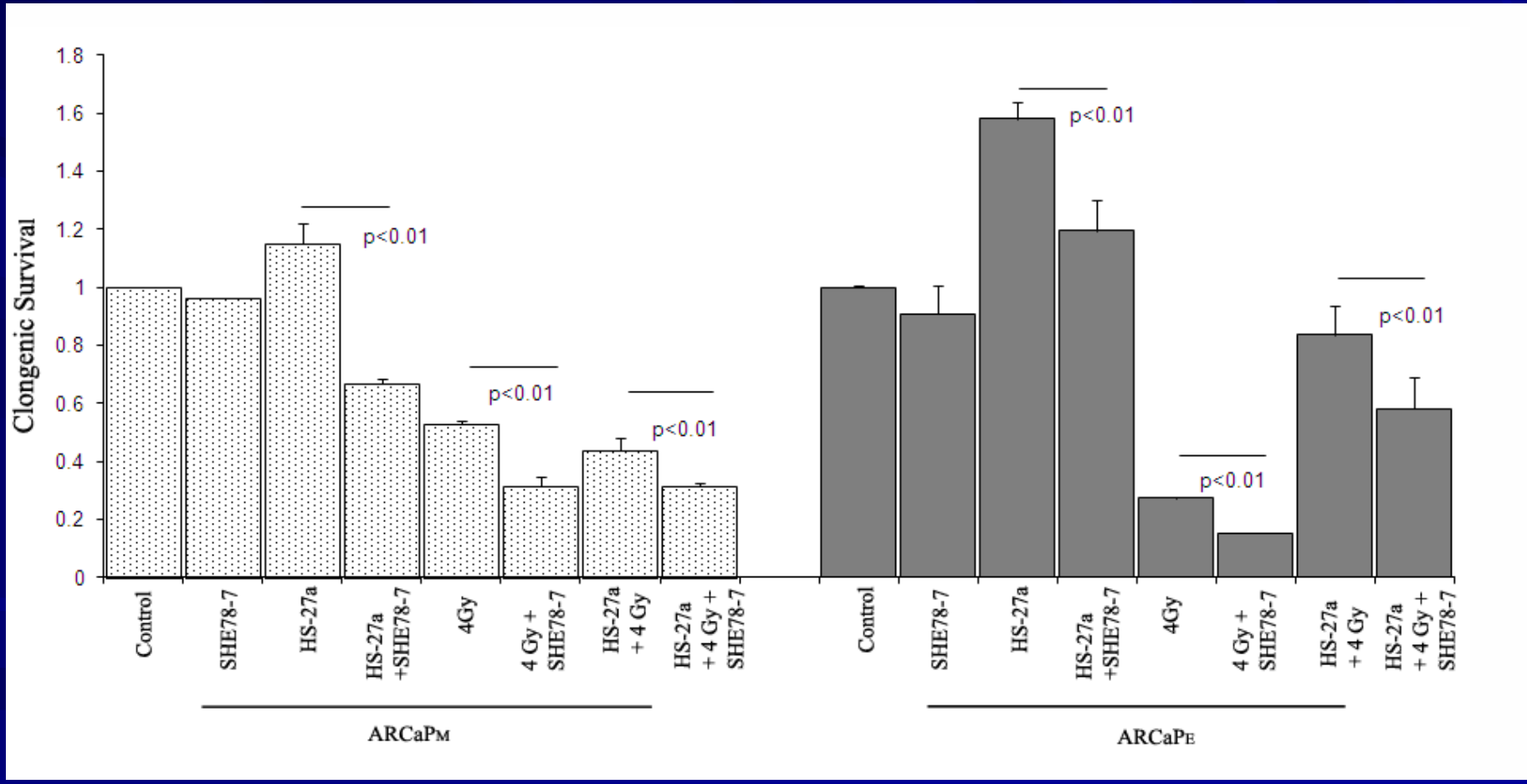
Blocking Cell-Cell Adhesion Increases Radiation Sensitivity



