

Tumor Microenvironment: Tumor Vasculature, Oxygenation/Hypoxia, and Angiogenesis

Jacky Williams
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Tumor Microenvironment

Solid tumor formation results in a unique biologic compartment

- Architecturally unique – tumor cells, tumor stroma, tumor vessels

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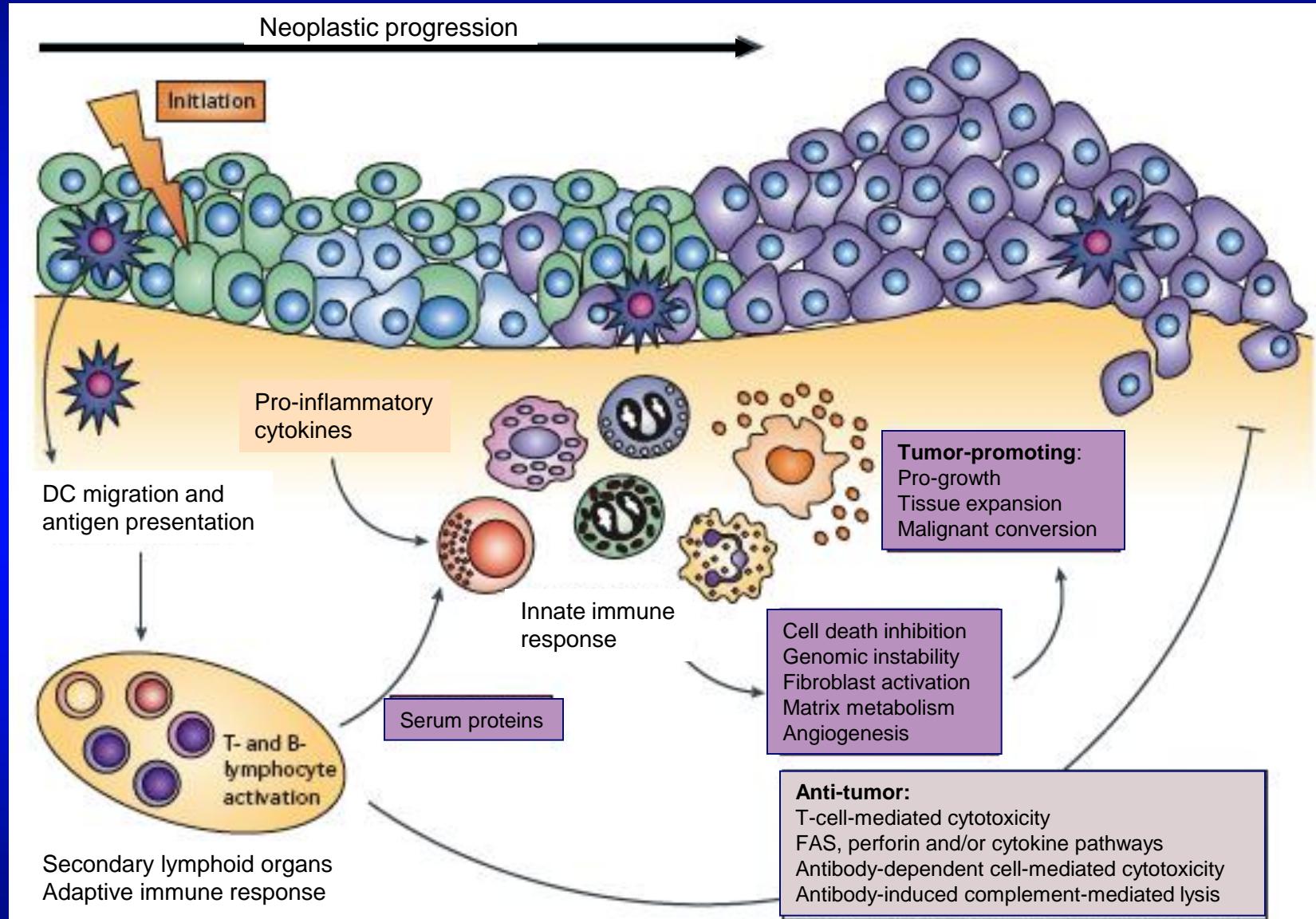
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- Immunologically unique – privileged

Local Site of Immune Privilege

Tumors create local environment that evades surveillance, recognition and elimination by innate/adaptive immune systems

- Tumor release of suppressive immune mediators (e.g. TGF β , VEGF, IL10, etc)
- Mesenchymal production of inhibitors
- Tolerance to presence of immuno-regulatory cells (e.g. T_{Reg}s, APCs)

Local Site of Immune Privilege



Tumor Microenvironment

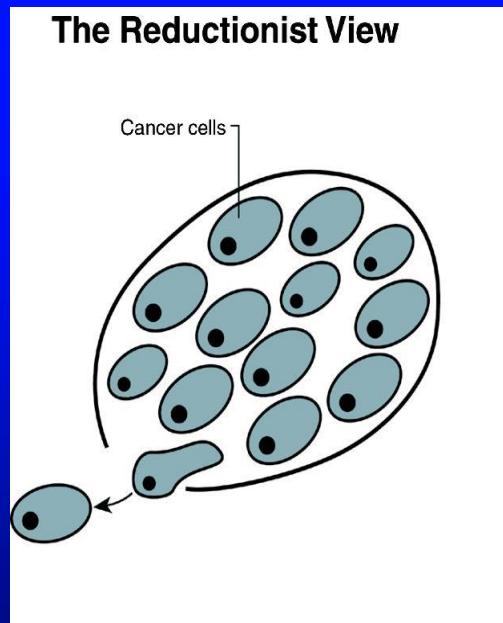
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Tumor Microenvironment

The interactions between cancer cells and their intrinsic and extrinsic (micro)environment create a context that promotes tumor growth

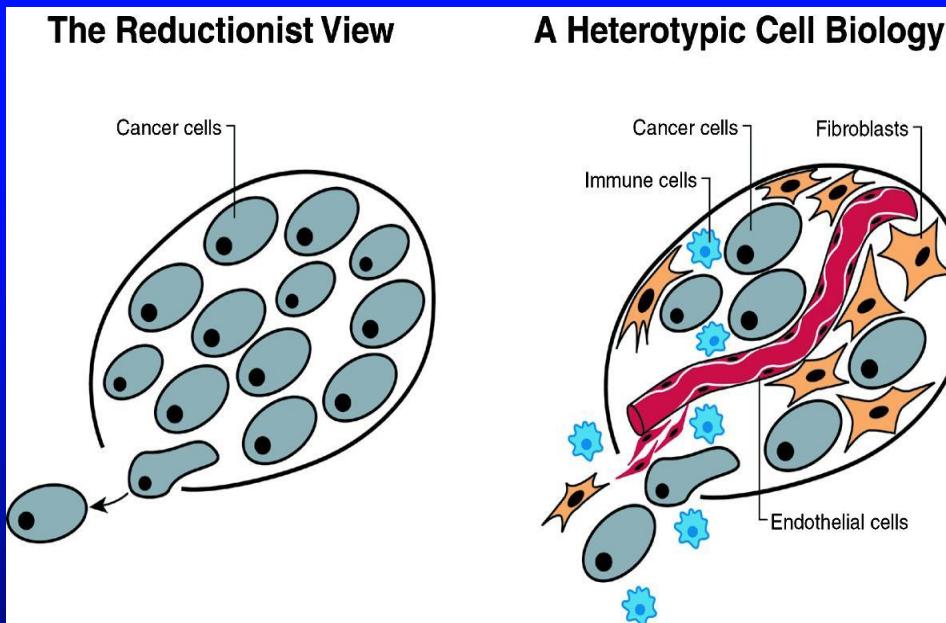
Genetic changes in cancer cells drive tumorigenesis



Tumor Microenvironment

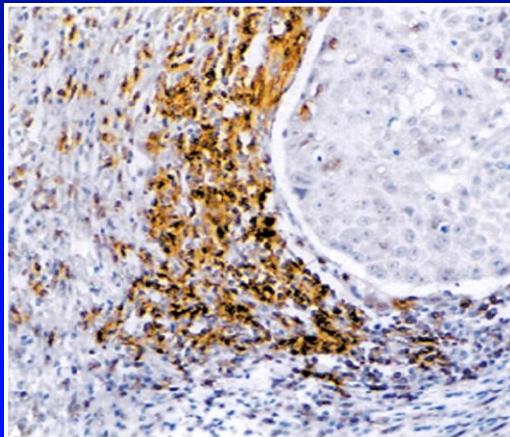
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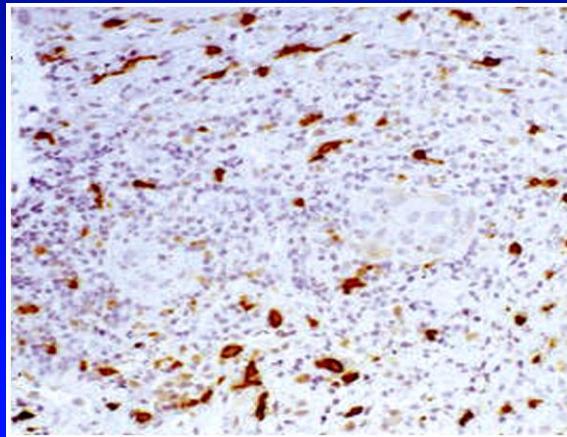


Tumors are complex tissues in which mutant cancer cells have subverted normal cell types in their microenvironment to serve as active collaborators in promoting tumor growth

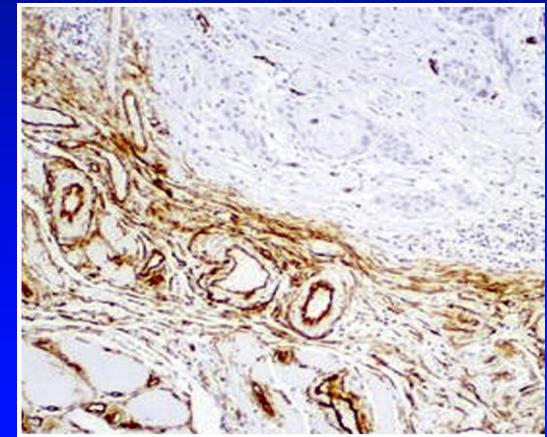
Tumor Stroma



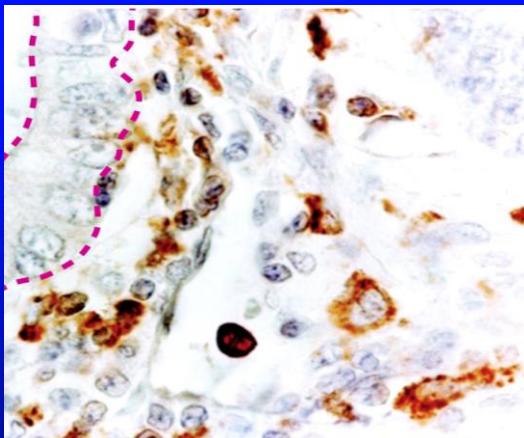
CD4+ve T-lymphocytes NSCLC



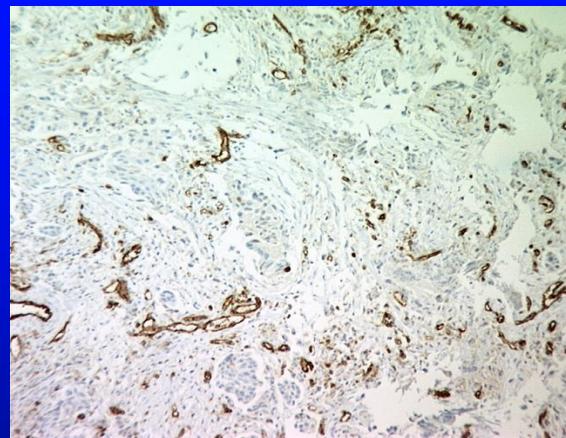
CD117+ve mast cells



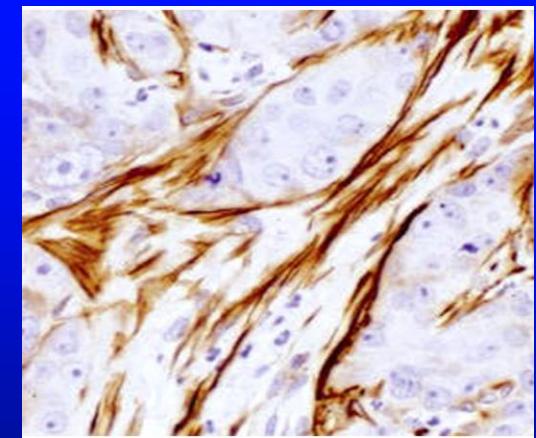
CD34+ve fibrocytes H&N



CD11b+ monocytes



CD31+ve endothelial cells



α-smooth muscle actin
myofibroblasts

Tumor Stroma

- Immune cells
 - Lymphocytes, dendritic cells
- Inflammatory cells
 - Monocytes, granulocytes
- Muscle and myofibroblasts
- Vascular cells
 - Lymph-endothelial, vascular-endothelial, pericytes, smooth muscle cells
- Extracellular matrix (ECM)
 - Basement membrane
 - Fibers
 - Fibronectin
 - Laminin
 - Collagen
 - Elastic
 - Soluble component
- Adipocytes

While none of these cells are malignant, due to their environment, their interactions with each other (and directly or indirectly with cancer cells) means that these cells acquire an abnormal phenotype and altered function

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Fibroblasts (CAFs):

- Activated phenotype (similar to wound healing)
- Spindlyloid and express α -smooth muscle actin
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 - Roles in ?cancer **initiation** and **proliferation** (?transformed epithelial cells activate stroma or stromal changes transform epithelium?)

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Tumor Stroma

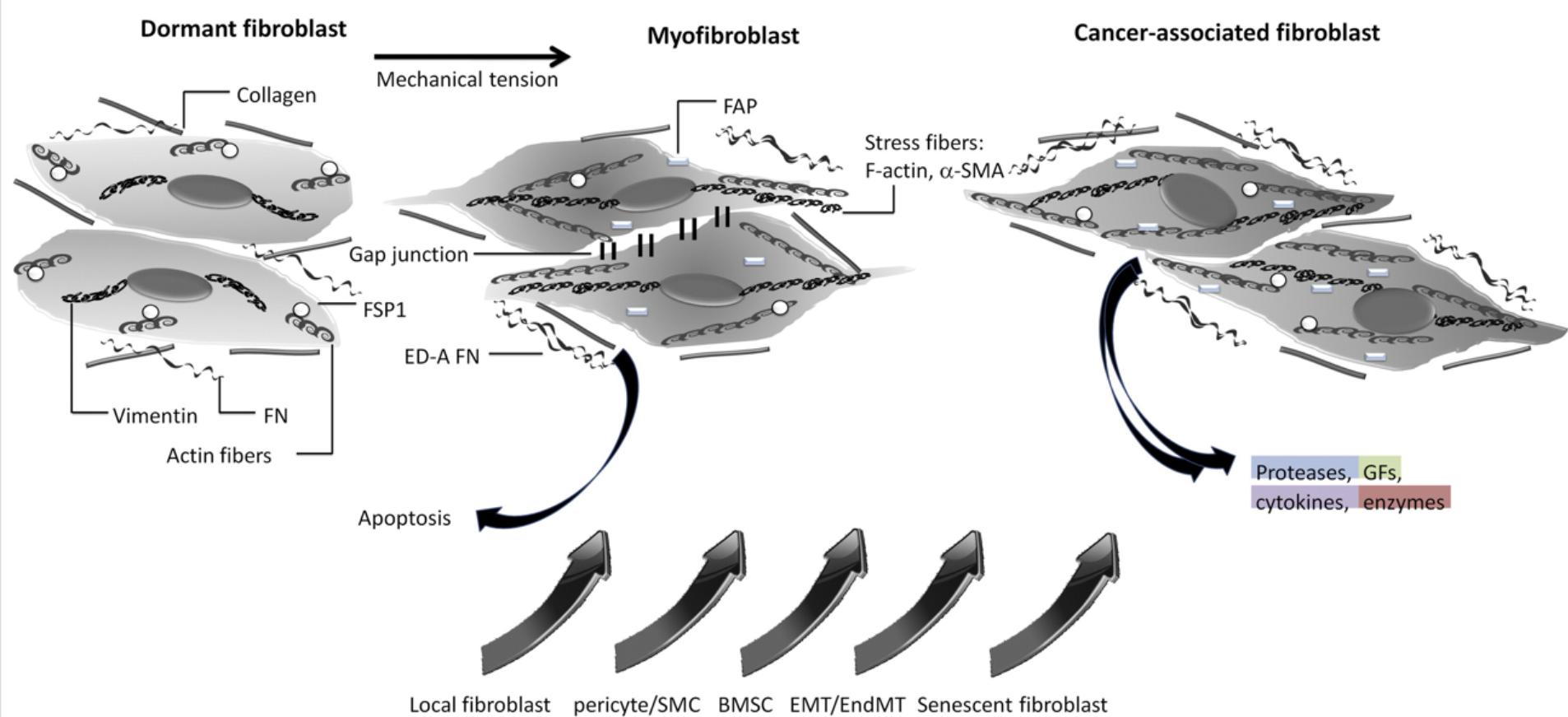
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Tumor Stroma



Other (and directly or indirectly with cancer cells) means that these cells acquire an abnormal phenotype and altered function

Tumor Stroma

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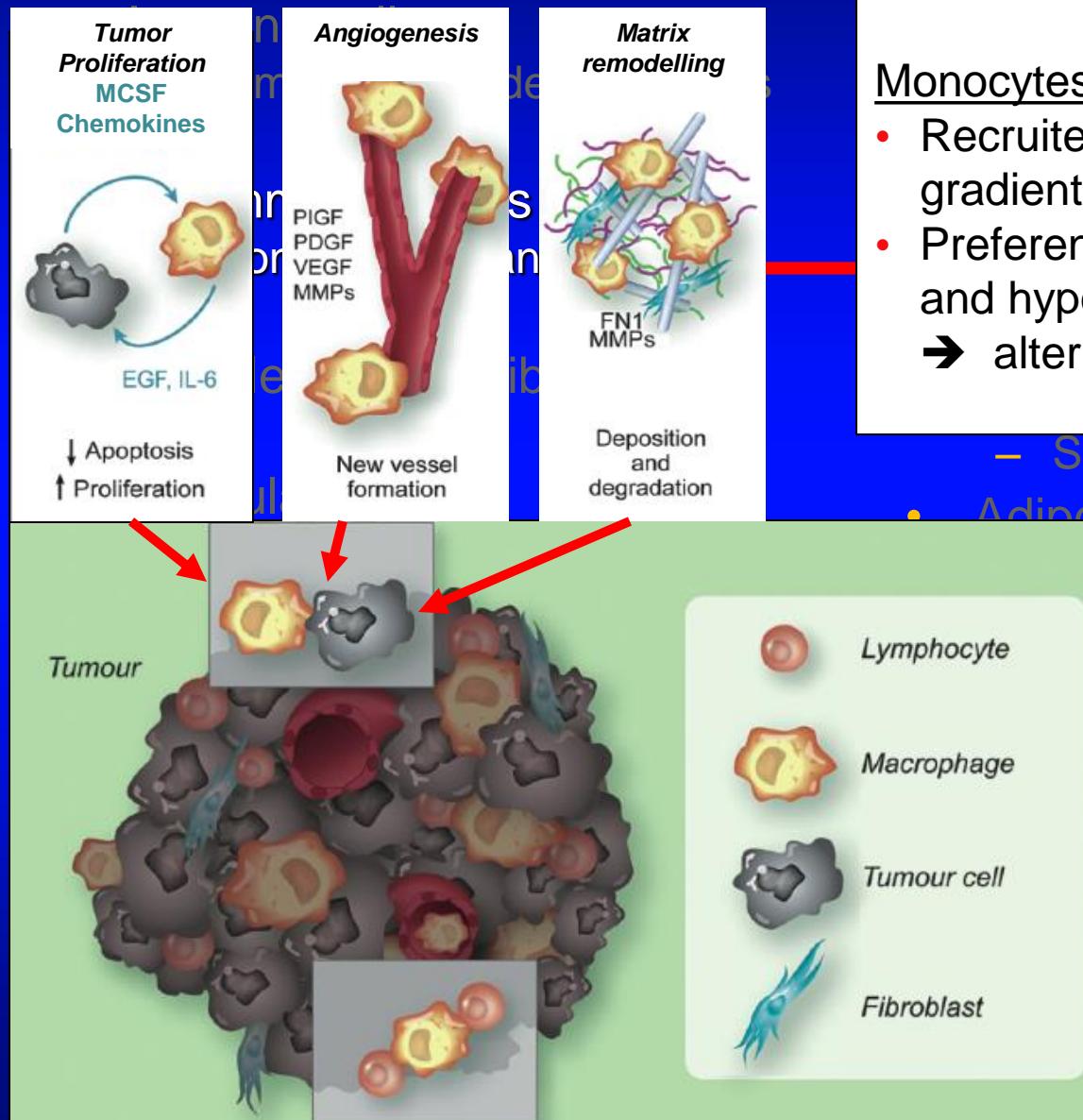
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Fibroblasts (CAFs):

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- Roles in ?cancer initiation and proliferation (force-/protease-mediation, growth & angiogenic factors, MMPs)
- ? source of CAFs
- Play a greater role in early vs. late tumor progression (target?)

While none of these cells are cancer cells, their environment, their interaction with each other (and directly or indirectly with cancer cells) means that these cells acquire an abnormal phenotype and altered function.