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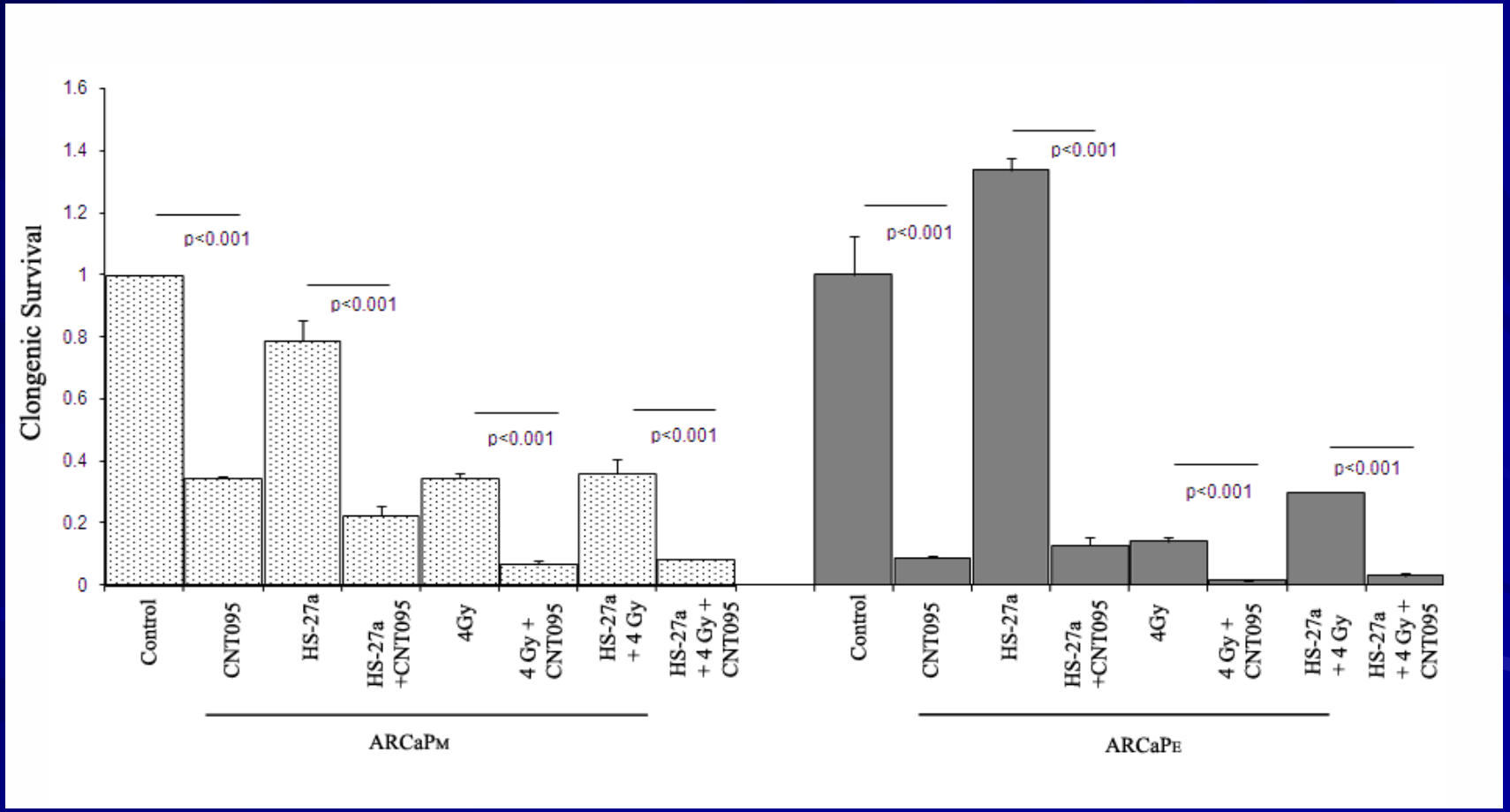
Blocking Cell-Cell Adhesion Increases Radiation Sensitivity



Establishment and Characterization of non-malignant and malignant cell lines from African American Prostate Cancer Patient.

African American Prostate Cell lines .

Table 1. Clinical features of African American and Caucasian patients of whom prostate cell lines were derived.

Cell line	Age	Race	Morphology	Clinical Stage	Tumor Grade	Gleason Score
RC77N	62	AA	Epithelial	Non-malignant	NA[c]	NA[c]
RC44N	59	AA	Epithelial	Non-malignant	NA[c]	NA[c]
RC77T	62	AA	Epithelial	Primary Adenocarcinoma	Poorly Differentiated	7
RC44T	59	AA	Epithelial	Primary Adenocarcionma	Poorly Differentiated	7
MDA-2Pca-2b	63	AA	Epithelial	Adenocarcinoma Metastatic tumor	NA	NA
PrEC	59	White	Epithelial	Non-malignant	NA[c]	NA[c]
RC-92a	57	White	Epithelial	Primary Adenocarcinoma	Well-Differentiated	3 + 3
PC-3	62	White	Epithelial	Metastatic Adenocarcinoma	Undifferentiated	NA[c]

AA = African American
NA = not applicable
NA[c] = Not available

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Properties of Newly Established Cell lines

Table 1. Properties of RC-77T/E and RC-77N/E cell lines

	RC-77T/E	RC-77N/E
Life Span		
	>40	>40
Gene Expression by RT-PCR		
E6	+	+
NKX3.1	+	+
Cytokeratin 8	+	+
AR	+	+
p16	+	+
PSA	+	+
GAPDH	+	+
3D-organoid formation	+	-
Tumorigenicity in SCID mice	3/3	0/3

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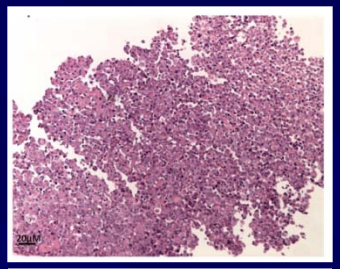
Figure 2

A.



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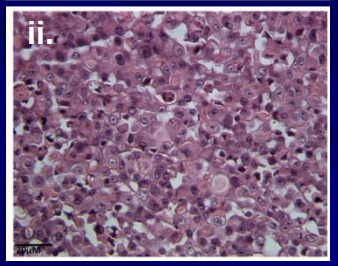