Tumor Stroma



Monocytes (TAMs):

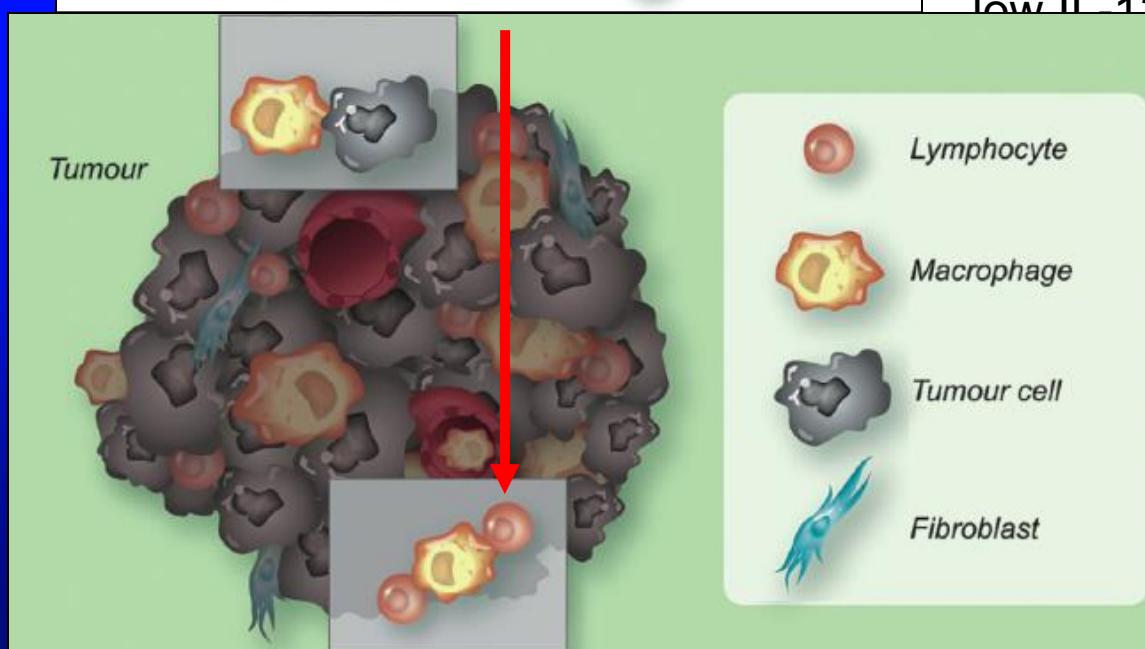
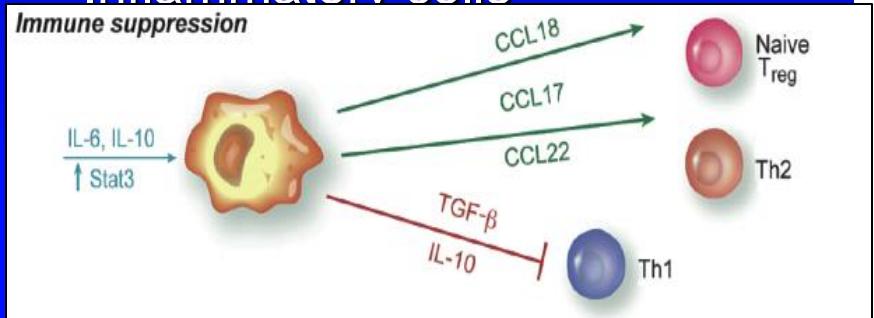
- Recruited along chemotactic gradients
- Preferentially differentiate in necrotic and hypoxic areas (rich in Th2 cytokines)
→ alternately activated ~M2 (TAMs)

- Soluble component
- Adipocytes

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Tumor Stroma

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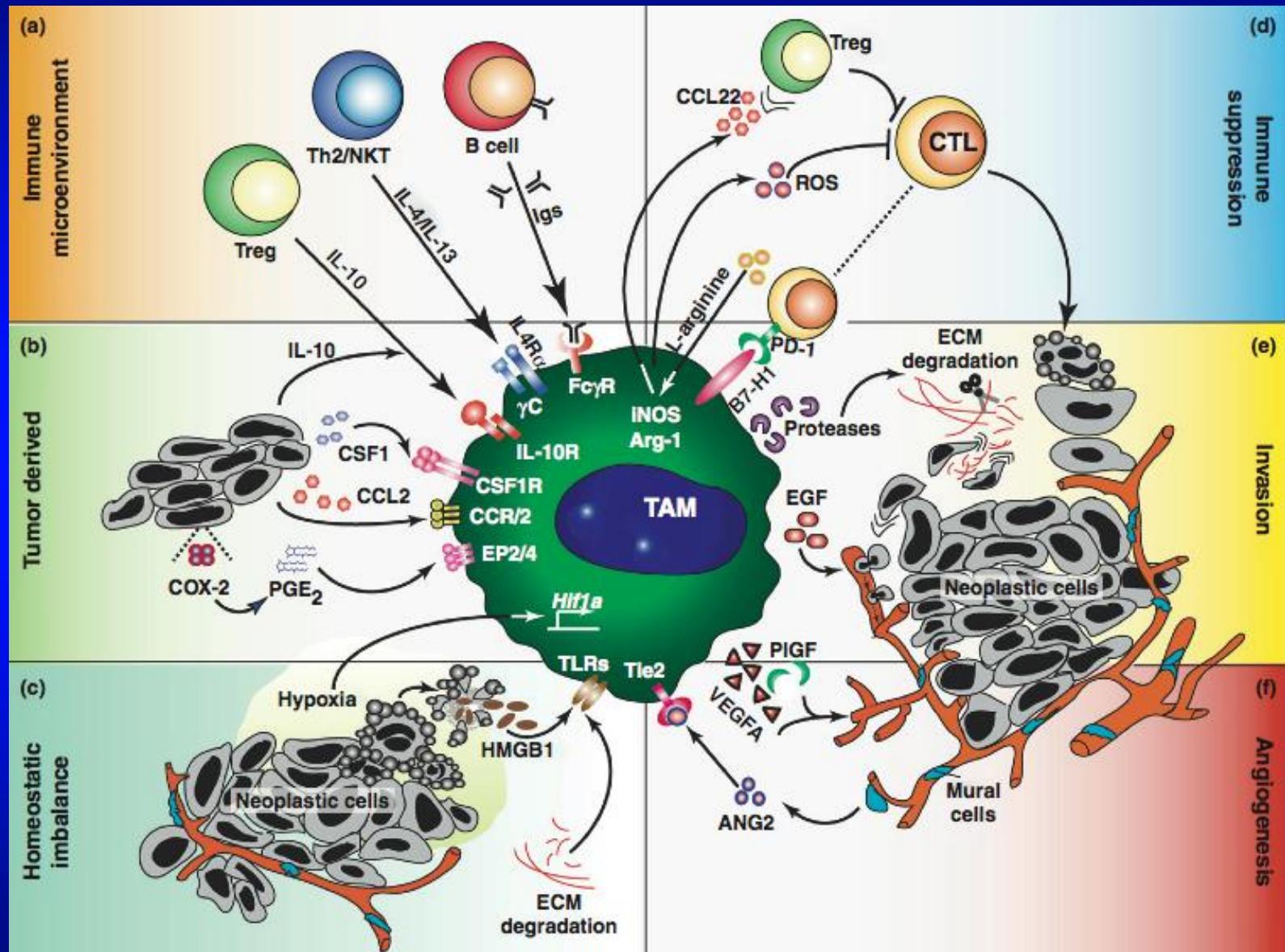


Monocytes (TAMs):

- Recruited along chemotactic gradients
- Preferentially differentiate in necrotic and hypoxic areas (rich in Th2 cytokines)
→ alternately activated ~M2 (TAMs)
- TAMs express VEGF, MMPs, IL-6; immune-suppressive: IL-10, TGF β , low IL-12, MHCII

alignant, due to interactions with each other and with cancer cells. Cells acquire an altered function

Tumor Stroma

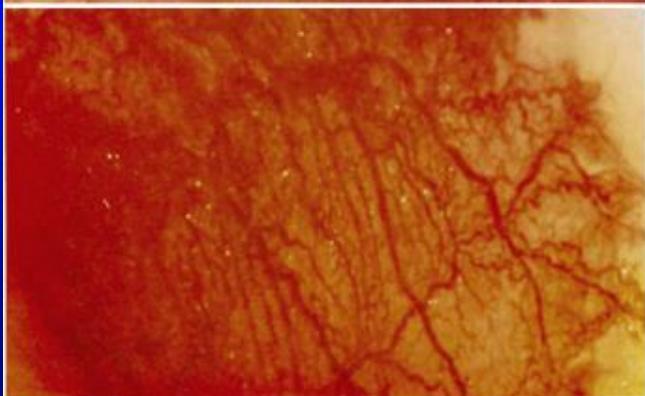


Tumor Microenvironment

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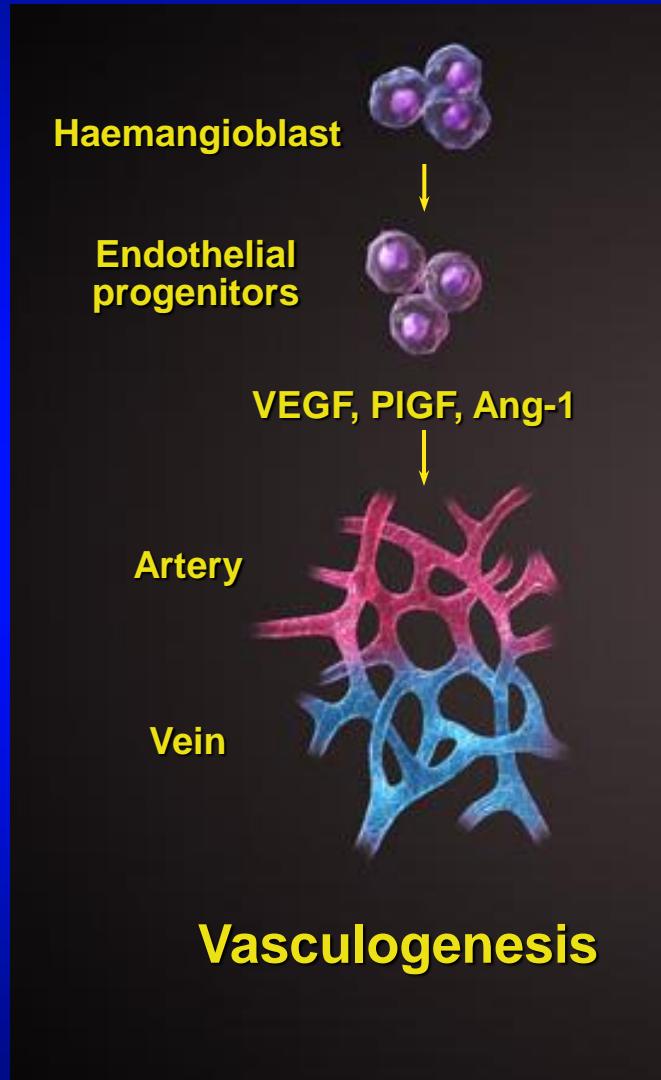
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Tumor Vasculature



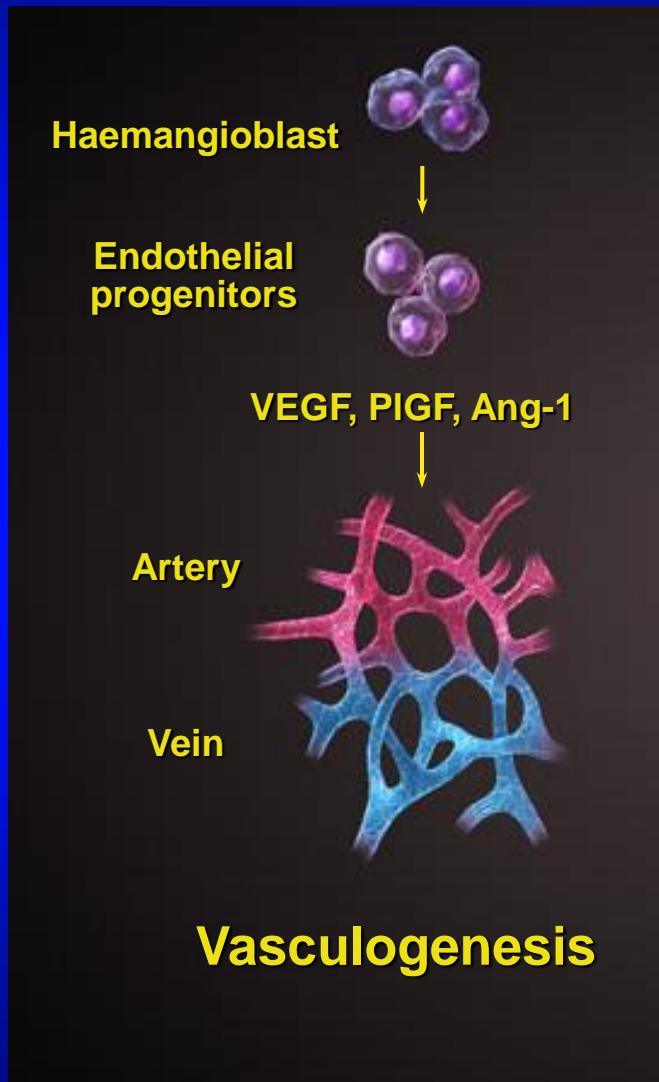
Indications in a rat dorsal air sac model that tumors express signal(s) that induce the formation of new vessels: tumor angiogenic factor (TAF)

Normal Vessel Formation



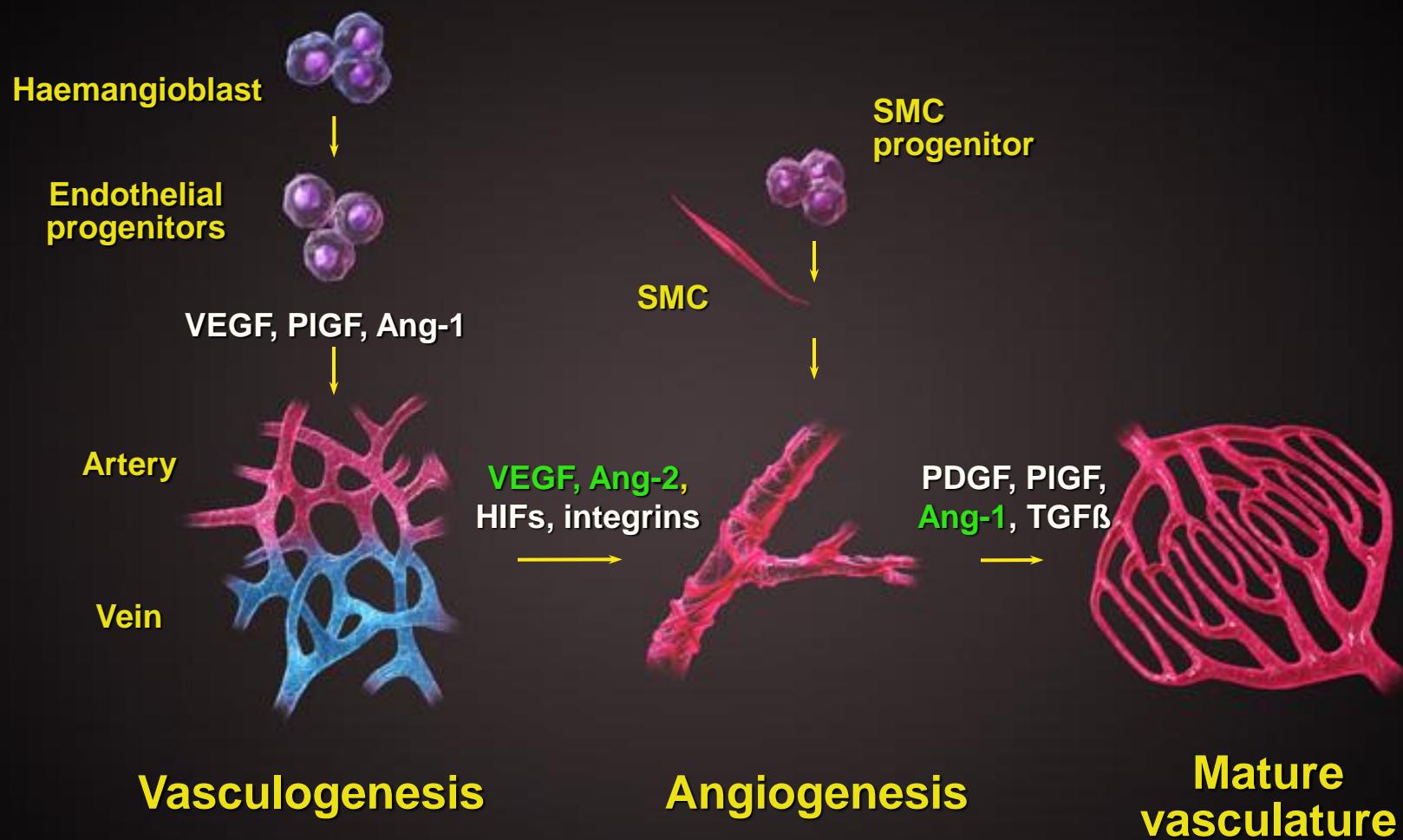
Endothelial progenitor cells (EPCs) contribute to vessel growth in embryos (angioblasts)

Normal Vessel Formation

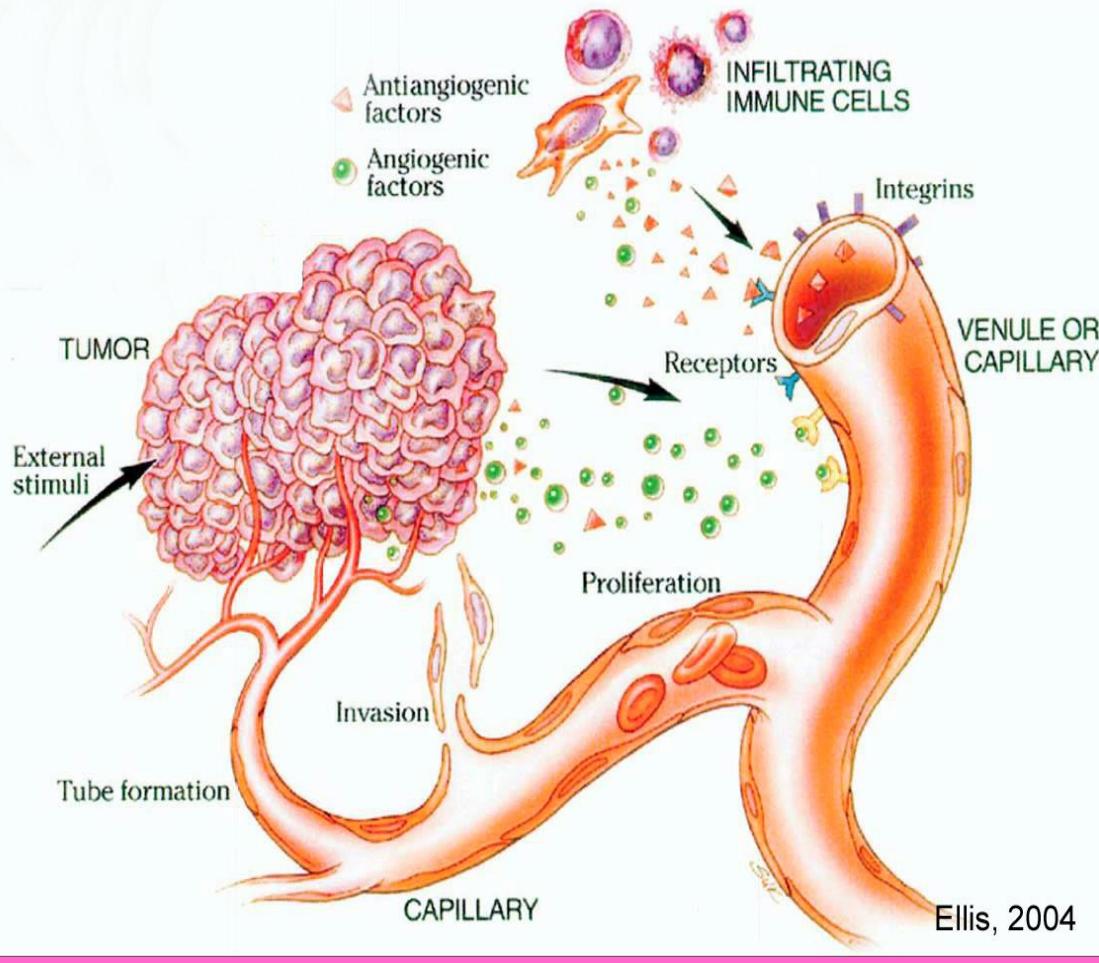


Endothelial progenitor cells (EPCs) contribute to vessel growth in embryos (angioblasts) and ischemic, malignant and inflamed tissue in adults (+ mesoangio-blasts, multi-potent adult progenitor cells)
Recruitment and differentiation of progenitor cells: VEGF, PIGF, Ang-1, Id proteins, cytokines, etc.