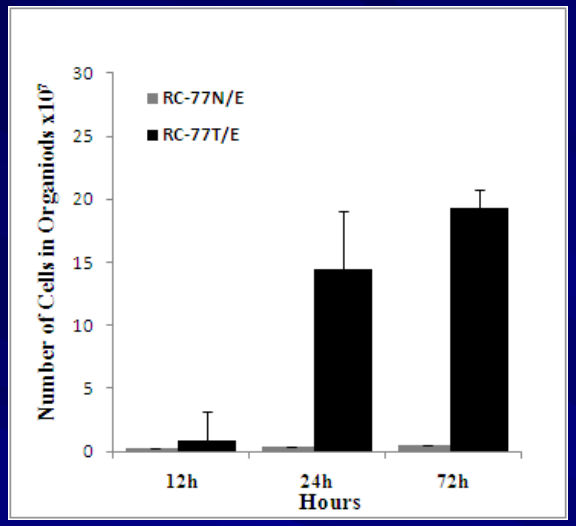

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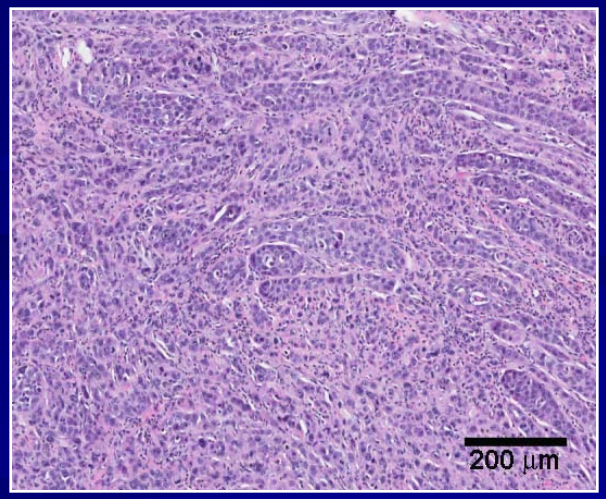
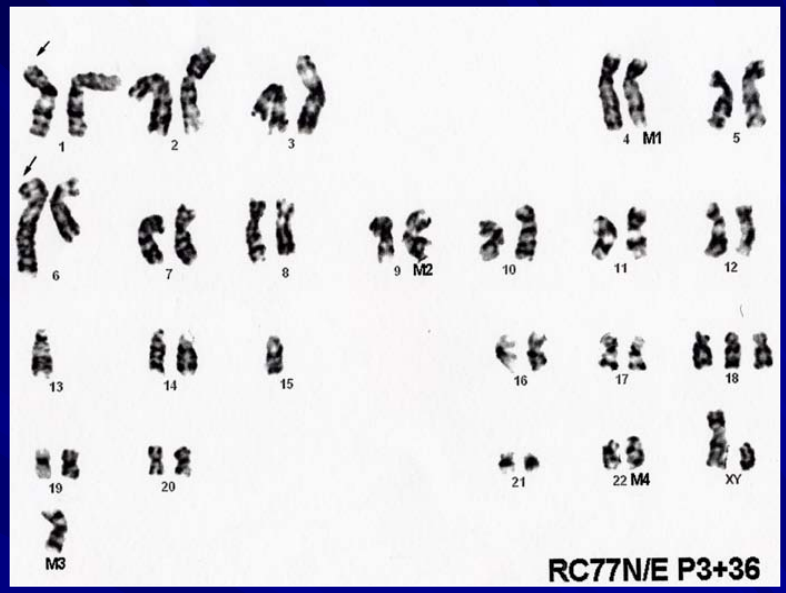


C.

i.



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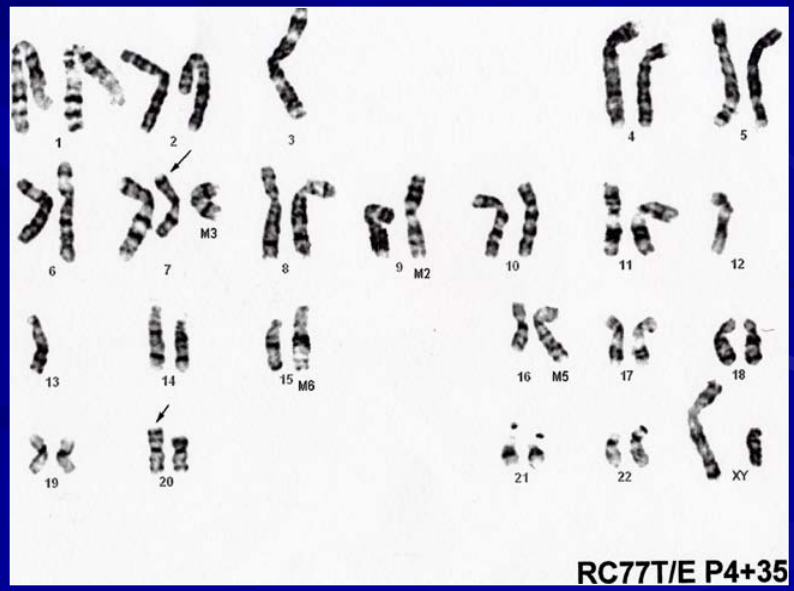

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The Lab

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Sajni Josson

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Tim Turner

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