Normal Vessel Formation



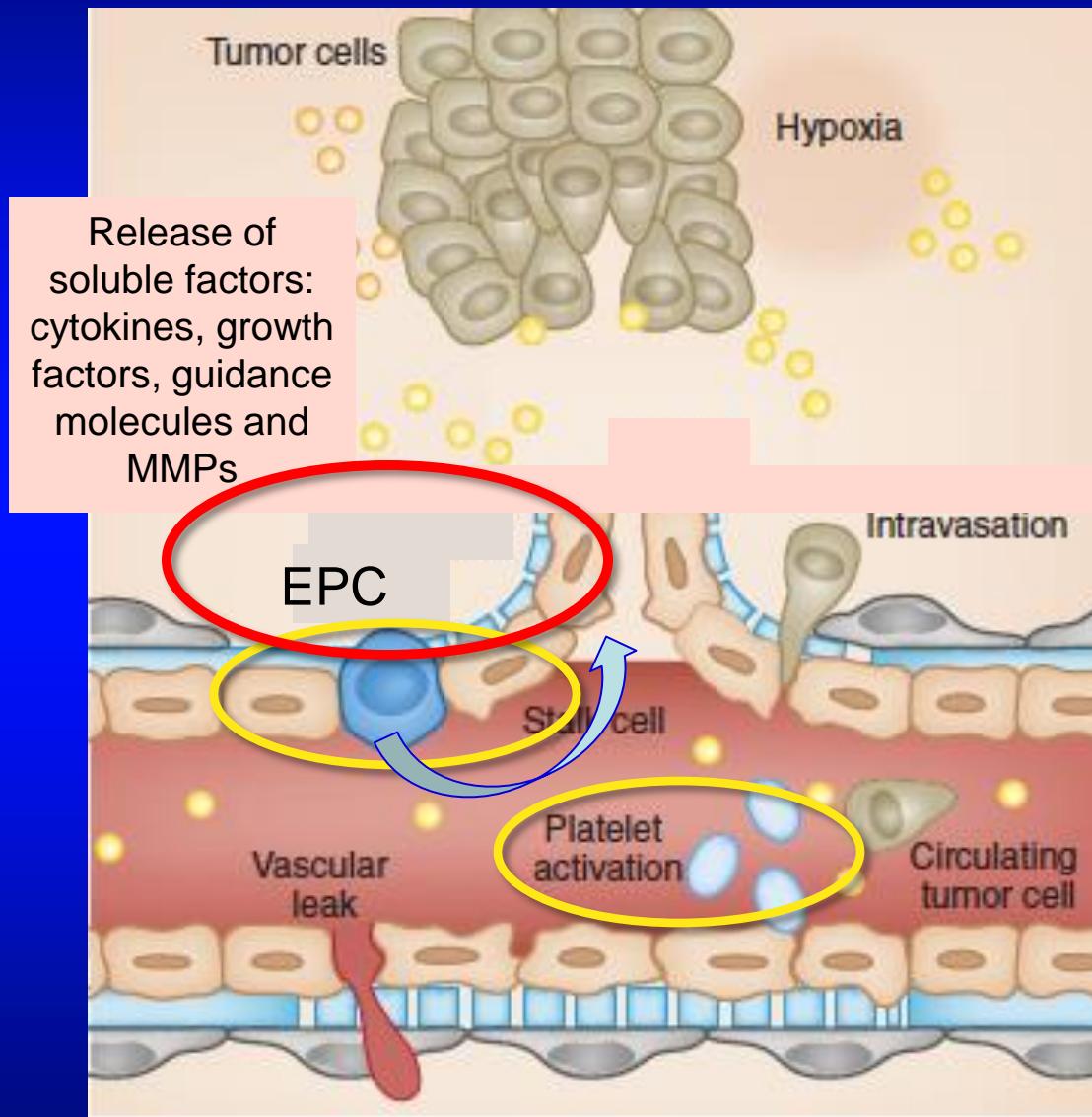
Tumor Angiogenesis



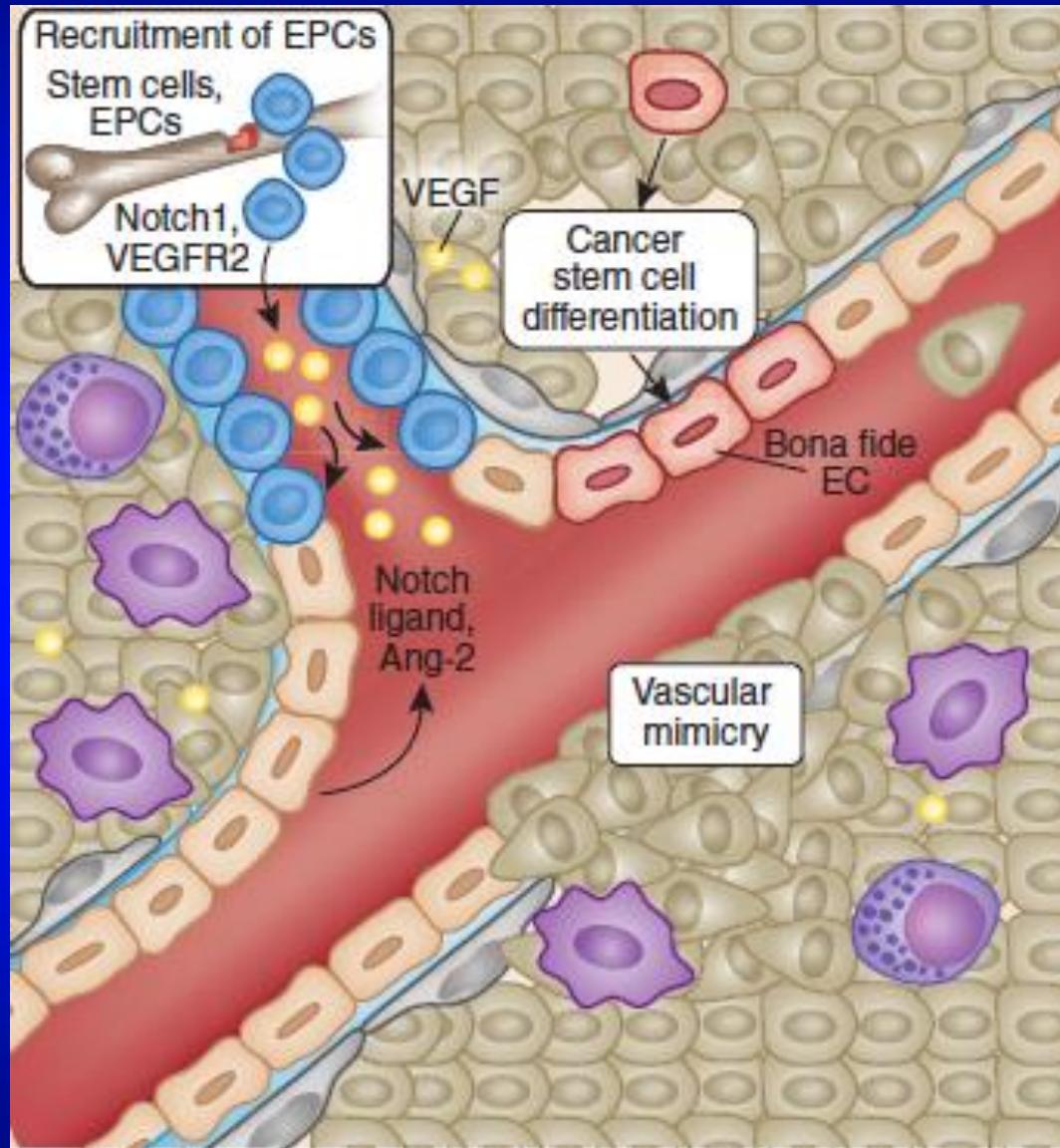
- Tumor cells proliferate avascularly
- Angiogenic balance shifts
- Endothelial cells activated (EPC)
- Proliferation and migration
- MMPs secreted
- Buds sprout
- Lumen formed
- Network and blood flow established
- Excess vessels pruned

VEGF, FGF-2, angiopoietins, PDGF, NOS, FGF1, PIGF, IL8, TGF β 1

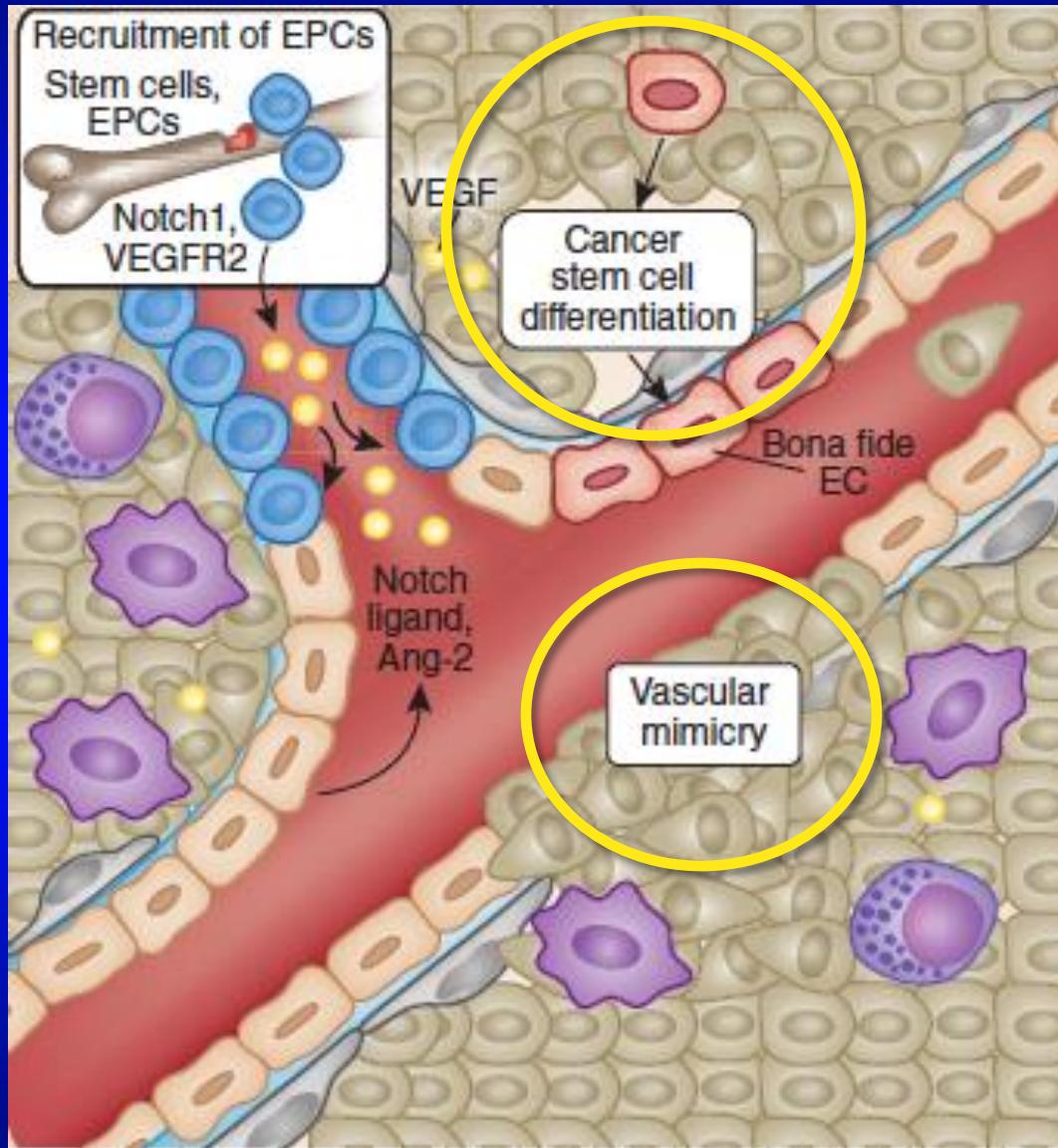
Tumor Angiogenesis



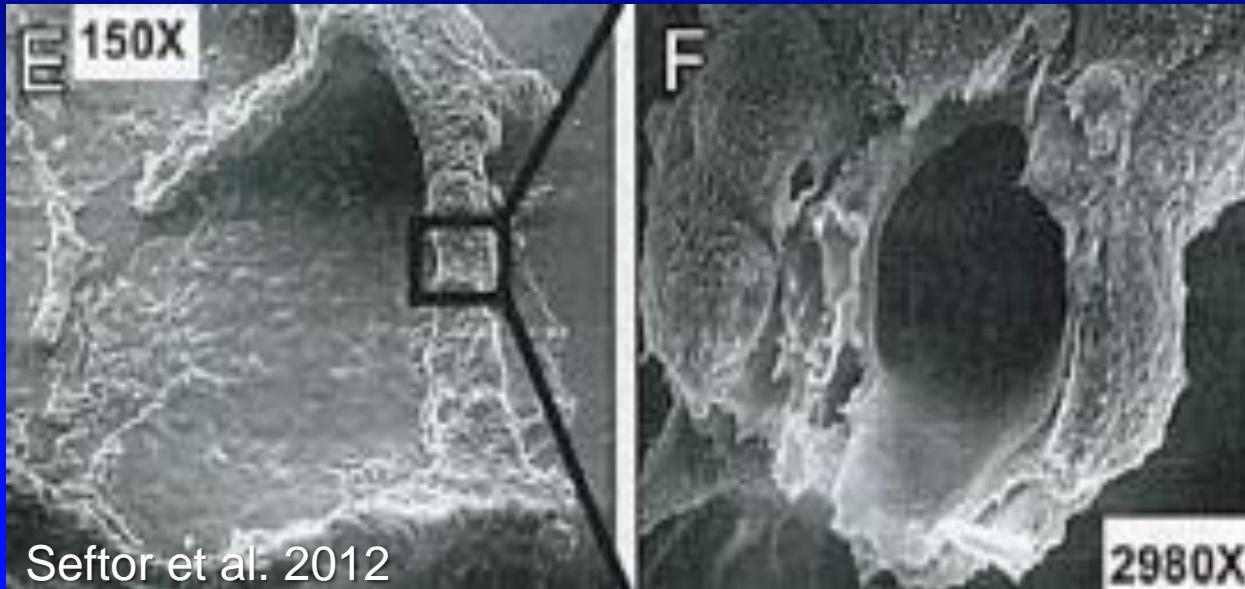
Normal Vasculogenesis



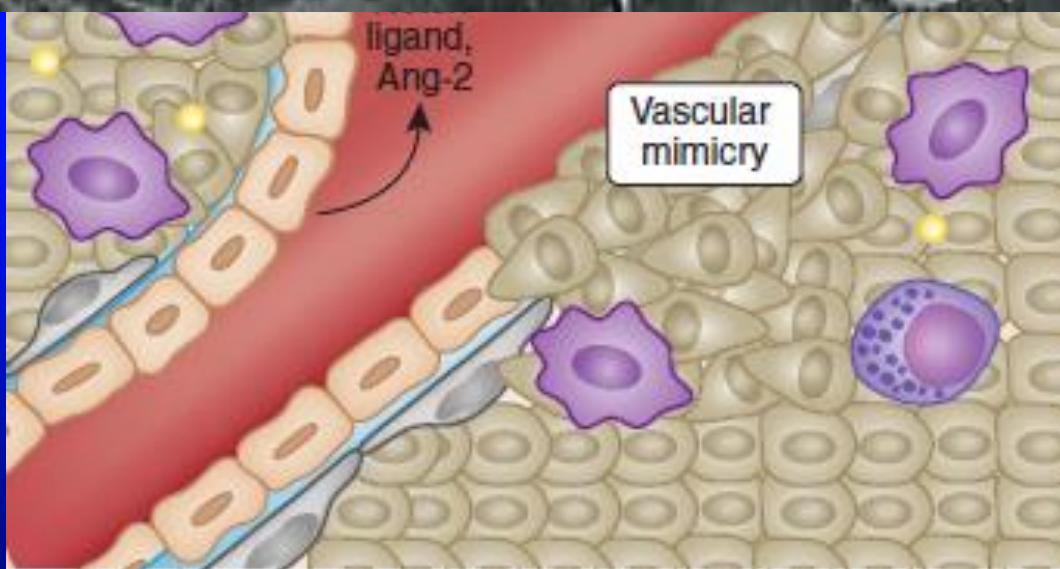
Tumor Vasculogenesis



Tumor Vasculogenesis

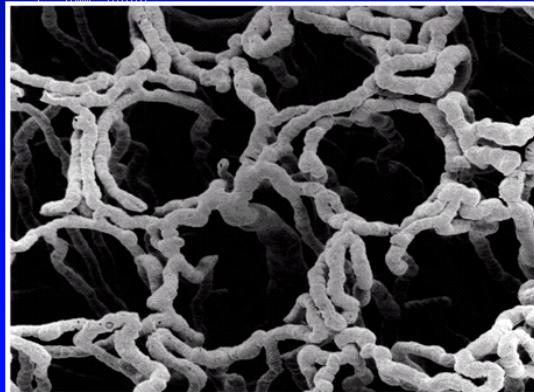


Seftor et al. 2012

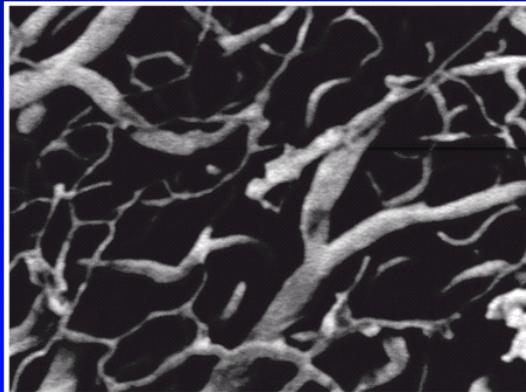


Normal vs. Tumor Vasculature

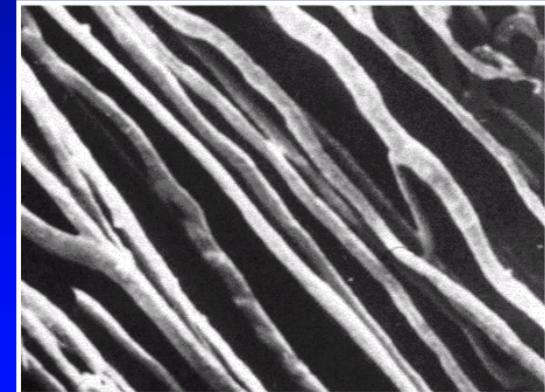
Fenestrated



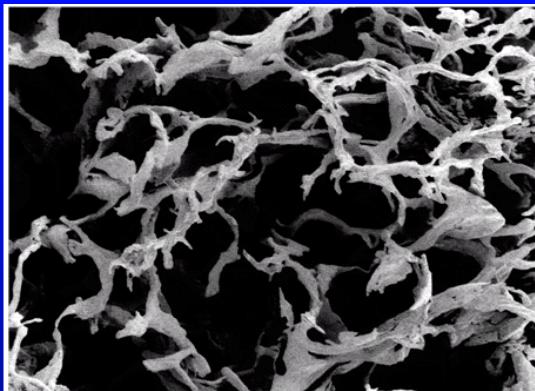
Discontinuous



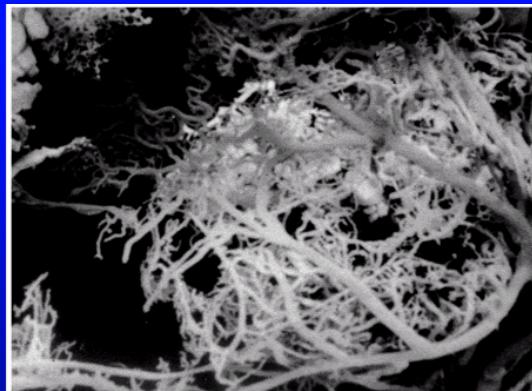
Continuous



Colon



Subcutis



Muscle



Colon carcinoma

Melanoma

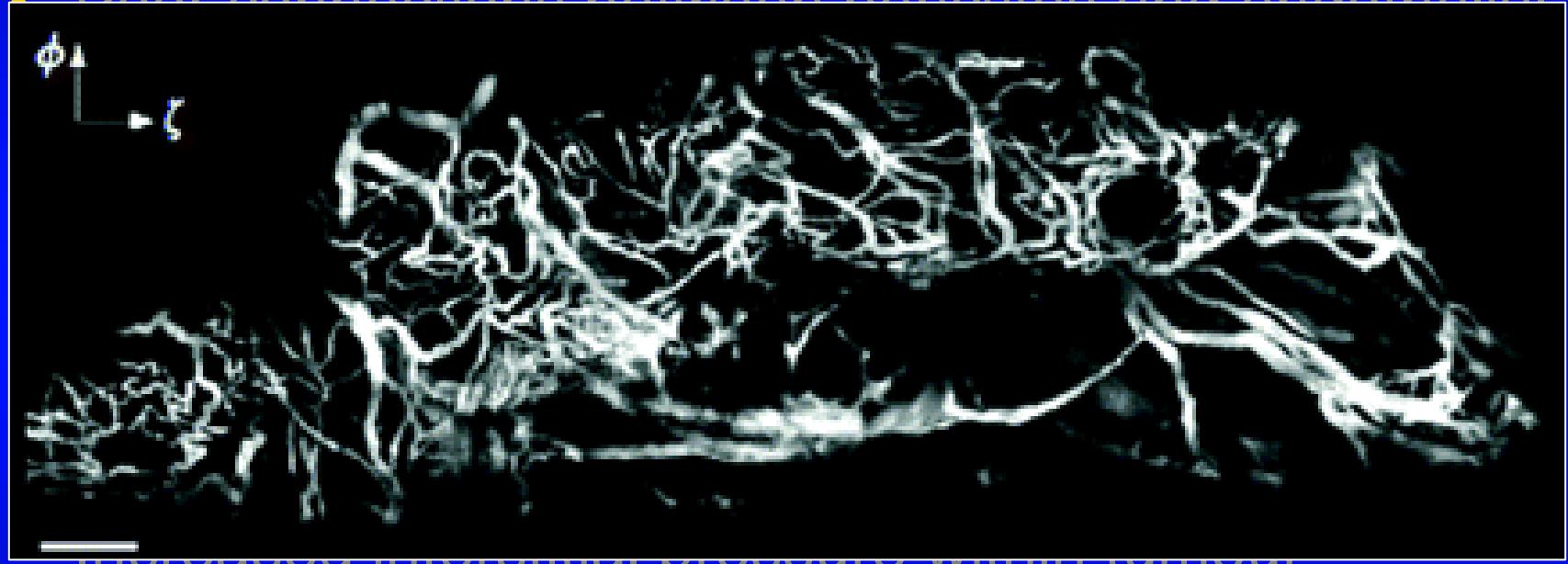
Sarcoma

Tumor Vasculature

- Increased vessel tortuosity and variable vessel diameter
- Poor connections between pericytes and endothelial cells
- Irregularly shaped endothelial cells and basement membrane
- Poorly developed and fragile vessel walls
- Variable flow rates leading to micro-regional tumour hypoxia
- Increased interstitial pressure within tumour
- Increased vessel permeability
- Lack of lymphatic drainage
- Lack of vascular smooth muscle

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- Poor connections between pericytes and endothelial

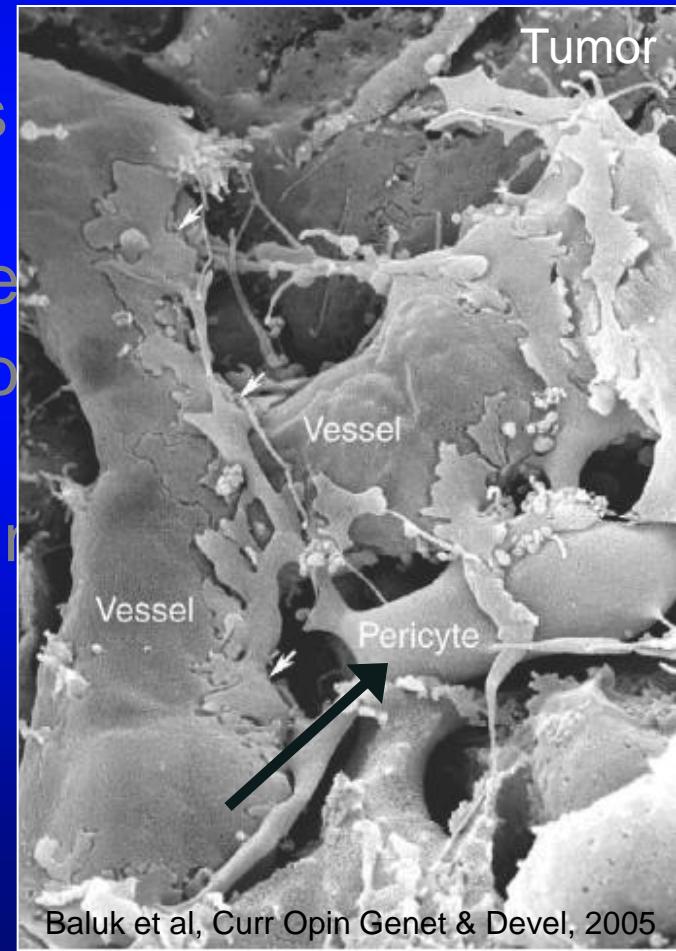


Increased interstitial pressure within tumor

- Increased vessel permeability
- Lack of lymphatic drainage
- Lack of vascular smooth muscle

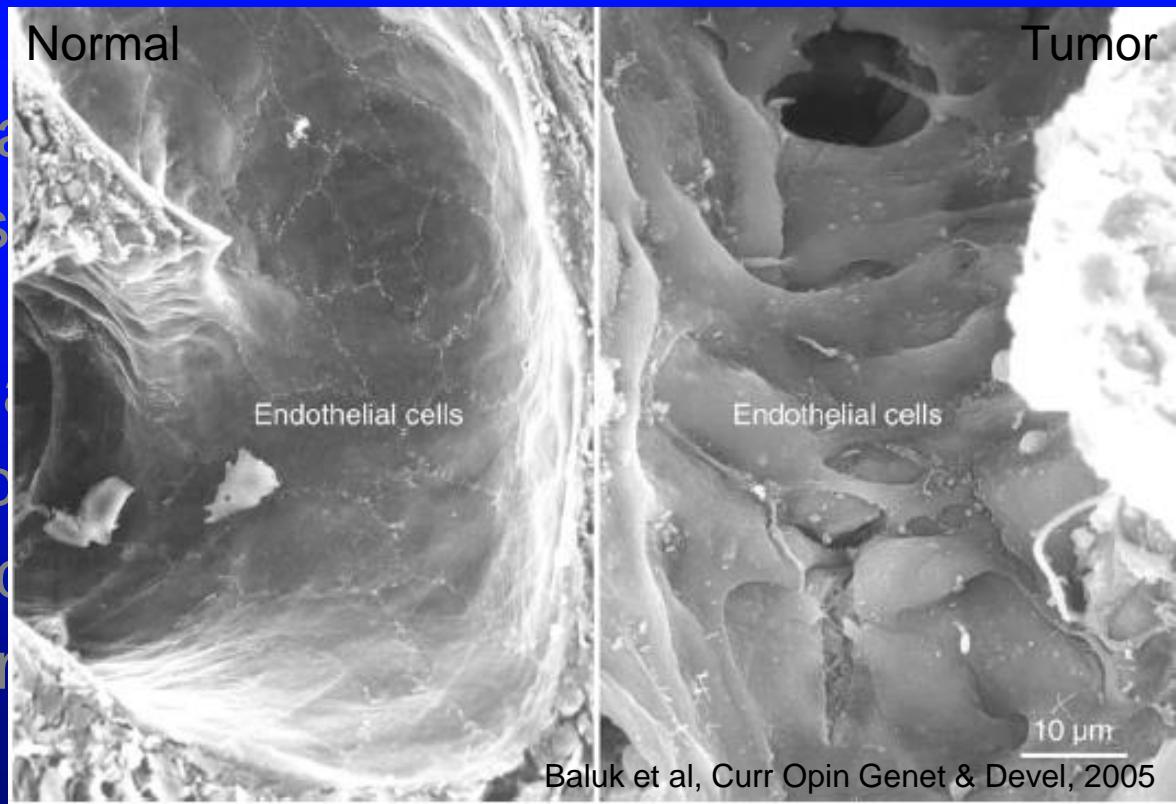
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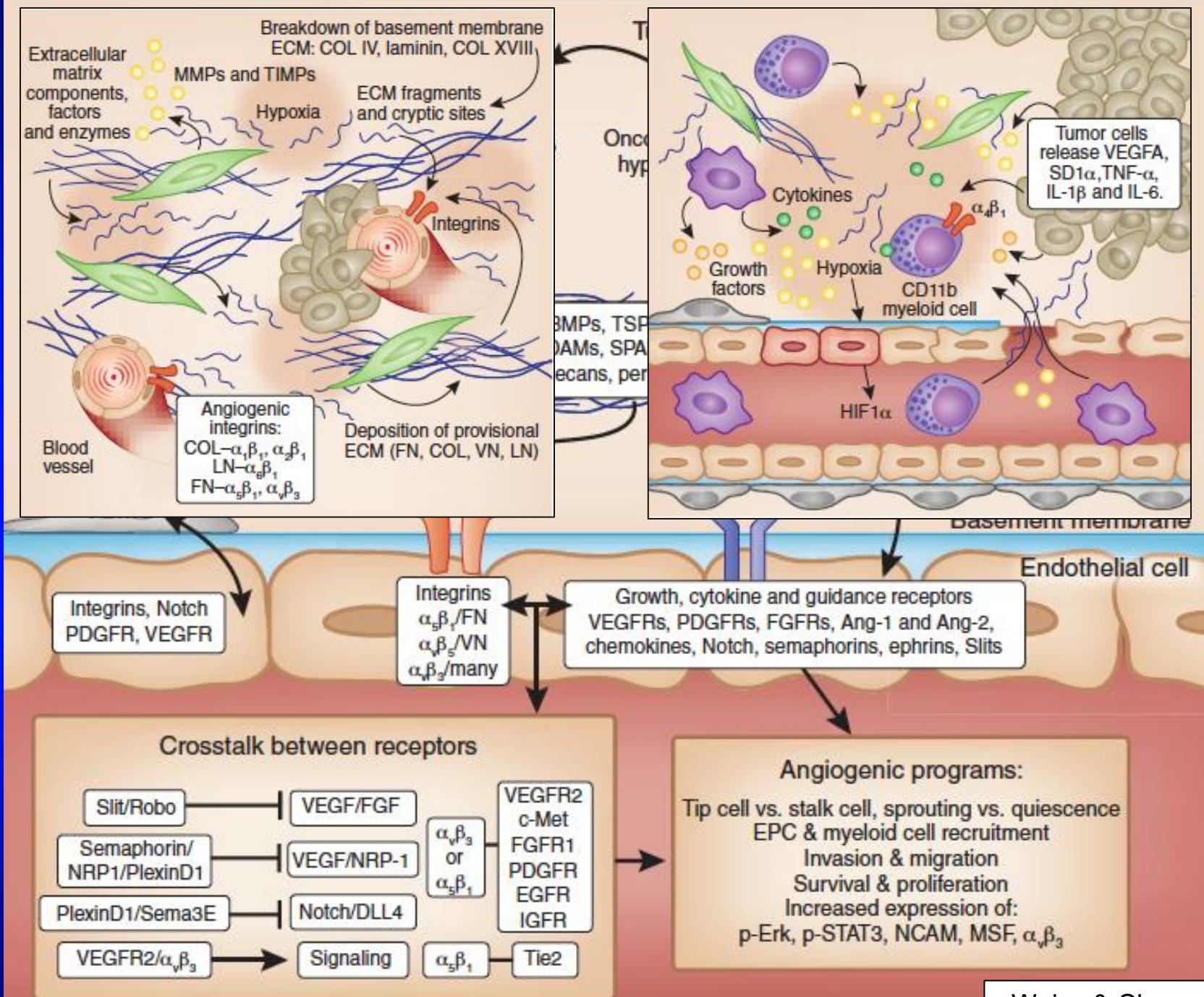
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- Poor connections between pericytes and endothelial cells
- Irregularly shaped endothelial cells membrane
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Tumor Vasculature

- Increased vessel tortuosity and variable vessel diameter
- Poor connections between pericytes and endothelial cells
- Irregularly shaped endothelial cells and basement membrane
- Poorly developed anastomoses
- Variable flow rates due to hypoxia
- Increased interstitial fluid
- Increased vessel permeability
- Lack of lymphatic drainage
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Tumor Microenvironment

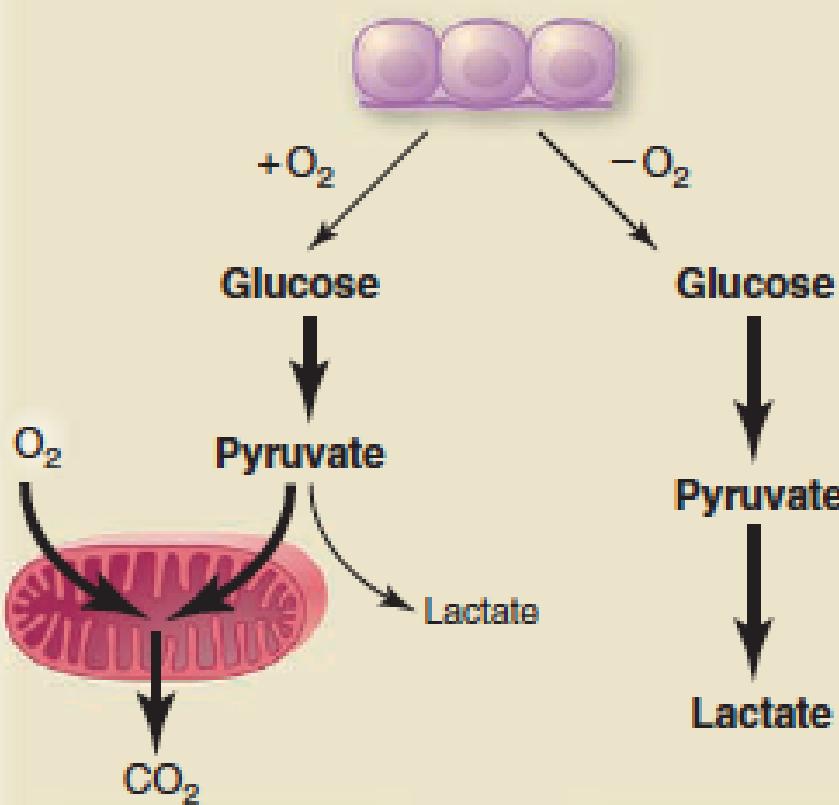
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- Demand for O_2 and nutrients is not matched by angiogenesis (\uparrow proliferation) \rightarrow imbalance (temporal insufficiencies in oxygenation)
- Warburg hypothesis \rightarrow tumor cells metabolize glucose by glycolysis even in presence of O_2

Differentiated tissue



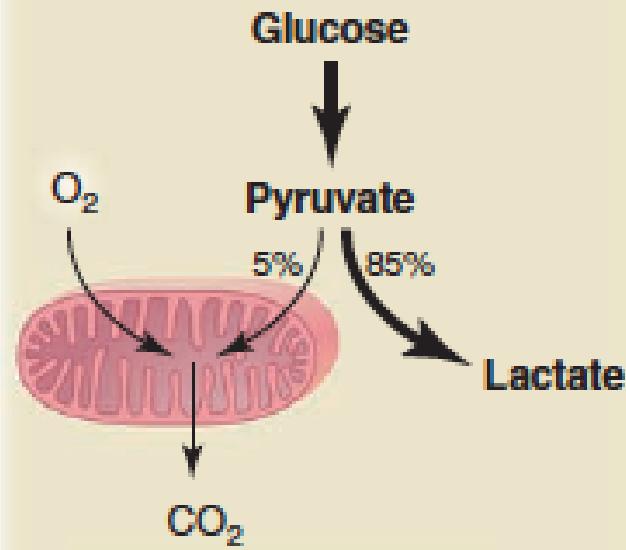
Oxidative phosphorylation
~36 mol ATP/mol glucose

Anaerobic glycolysis
2 mol ATP/mol glucose

Proliferative tissue

or

Tumor



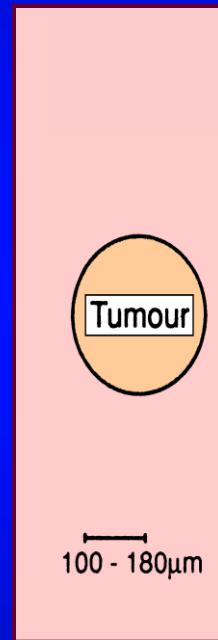
Aerobic glycolysis
(Warburg effect)
~4 mol ATP/mol glucose

Tumor Microenvironment

- Demand for O_2 and nutrients is not matched by angiogenesis (\uparrow proliferation) \rightarrow imbalance (temporal insufficiencies in oxygenation)
- Warburg hypothesis \rightarrow tumor cells metabolize glucose by glycolysis even in presence of O_2 – altered gene expression / mitochondrial dysfunction [result of mutation]
- Hypoxia increases \rightarrow glycolysis
- Glycolysis + waste accumulation \rightarrow acidic environment (acidosis)

Hypoxia - Chronic

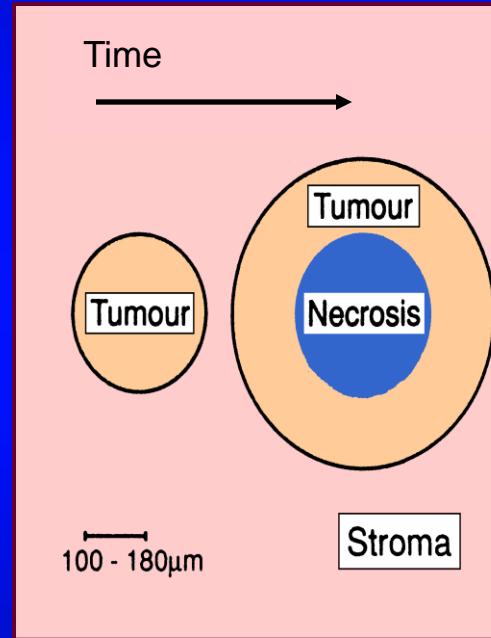
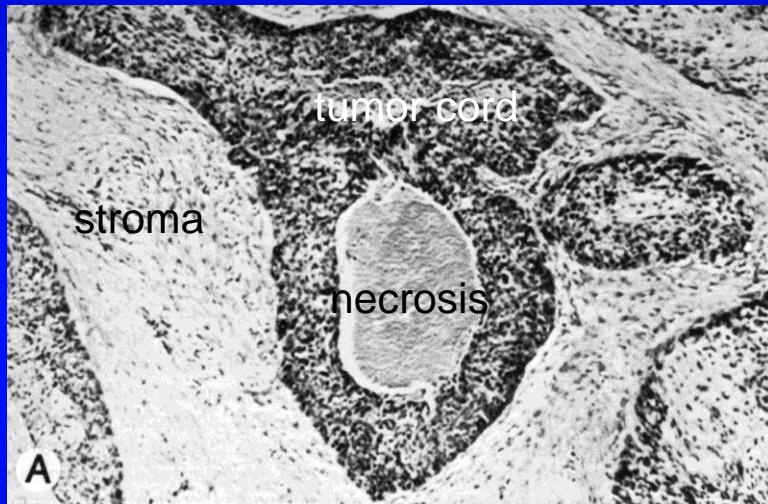
Due to limited diffusion capacity of oxygen



bronchial carcinoma

Hypoxia - Chronic

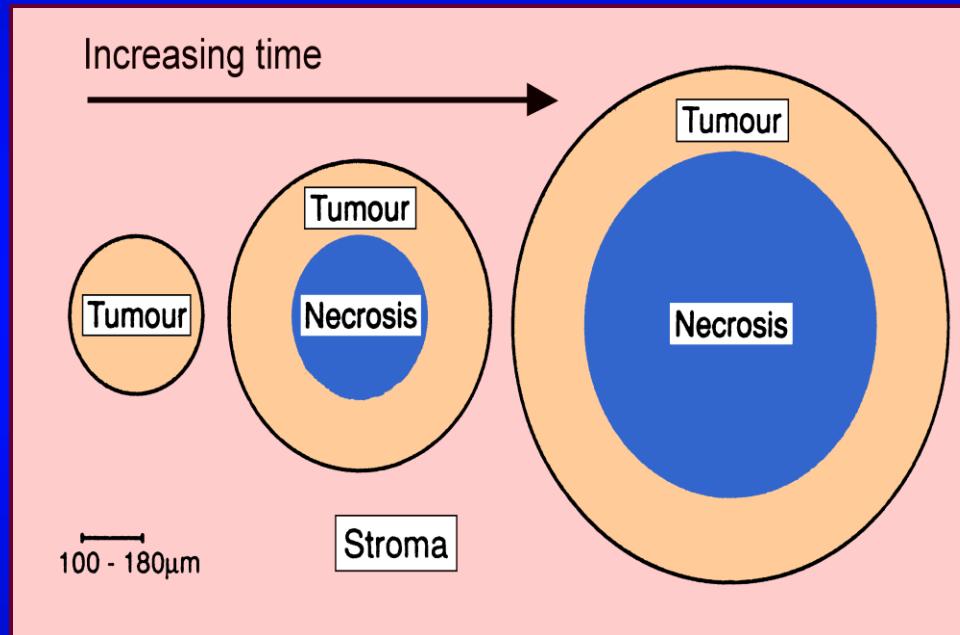
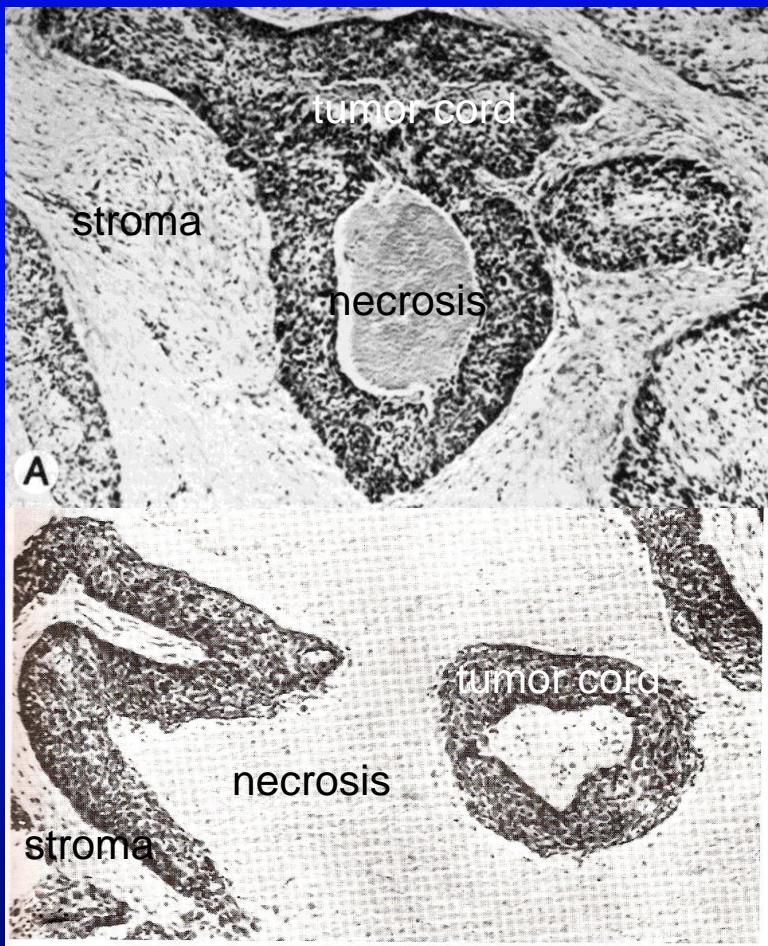
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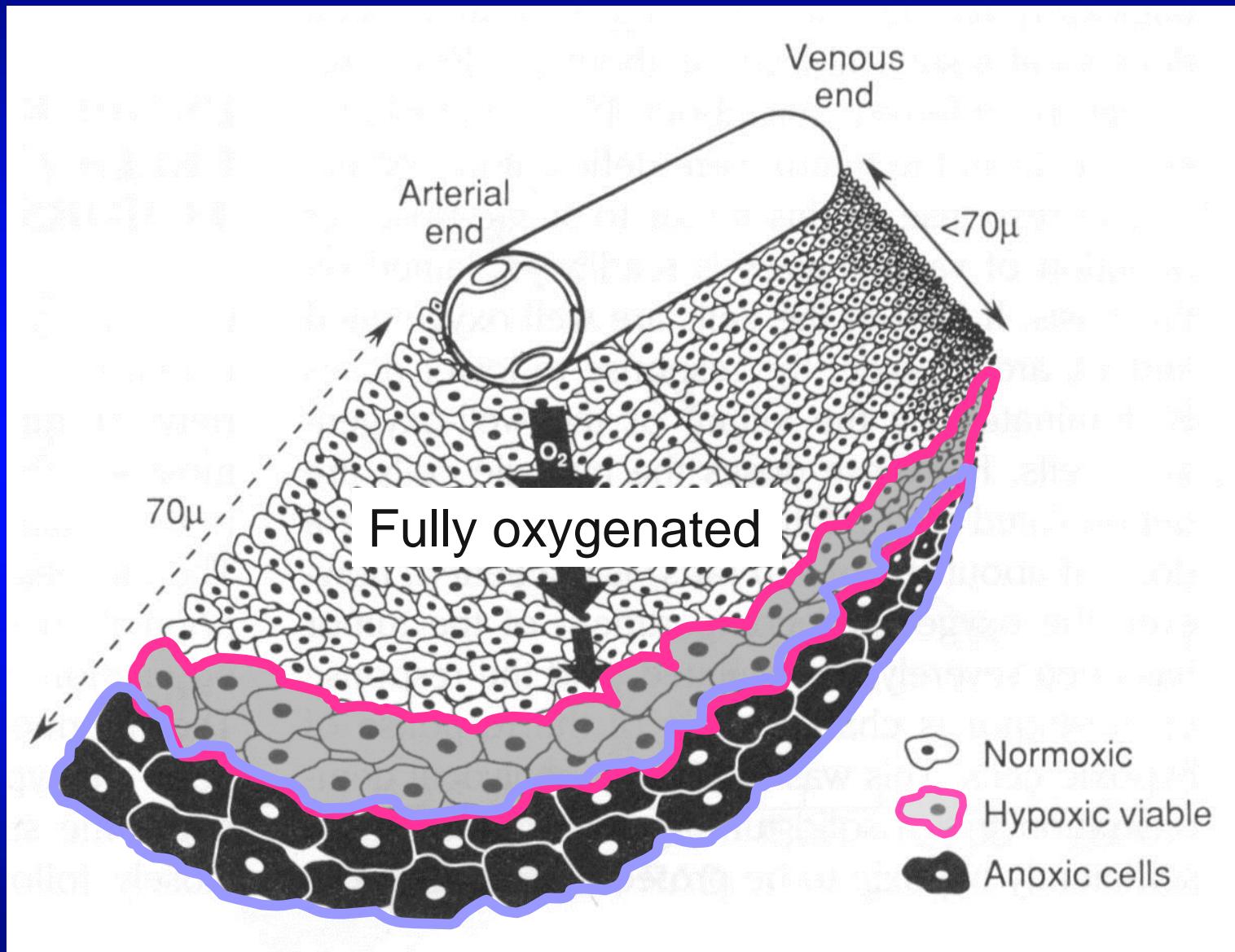
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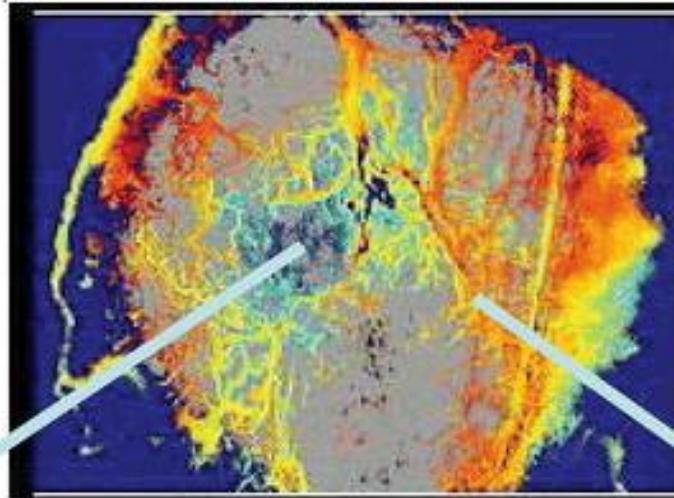


Variable Tumor Oxygen Status

- Relatively sparse arteriolar supply
Few co-opted arterioles (low vascular density)
→ hypoxia between vessel segments
New vessels devoid of smooth muscle - loss of O₂ loading (anemic hypoxia)
- Inefficient orientation of vessels
Increased pO₂ variability, ↑ hypoxia
- Hypoxia/acidosis → increased blood viscosity (red cell crenation) → increased blood viscosity:
 - ❖ Altered flow distribution of red blood cells: some vessels contain only plasma (no red blood cells)
 - ❖ Increased flow resistance in microvessels (low flow/stasis)
 - ❖ Temporal fluctuations in hematocrit → **intermittent hypoxia**
- Intermittent/acute/cycling hypoxia: IFP or RBC flux

low oxygen saturation

high oxygen saturation



Low Tide

High Tide



$pO_2 \uparrow$



$pO_2 \uparrow$

fast, intermediate and slow

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Tumor Hypoxia

Tumor
hypoxia

sustained >6-8 hrs;
fluctuating ($pO_2 \leq 7\text{ mm Hg}$)

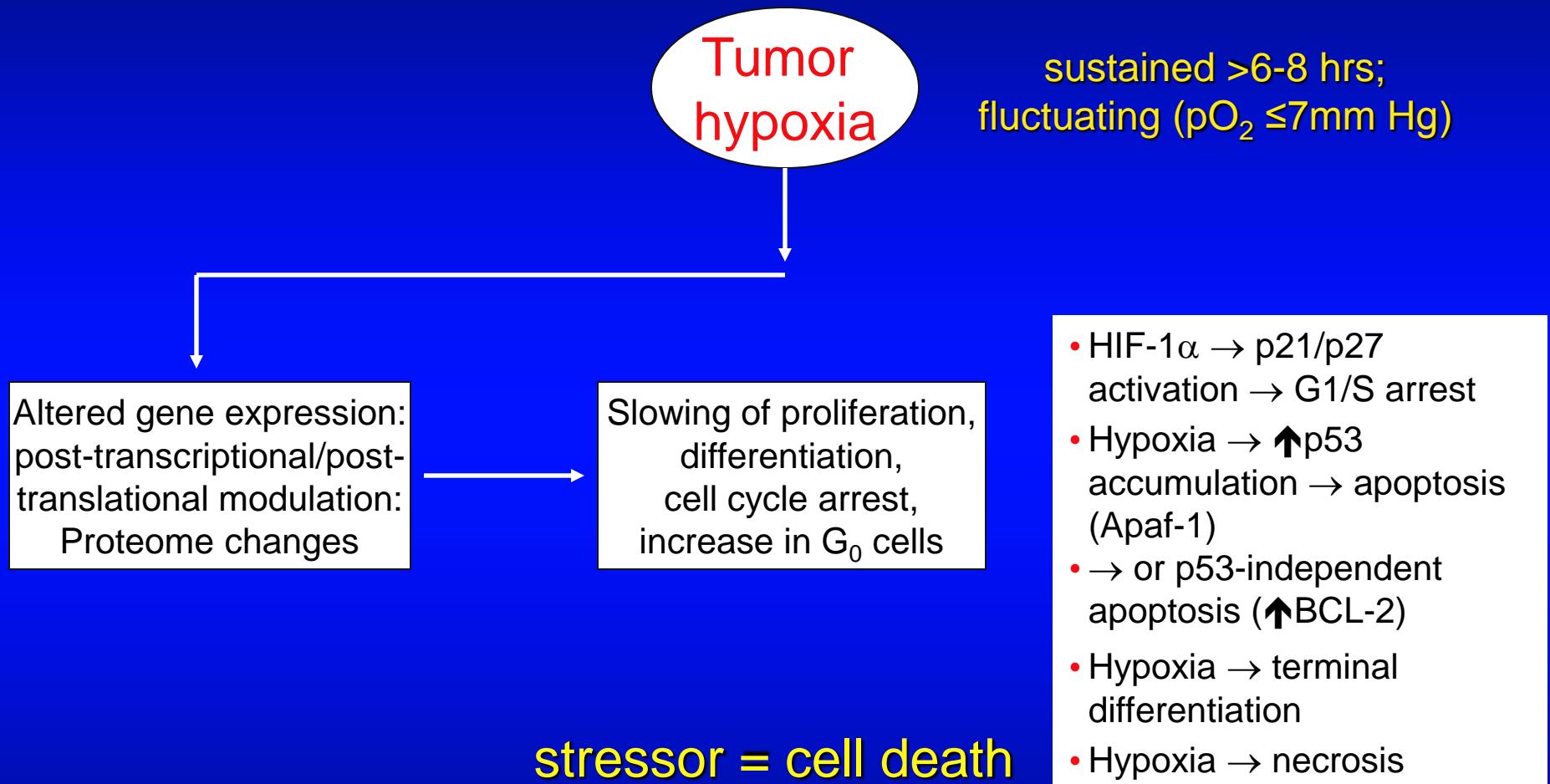


Altered gene expression:
post-transcriptional/post-
translational modulation:
Proteome changes

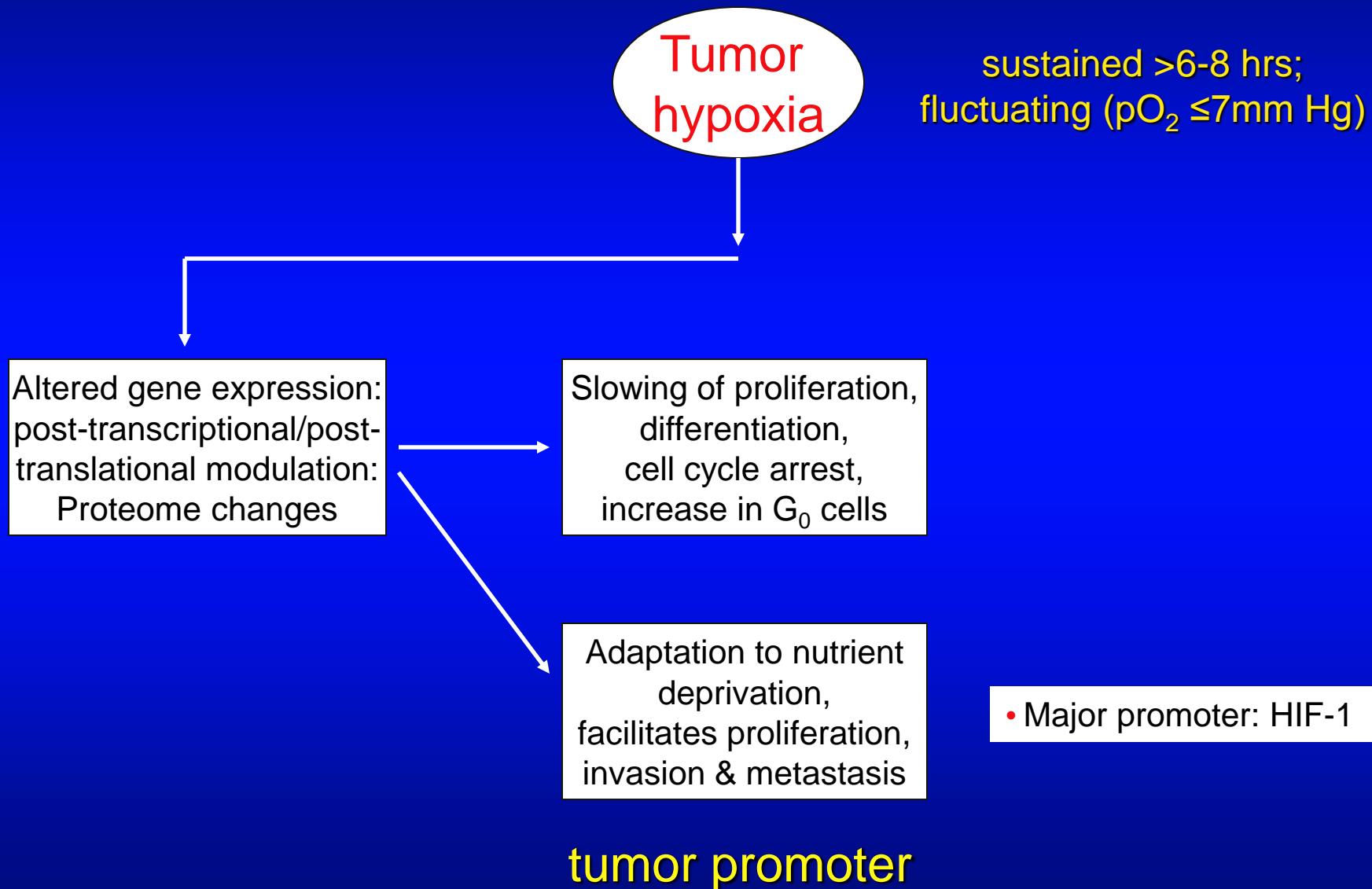
Hypoxic Gene Regulation

Transcription factors	Hypoxia-inducible factor (HIF)-1 α , HIF-2 α ; Activator protein (AP-1); Jun; Nuclear factor- κ B (NF- κ B); Insulin-like growth factor (IGF) bonding protein-1, -2, -3; cyclic AMP responsive-element binding protein (CREB)
O ₂ transport and iron metabolism	Erythropoietin (Epo); Ferritin; Heme oxygenase-1; Transferrin
Angiogenesis	Vascular endothelial growth factor (VEGF); VEGF receptor-1; Cyclooxygenase-2 (COX-2); Endothelin-1, -2; Fibroblast growth factor (FGF)-3; Nitric oxide synthase (NOS); Placental growth factor (PIGF); Transforming growth factor (TGF)- α ; TGF β 1, TGF β 3
Glycolysis and glucose uptake	Glucose transporter-1, -3 (GLUT1, GLUT3) Pyruvate kinase
pH regulation	Carbonic anhydrase-9, -12
Growth factors/cytokines	IGF-2 Platelet-derived growth factor (PDGF)
Extracellular matrix/coagulation	Metalloproteinases Matrix metalloproteinase (MMP)-13 Plasminogen activator inhibitor-1 Urokinase receptor α -integrin
Drug resistance	Multi-drug resistance

Tumor Hypoxia

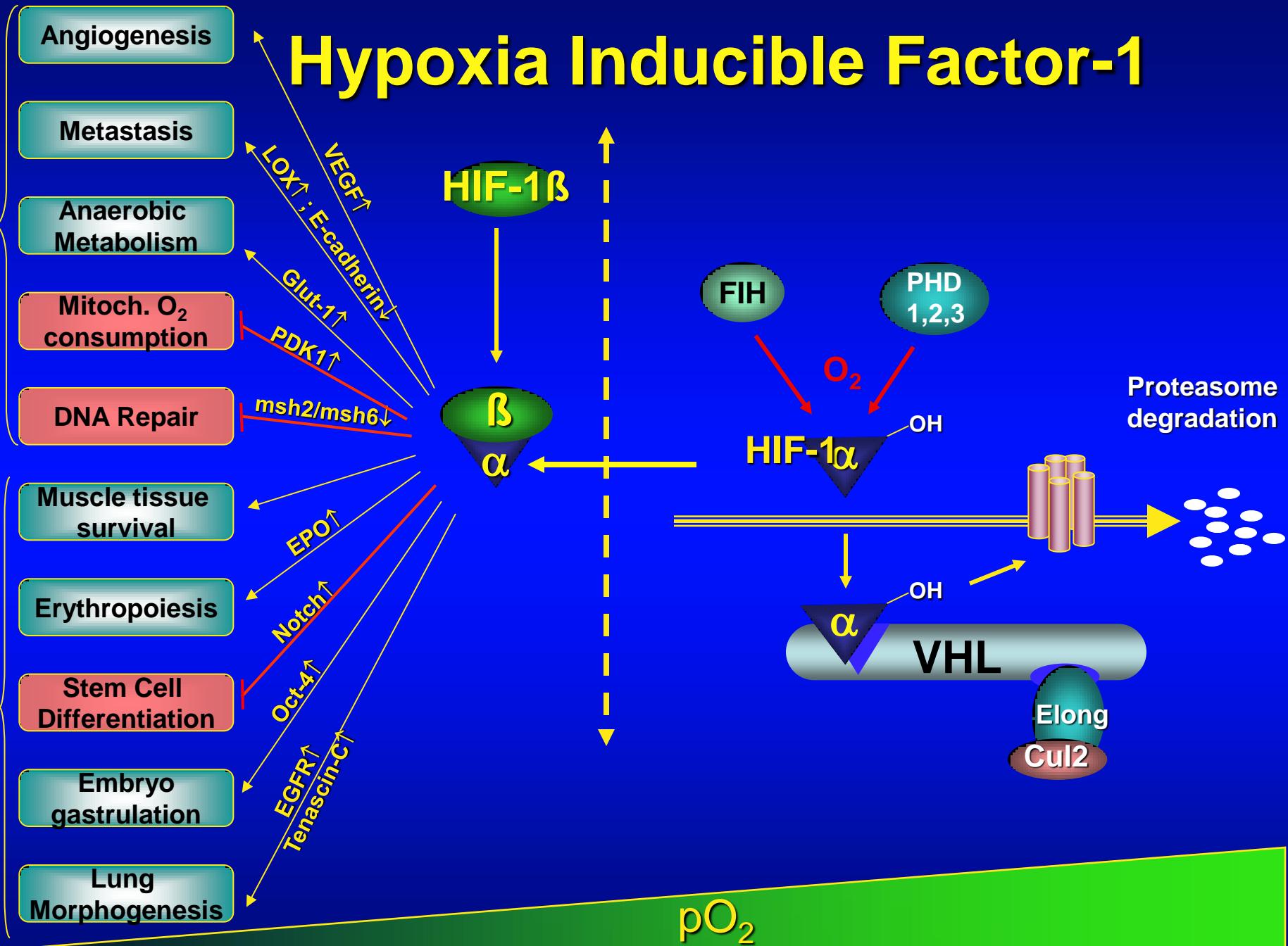


Tumor Hypoxia



Hypoxia Inducible Factor-1

Tumorigenesis
Differentiation-Development



Adapted from Maxwell & Coumenis, 2006.

Hypoxia Inducible Factor-1

Tumorigenesis

Angiogenesis

Metastasis

Anaerobic Metabolism

Mitoch. O₂ consumption

DNA Repair

Muscle tissue survival

Erythropoiesis

Stem Cell Differentiation

Embryo gastrulation

Lung Morphogenesis

VEGF↑ IF-1β

LOX↑; E-cadherin↓
Glut-1↑ PDK1↑

msh2/msh6↓

EPO↑

Notch↑

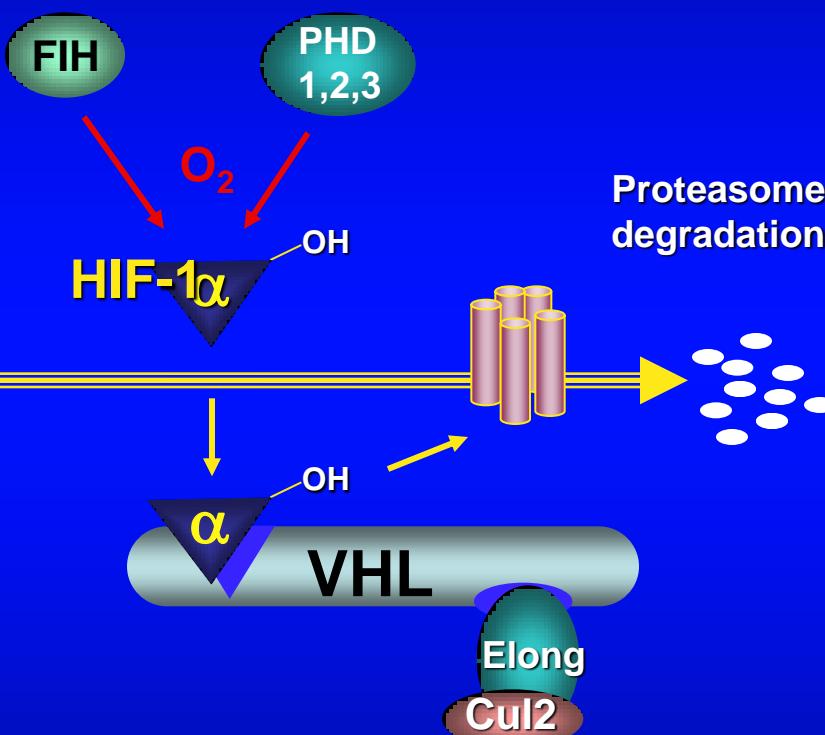
Oct-4↑

EGFR↑

Tenascin-C↑

β
α

pO₂



Adapted from Maxwell & Coumenis, 2006.

Hypoxia Inducible Factor-1

Tumorigenesis

Angiogenesis

Metastasis

Anaerobic Metabolism

Mitoch. O₂ consumption

DNA Repair

Muscle tissue survival

Erythropoiesis

Stem Cell Differentiation

Embryo gastrulation

Lung Morphogenesis

HIF-1 β

GLUT-1 \uparrow

β
 α

VEGFR \uparrow ; E-cadherin \downarrow
LOX \uparrow ; VEGF \uparrow
msh2/msh6 \downarrow
EPO \uparrow
Notch \uparrow
Oct4 \uparrow
EGFR \uparrow
Tensin-C \uparrow

FIH

PHD
1,2,3

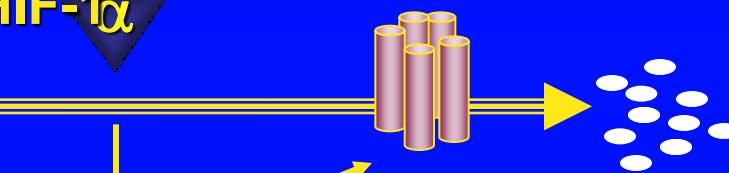
HIF-1 α

VHL

Elong
Cul2

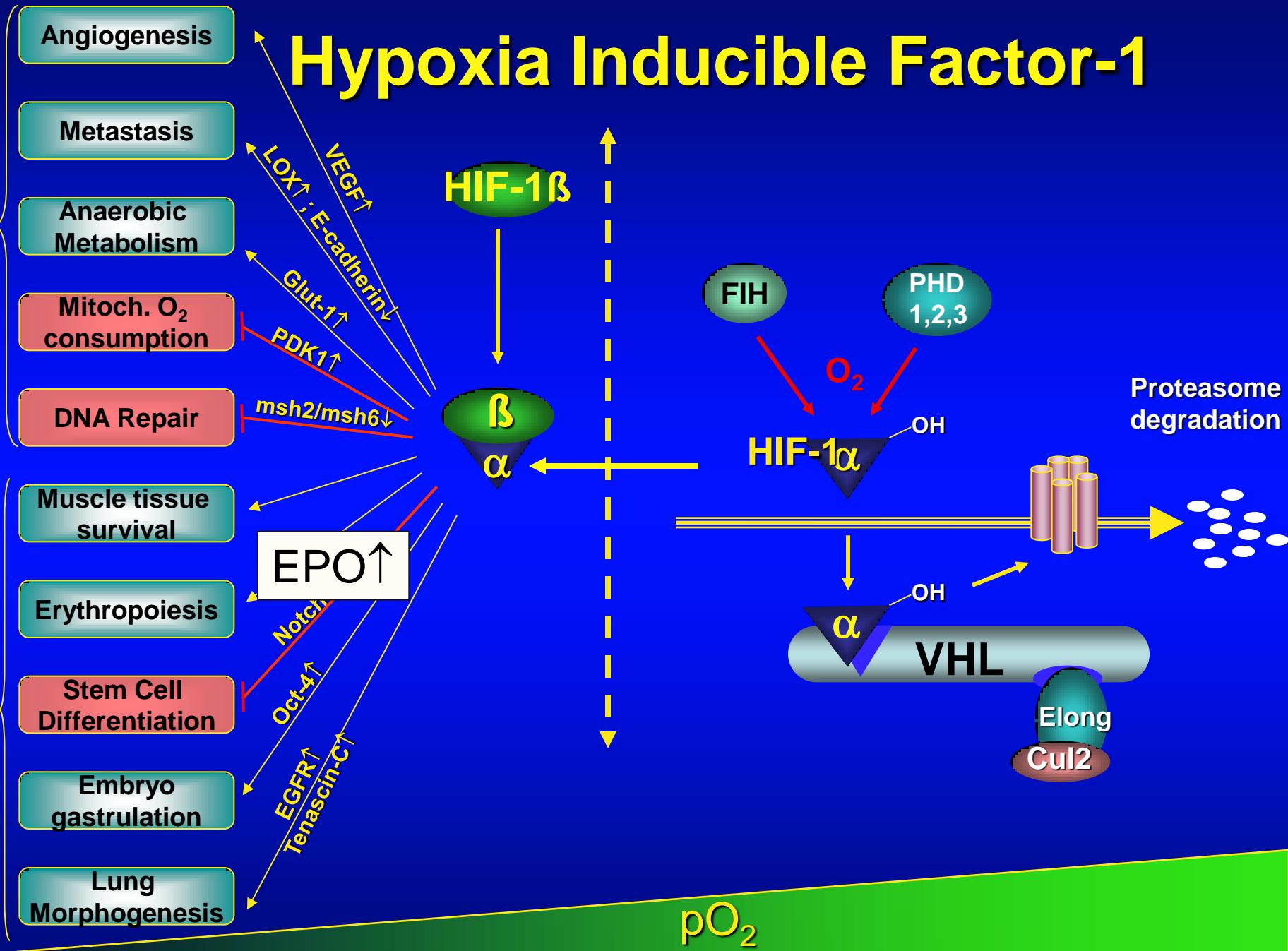
pO₂

Proteasome degradation



Hypoxia Inducible Factor-1

Tumorigenesis
Differentiation-Development



Adapted from Maxwell & Coumenis, 2006.

Tumor Hypoxia

$pO_2 \leq 0.7\text{ mm Hg}$

Tumor
hypoxia



Altered gene expression:
post-transcriptional/post-
translational modulation:
Proteome changes

Slowing of proliferation,
differentiation,
cell cycle arrest,
increase in G_0 cells

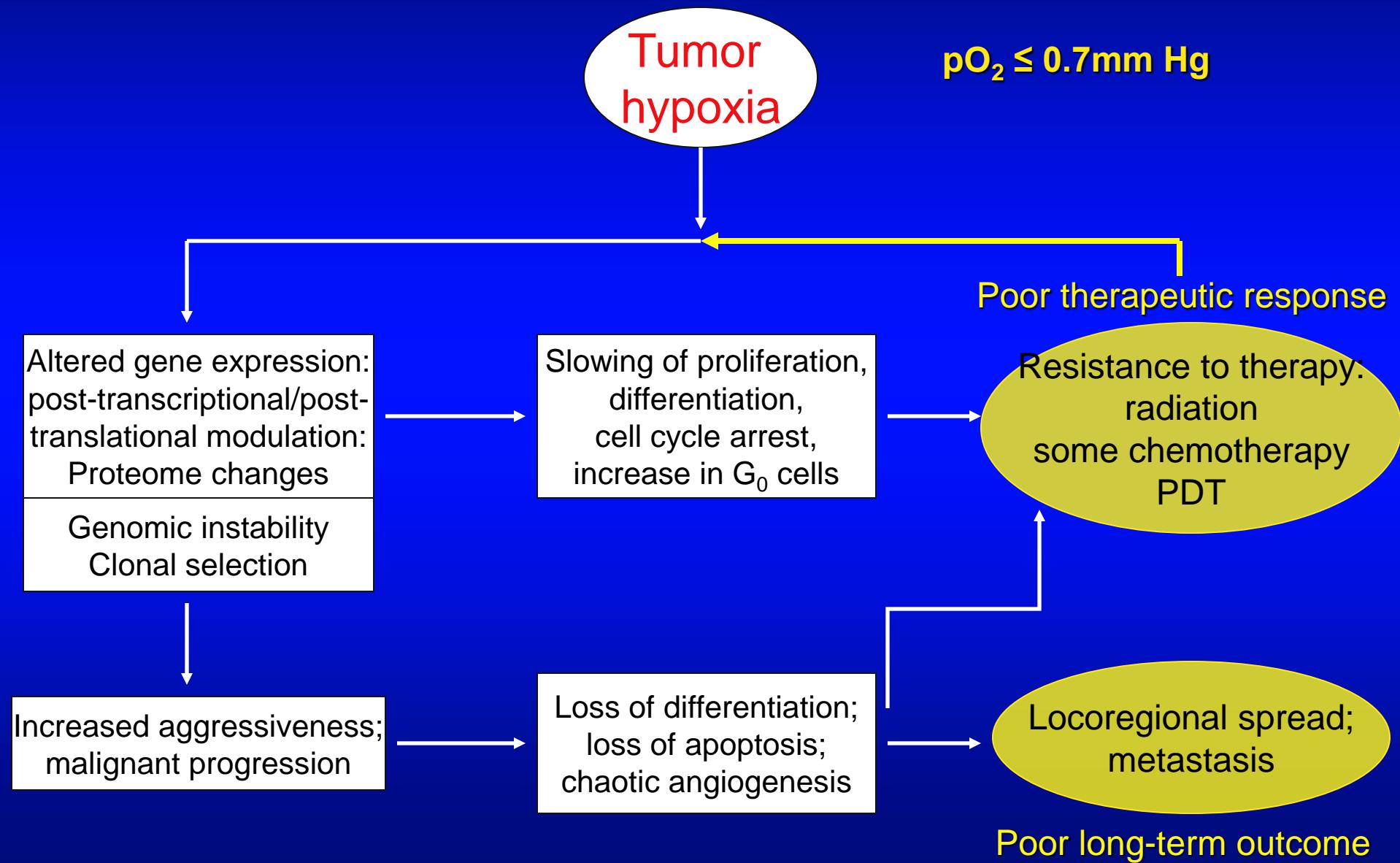
Genomic instability
Clonal selection



Increased aggressiveness;
malignant progression

Loss of differentiation;
loss of apoptosis;
chaotic angiogenesis

Tumor Hypoxia



Hypoxia in Human Tumors

Endpoints for measuring hypoxia in human tumors have included:

Old - tumor vascularization, oxygen saturation of hemoglobin, changes in tumor metabolism

Newer - **oxygen probes**, hypoxia markers, hypoxia-related proteins, non-invasive (F-MISO)

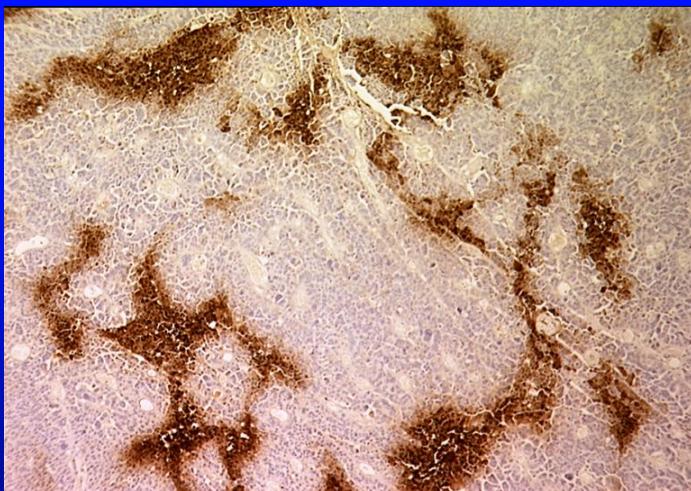


Hypoxia in Human Tumors

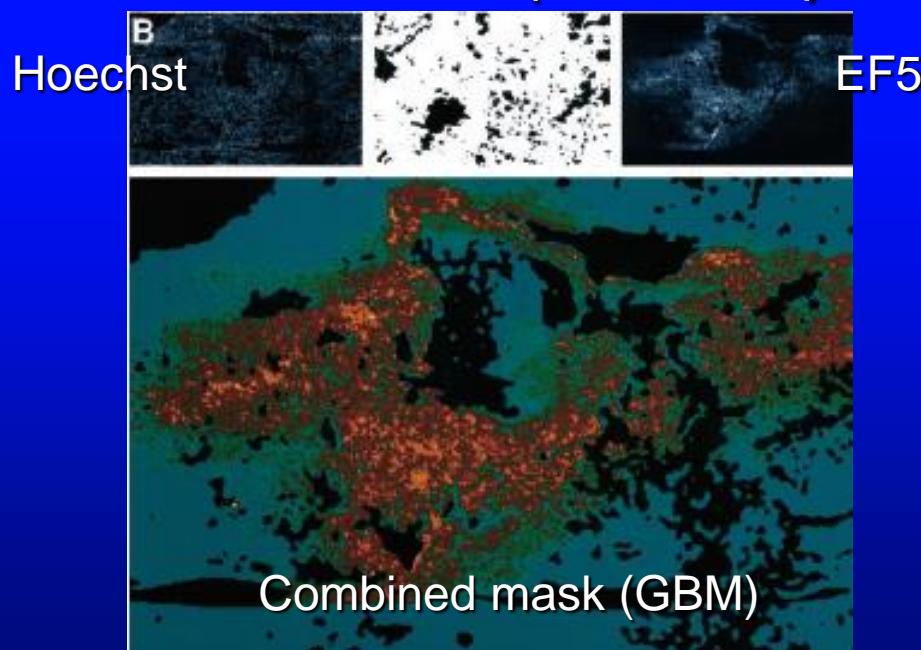
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Pimonidazole



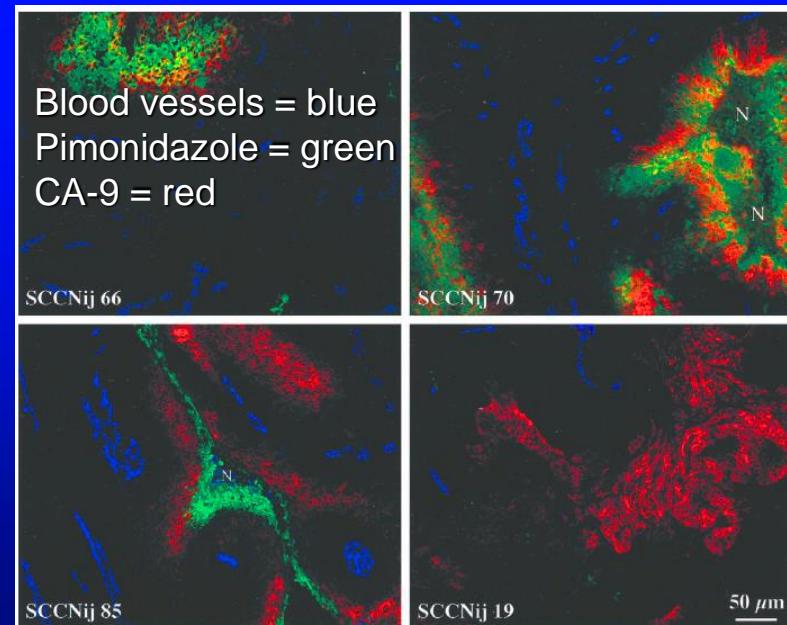
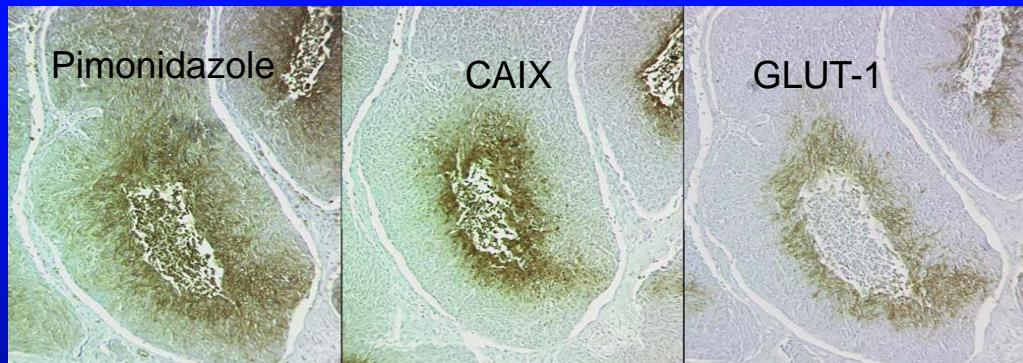
Combined mask (GBM)

Hypoxia in Human Tumors

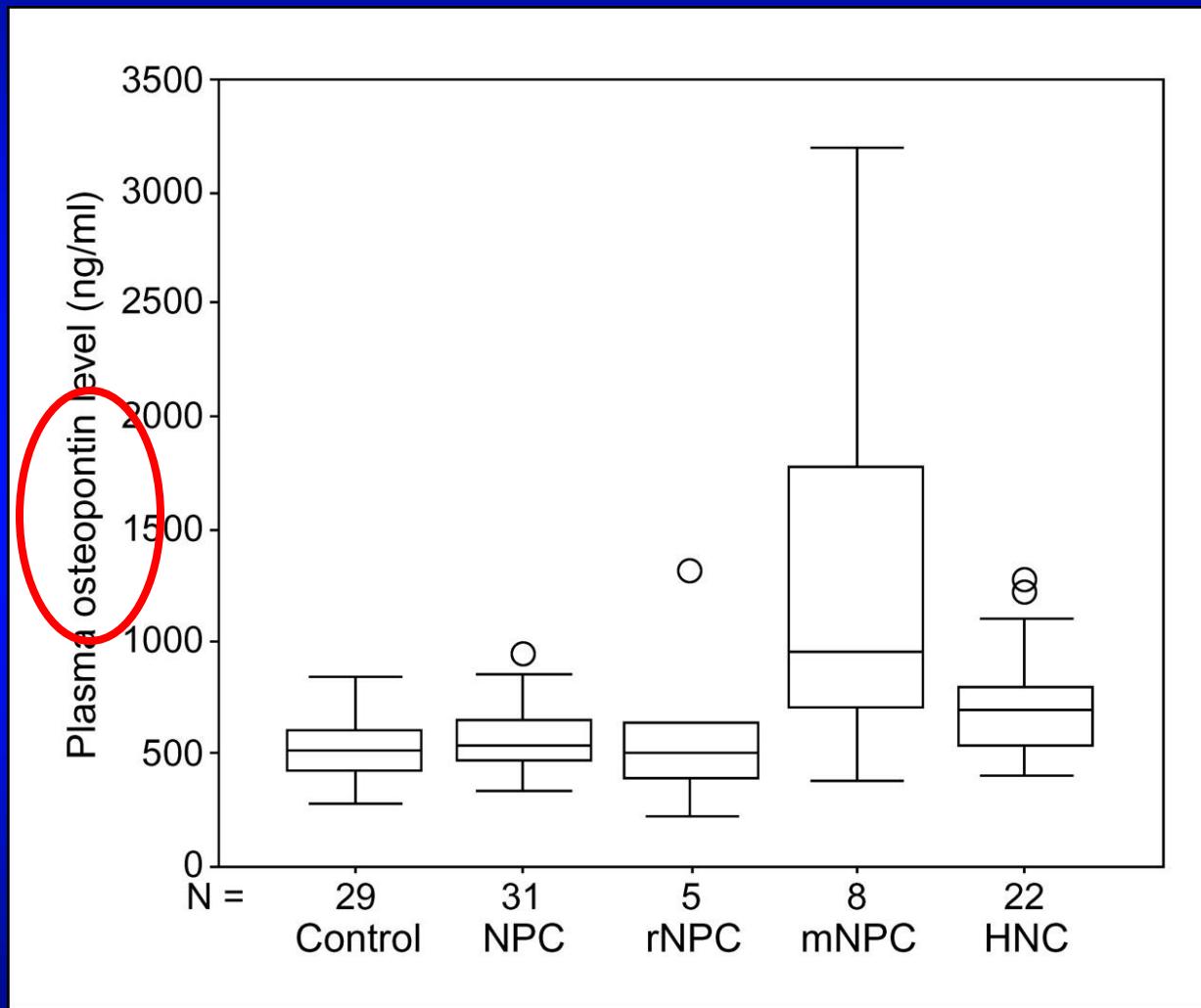
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Box and whisker plots showing plasma osteopontin levels in healthy control subjects (control) and patients of locoregional nasopharyngeal cancer, locoregional recurrent nasopharyngeal cancer, metastatic nasopharyngeal cancer, or head and neck cancer.



Hui E P et al. Clin Cancer Res 2008;14:7080-7087

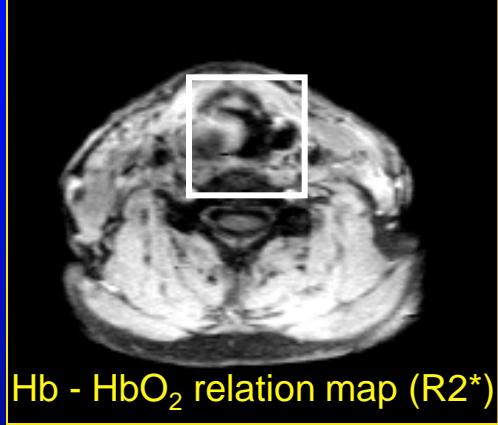
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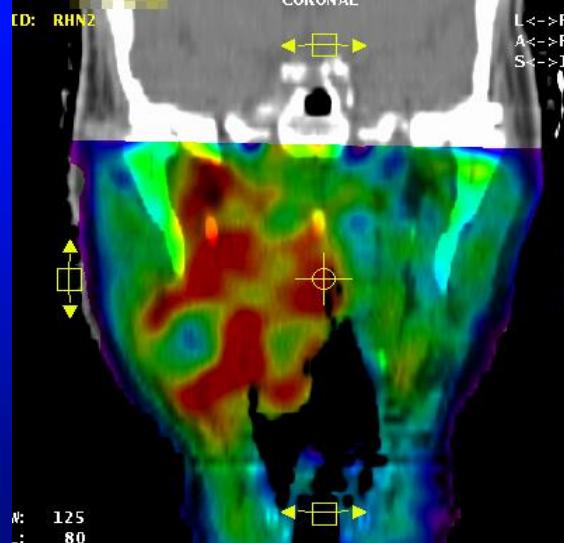
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Dynamic MRI



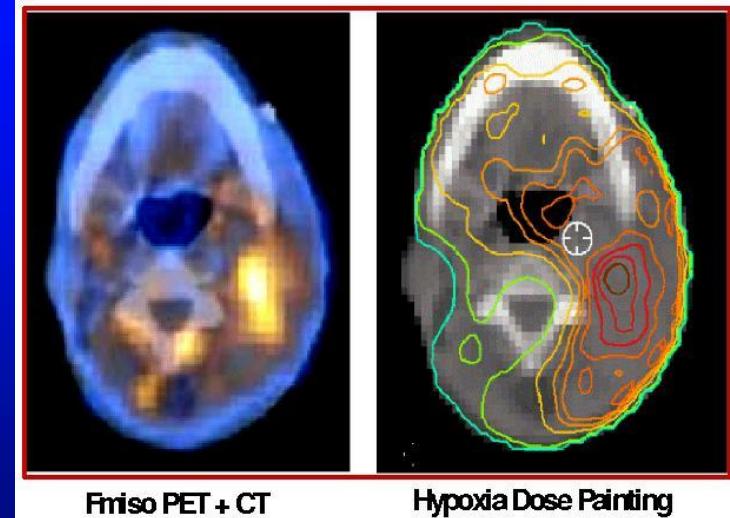
Rijkema 2001.

PET - CuATSM

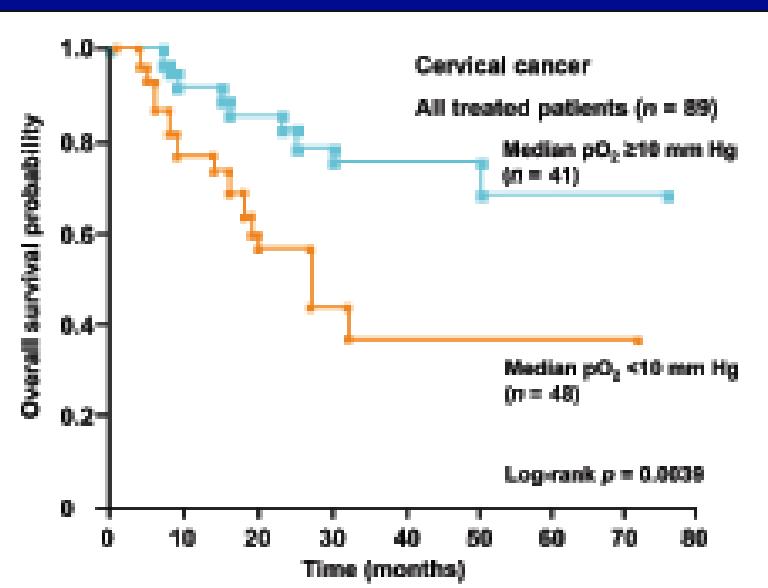


Chao, IJROBP, 2001.

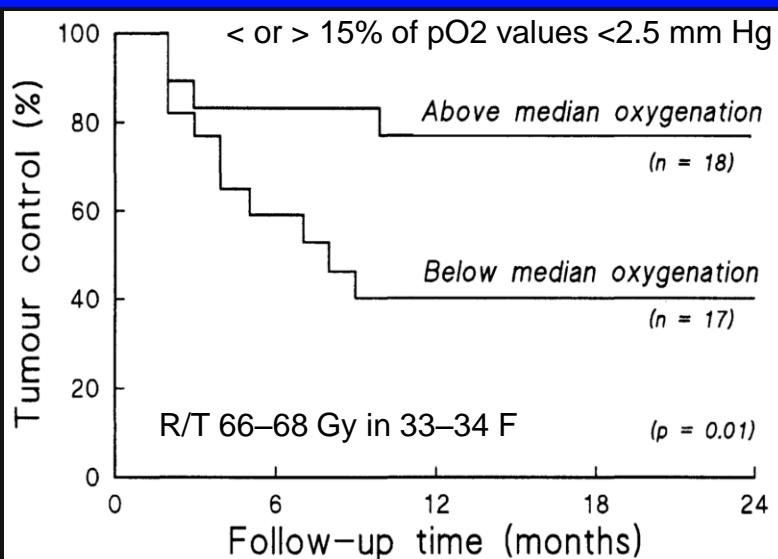
PET - F-MISO



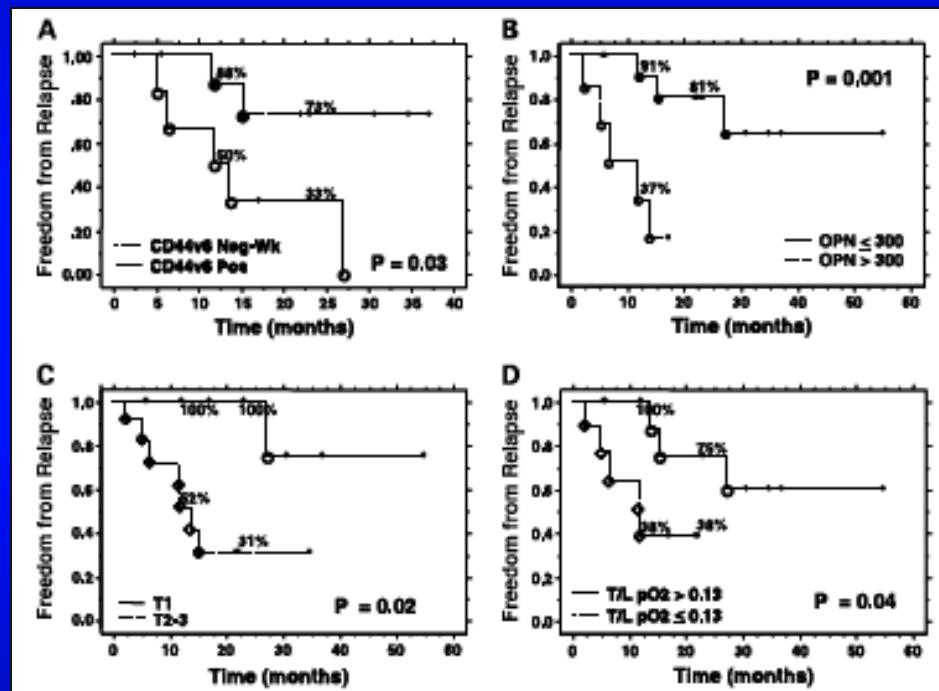
Hypoxia in Human Tumors



Hockel et al., Cancer Res, 1996.



Nordsmark et al., Radiother Oncol, 1996.



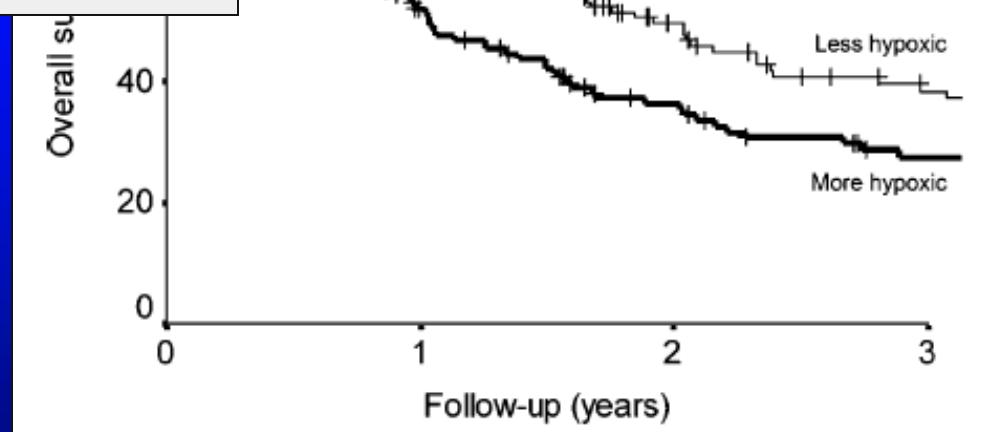
Le et al., Clin Cancer Res, 2006.

Hypoxia in Human Tumors

Univariate analysis of three-year survival among 310 patients^a with low or high oxygenation status according to three different measures

Individual tumor oxygenation measure	3-year survival		2P	2P stratified for center
	Oxygenation below sample median (%)	Oxygenation above sample median (%)		
Median pO ₂	30±5	36±4	0.16	0.86
HP ₅	28±4	37±4	0.02	0.08
HP _{2.5}	28±4	38±4	0.006	0.012

^a These are the cases with valid data on all three oxygenation measures.



Targeting the Tumor Microenvironment

Solid tumor formation results in a unique biologic compartment

- Architecturally unique – tumor cells, tumor stroma, tumor vessels
- Environmentally unique – acidosis, hypoglycemia, elevated IFP, hypoxia
- Immunologically unique – privileged

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Targeting Tumor Stroma

- Fibroblasts/myofibroblasts/CAFs

Promote tumor cell growth; increase angiogenesis, invasion and metastasis

- Mechanically
- Physiologically (autocrine and paracrine factors)

Marker	Expression	Prognosis
PDGFR β	↑	Poor
CA IX	↑	Poor
α -SMA	↑	Poor
Cav1	↓	Poor
uPA	↑	Poor
PTEN	↓	Poor
Periostin	↑	Poor
Podoplanin	↑	Good

Targeting Tumor Stroma

- Fibroblasts/myofibroblasts/CAFs
 - PDGFR inhibitors: imatinib (Glivec), sorafenib (Nexavar), sunitinib (Sutent); TKI: pazopanib

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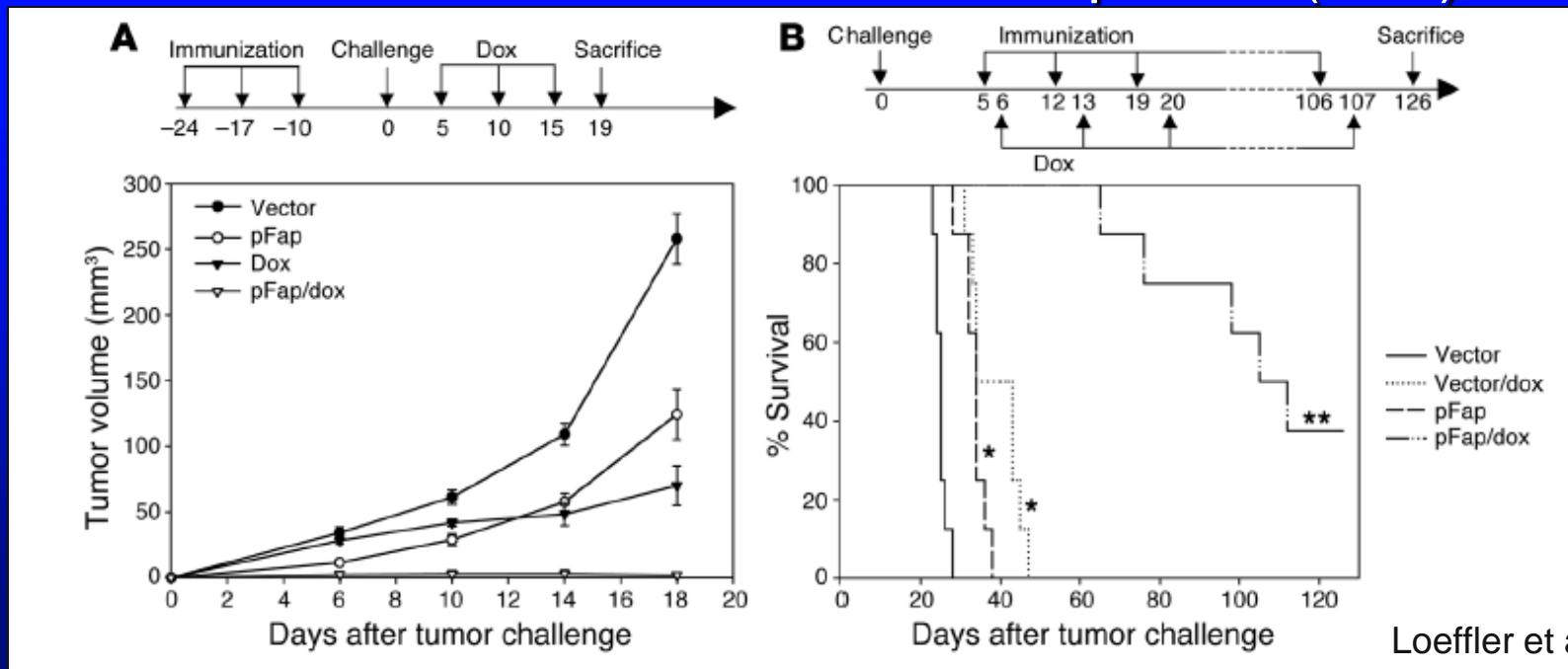
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Targeting Tumor Stroma

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 - uPA inhibitors: WX-671 (phase II breast cancer); A6 (phase I advanced gynecological)
 - DNA vaccine to fibroblast activation protein (FAP)



Targeting Tumor Stroma

- Fibroblasts/myofibroblasts/CAFs
- Inflammatory cells/TAMs

Clinical studies have shown correlation between density, activation and histological location of TAMs with treatment outcome

Inhibiting macrophage recruitment:

- Inhibitors of CCL2/CCR2 (e.g. Yondeli, RS102895)
- Inhibitors of M-CSF/M-CSFR (e.g. anti-M-CSF mAb, JNJ-28312141, GW2580)
- Inhibitors of other chemoattractants (e.g. CCL5, CXCL-12, VEGF)
- Inhibitors of pathways for recruitment (e.g. inhibitors of HIFs)

Suppressing TAM survival:

- Chemical drugs (e.g. bisphosphonates, dasatanib) that deplete macrophages directly
- Immunotoxin-conjugated mAbs (e.g. anti-FR β mAb) targeting membrane molecules
- Attenuating bacteria (e.g. *Shigella flexneri*) that induce macrophage apoptosis
- Agents that induce macrophages to express molecules (e.g. leguman, CD1d) that can be targeted by cytotoxic T lymphocytes

Enhancing M1 tumoricidal activity:

- Agonists of NF- κ B (e.g. TLR agonists, anti-CD40 mAb, anti-IL-10R mAb)
- Agonists of STAT1 (e.g. interferon)
- Agonists of other M1 pathways (e.g. SHIP)
- Other agents (e.g. GM-CSF, IL-12, thymosin α 1)

Blocking M2 tumor-promoting activity:

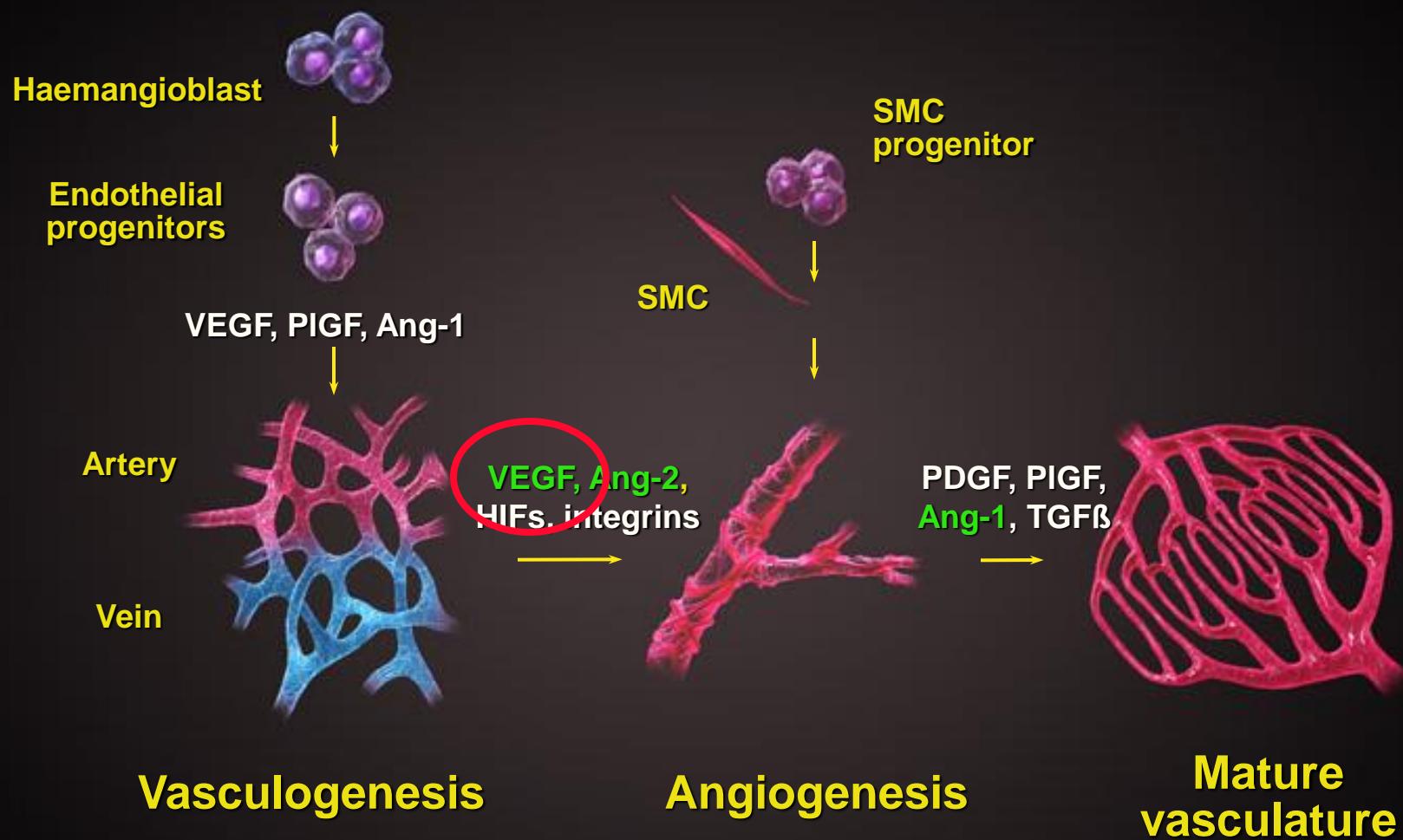
- Inhibitors of STAT3 (e.g. sunitinib, sorafenib, WP1066, corosolic acid & oleanolic acid)
- Inhibitors of STAT6
- Inhibitors of other M2 pathways (e.g. c-Myc, PPAR- α /g, PI3K, KLF4, HIFs)
- Other agents (e.g. HRG, CuNG, PPZ)

Targeting the Tumor Microenvironment

Solid tumor formation results in a unique biologic compartment

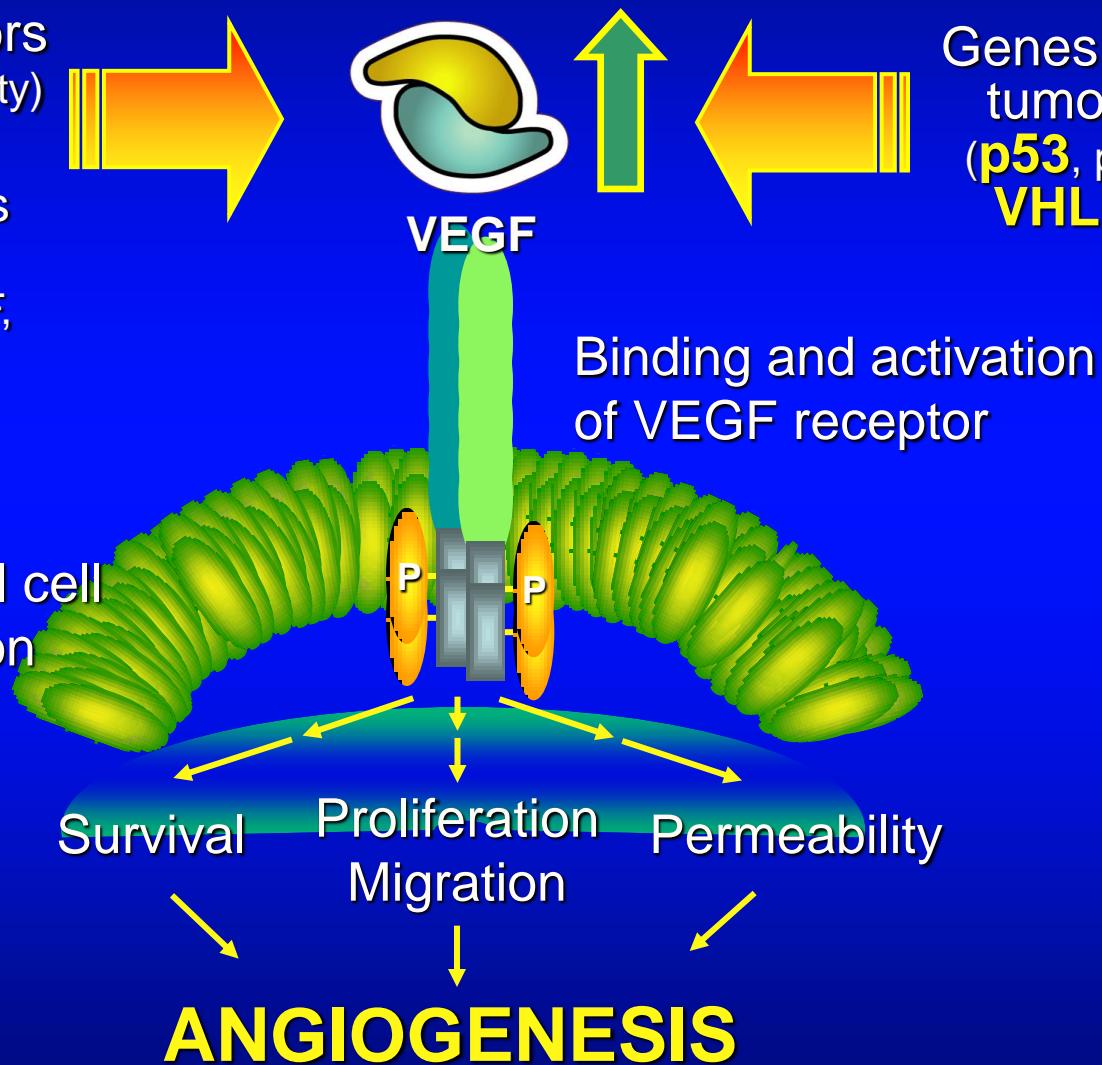
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- Environmentally unique – acidosis, hypoglycemia, elevated IFP, hypoxia
- Immunologically unique – privileged

Normal Vessel Formation



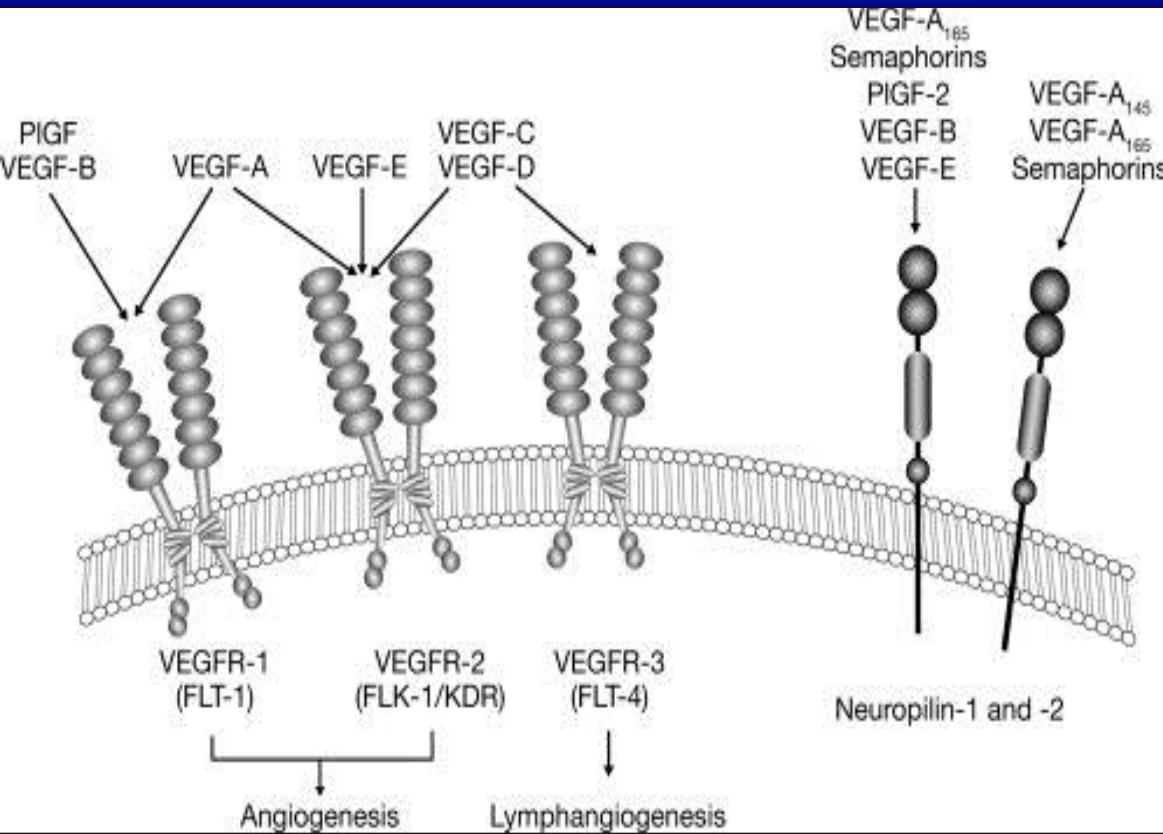
VEGF: The Central Mediator of Angiogenesis

Environmental factors
(Hypoxia, pH, cell density)
growth factors,
hormones, cytokines
(EGF, bFGF, PDGF,
IGF-1, IL-1 α , IL-6, TGF,
estrogen, NO)



Genes involved in tumorigenesis
(p53, p73, src, ras, VHL, Her2/neu)

VEGF



Abdullah et al., Cancer 2011

Vascular functions:

- Enhances endothelial cell (EC) proliferation/survival
- Increases migration and invasion of EC
- Increases permeability of existing vessels
- Forms lattice network for EC migration
- Enhances chemotaxis and homing of bone marrow-derived vascular precursor cells (pericytes, EC)

Non-vascular functions:

- Autocrine effects on tumor cell function (survival, migration, invasion)
- Immune suppression
- Homing of bone marrow progenitors to “prepare” organ for metastasis
- Increases vessel dilatation (turbulence, inefficient blood flow)
- Increased permeability → increased IFP (intermittent hypoxia)

VEGF-Targeted Therapies

Approved agents (+20 in clinical trials):

anti-VEGF monoclonal antibody, bevacizumab (Avastin); tyrosine kinase inhibitors, sorafenib (Nexavar), sunitinib (Sutent), pazopanib (Votrient) & axitinib (Inlyta)

Have been shown to be efficacious as single agents in renal cell carcinoma and hepatocellular carcinoma; combined with chemotherapy for metastatic colorectal, NSCLC, metastatic breast cancer.

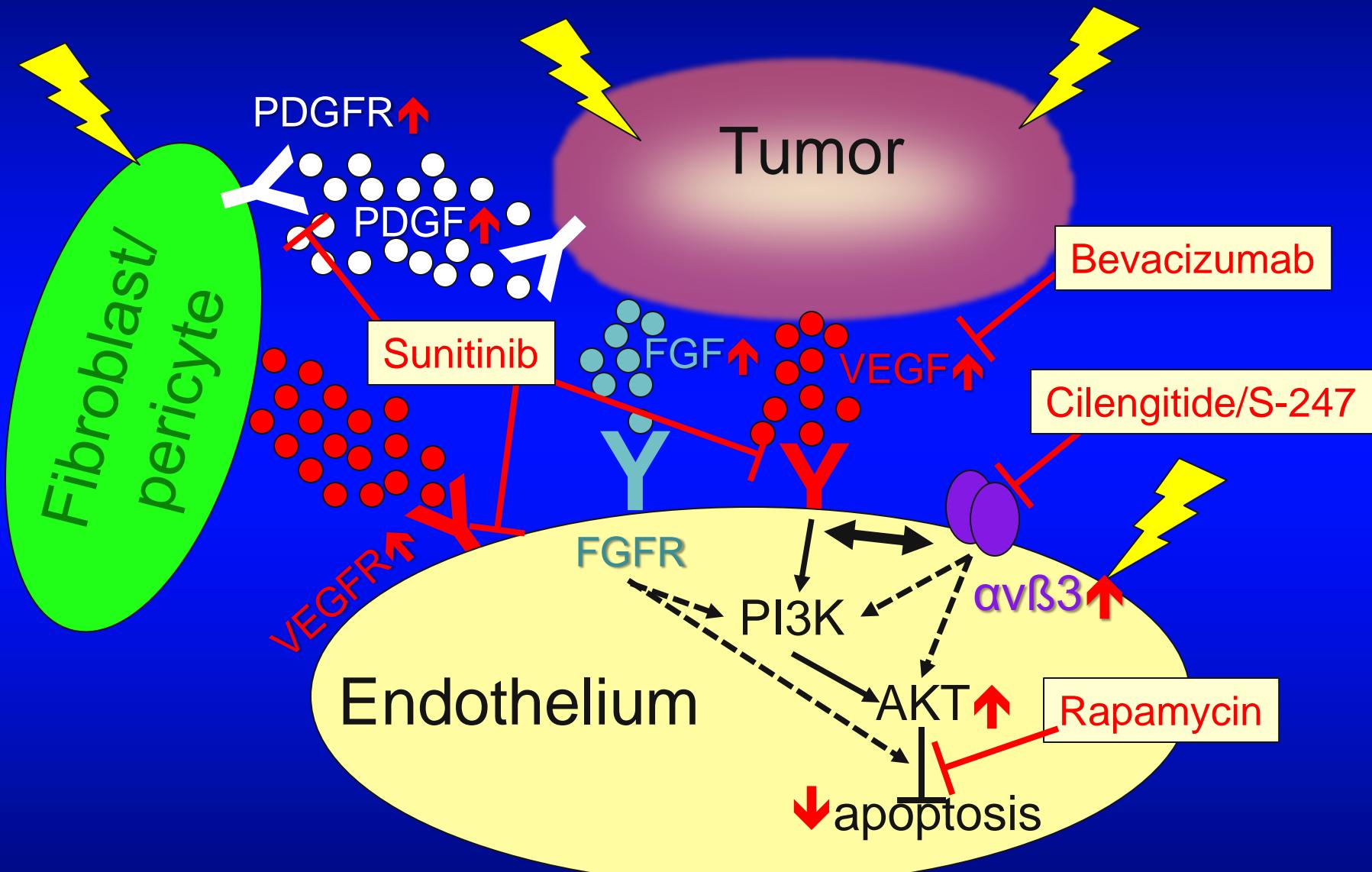
Lack of success may be due to:

- complexity of VEGF activity
- differentials in tumor dependence on angiogenesis
- induction of VEGF-targeted drug resistance
- induction of off-target toxicities
- normalization of vasculature

Tumor Evasion

Mechanism of action/class	Representative drugs	Current Clinical Phase
Vascular disrupting agents	ASA-404, AVE-8062, Ombrabulin	II-III
FGFR targeting	Dovitinib; BIBF-1120, Brivanib	III; II-III
Angiopoetin targeting	AMG-386	II-III
EphrinA2 targeting	Dasatinib	II-III
PI3K/mTOR targeting	BKM-120, Everolimus, Temsirolimus	II-III
EGFR targeting	Cetuximab, Erlotinib, Gefitinib	II-III
MET targeting	Cabozantinib	II-III
PDGFR targeting	Axitinib, Cediranib, Pazopanib	II-III
Src/Fak complex targeting	Dasatinib, Sunitinib	II-III

Tumor Evasion



Targeting the Tumor Microenvironment

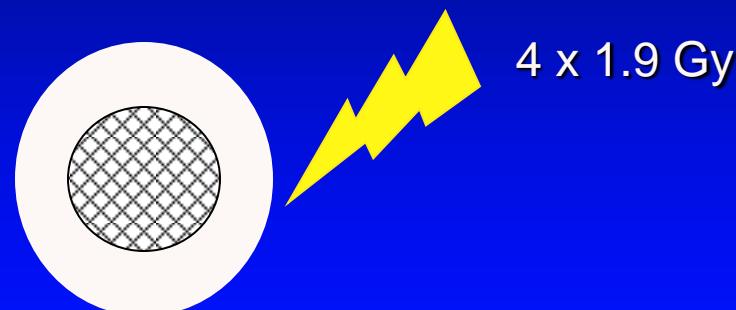
Solid tumor formation results in a unique biologic compartment

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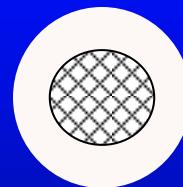
Reoxygenation

Concept from Van Putten and Kallman:

Transplantable mouse
sarcoma



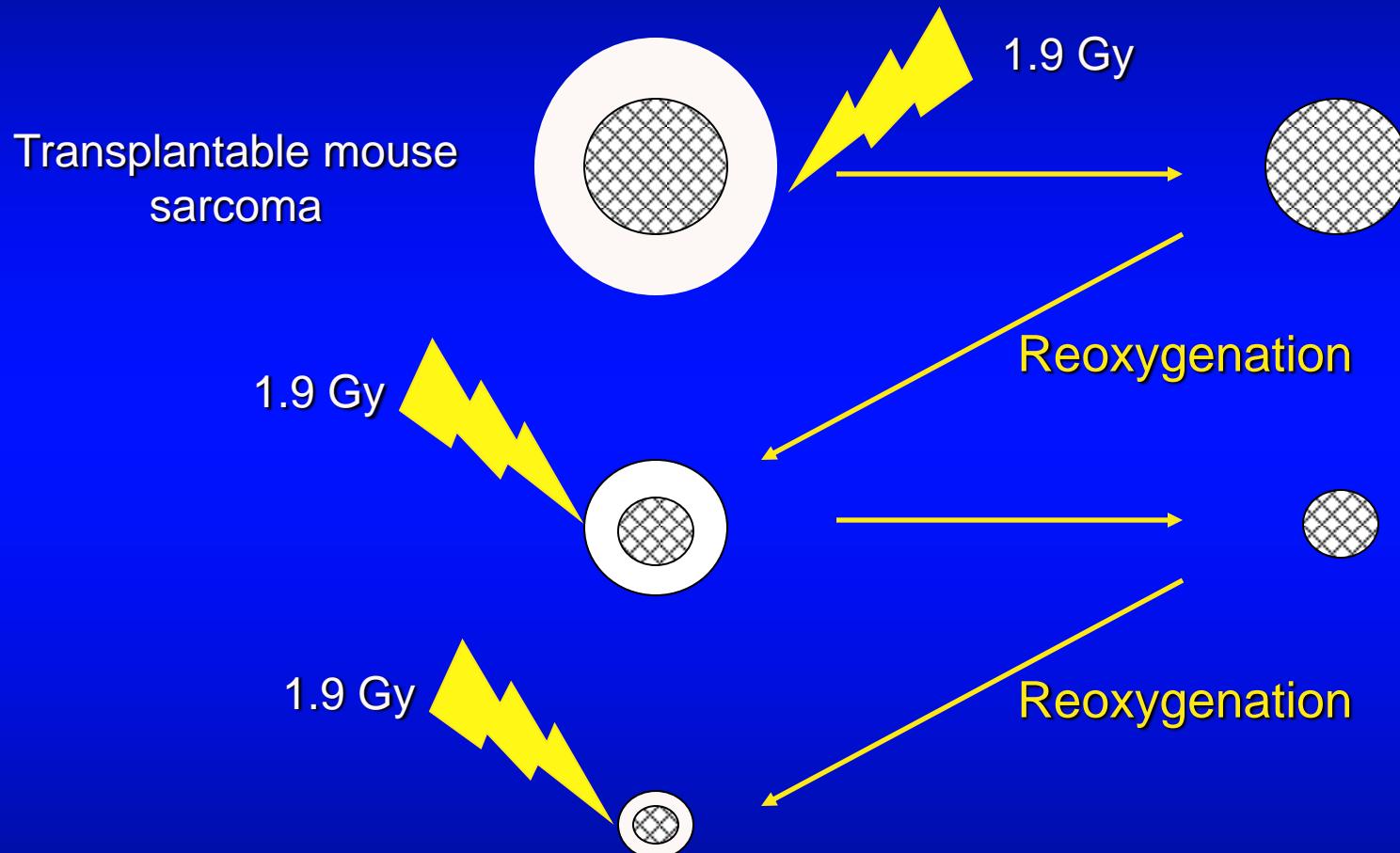
18% hypoxic cells



14% hypoxic cells

Reoxygenation

Concept from Van Putten and Kallman:



Factor: time between fractions

Hypoxia-Targeted Therapies

Fractionation scheduling:

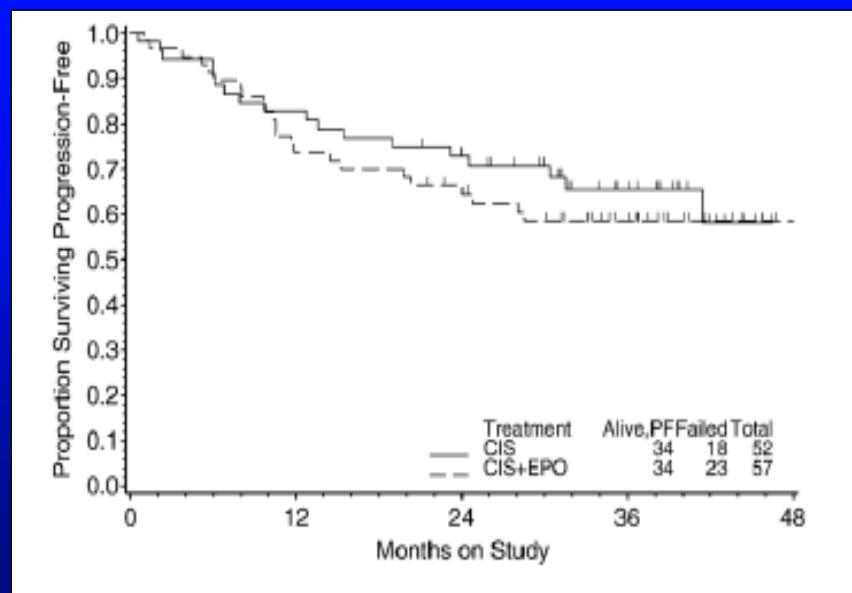
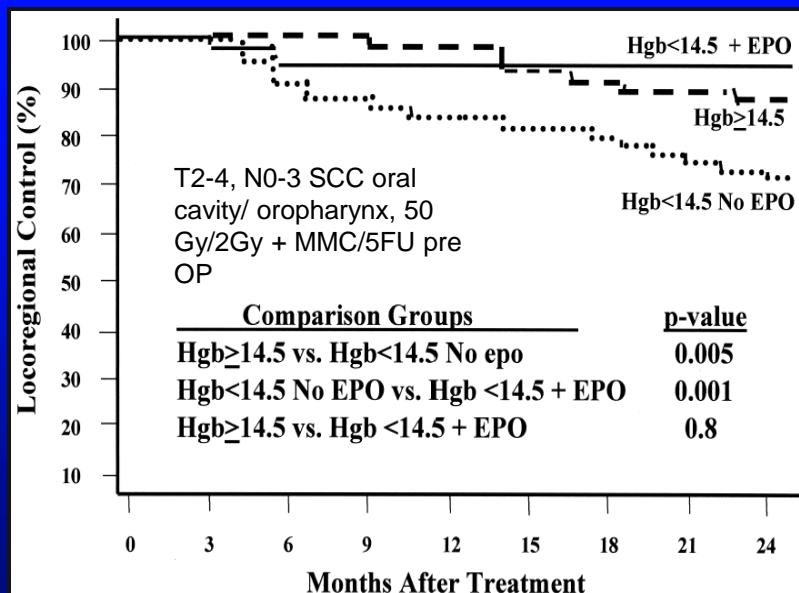
Rapid, well-reoxygenating tumors may benefit from hypofractionation schedule

Improve oxygen supply:

- Blood transfusions

Modify oxygen supply:

- EPO



Hypoxia-Targeted Therapies

Fractionation scheduling:

Rapid, well-reoxygenating tumors may benefit from hypofraction schedule

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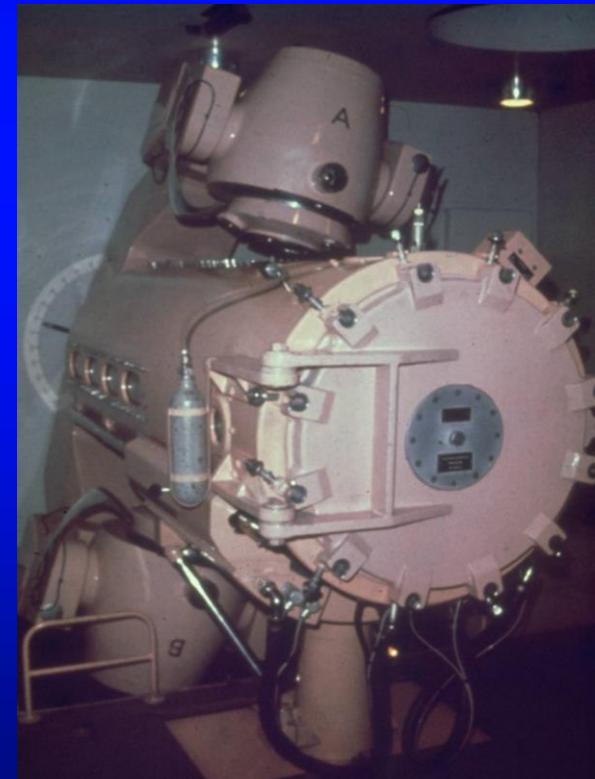
Increase oxygen levels:

- Hyperbaric oxygen (3 atm)

Trials: 6% improvement in tumor control

Disadvantages:

- Fire hazard
- Increased normal tissue damage
- Patient claustrophobia



Hypoxia-Targeted Therapies

Fractionation scheduling:

Rapid, well-reoxygenating tumors may benefit from hypofraction schedule

Improve oxygen supply:

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Modify oxygen supply:

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Increase oxygen levels:

- Hyperbaric oxygen
- Carbogen (95% O₂, 5% CO₂)



Hypoxia-Targeted Therapies

Fractionation scheduling:

Rapid, well-reoxygenating tumors may benefit from hypofraction schedule

Improve oxygen supply:

- Blood transfusions

Modify oxygen supply:

- EPO

Increase oxygen levels:

- Hyperbaric oxygen
- Carbogen (95% O₂, 5% CO₂)
+ nicotinamide (B₃ analogue)



ARCON

A = accelerated radiation - counteracts repopulation
 R = hyperfractionation - reduce late normal tissue effects
 CO = carbogen - reduce chronic hypoxia
 N = nicotinamide - reduce transient hypoxia

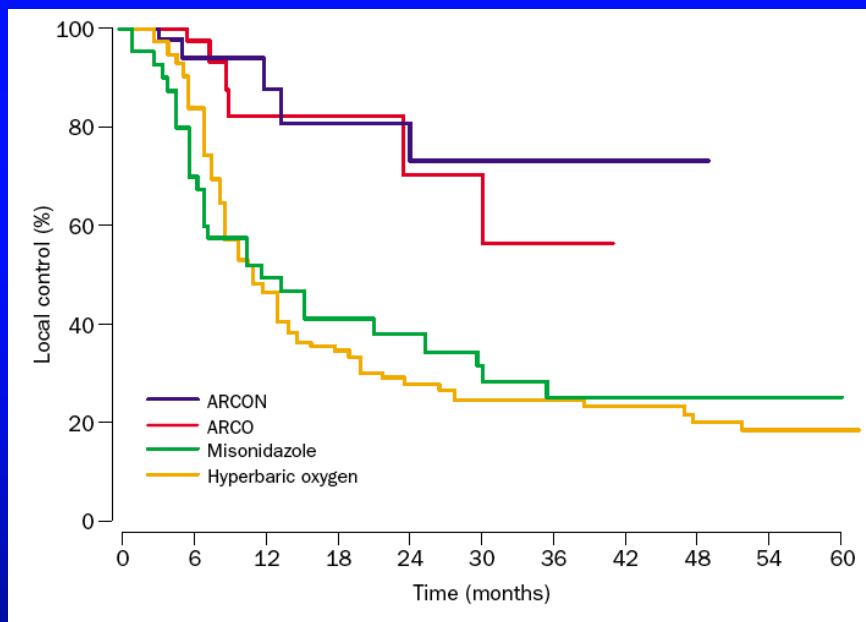


Table 1. Clinical experience with ARCON

Ref	Tumour site	Number of patients			Conclusions
		Carbogen	Nicotinamide	Carbogen plus Nicotinamide	
23	Head and neck	32	..	18	24
24		11	51
26		215
55		8	12	..	15
56		6
57		11	10	..	17
52	Breast	6	..
62	Glioma	16	..
63		19	..
64		..	8	..	21
66		23	28	..	56
66	Bronchus	10	11	..	14
67	Bladder	30	31
51	Various	8

Notes from the table:

- Ref 23: Head and neck, 32 patients, Carbogen plus Nicotinamide, 24 months.
- Ref 24: Head and neck, 11 patients, Carbogen plus Nicotinamide, 51 months.
- Ref 26: Head and neck, 215 patients, Carbogen plus Nicotinamide, 215 months.
- Ref 55: Head and neck, 8 patients, Nicotinamide, 15 months.
- Ref 56: Head and neck, 6 patients, Carbogen plus Nicotinamide, 6 months.
- Ref 57: Head and neck, 11 patients, Nicotinamide, 17 months.
- Ref 52: Breast, 6 patients, Carbogen plus Nicotinamide, 6 months.
- Ref 62: Glioma, 16 patients, Carbogen plus Nicotinamide, 6 months.
- Ref 63: Glioma, 19 patients, Carbogen plus Nicotinamide, 6 months.
- Ref 64: Glioma, 8 patients, Nicotinamide, 21 months.
- Ref 66: Glioma, 23 patients, Nicotinamide, 56 months.
- Ref 66: Bronchus, 10 patients, Nicotinamide, 14 months.
- Ref 67: Bladder, 30 patients, Carbogen plus Nicotinamide, 31 months.
- Ref 51: Various, 8 patients, Carbogen plus Nicotinamide, 6 months.

Kaanders et al., The Lancet, 2002.

May be changes in hemoglobin levels important, not absolute values

Hypoxia-Targeted Therapies

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Rapid, well-reoxygenating tumors may benefit from hypofraction schedule

Improve oxygen supply:

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Modify oxygen supply:

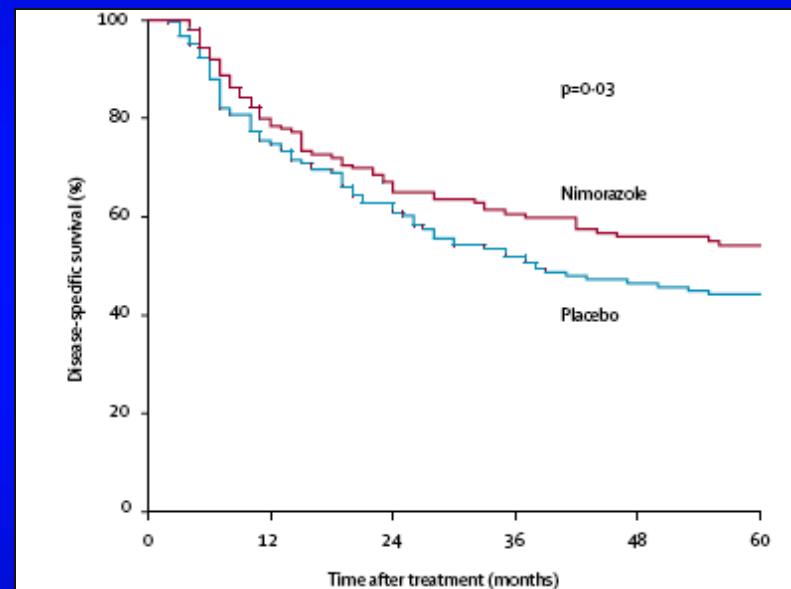
- EPO

Increase oxygen levels:

- Hyperbaric oxygen
- Carbogen (95% O₂, 5% CO₂) + nicotinamide (B₃ analogue)

Hypoxic cell sensitizers:

- e.g. misonidazole, etanidazole, nimorazole



Overgaard et al., Lancet Oncol, 2005.

Hypoxia-Targeted Therapies

Fractionation scheduling:

Rapid, well-reoxygenating tumors may benefit from hypofractionation schedule

Improve oxygen supply:

- Blood transfusions

Modify oxygen supply:

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Increase oxygen levels:

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Hypoxic cell sensitizers:

- e.g. misonidazole

Hypoxic cytotoxins

- e.g. tirapazamine

Try, try again:
HIF-1 targeted agents

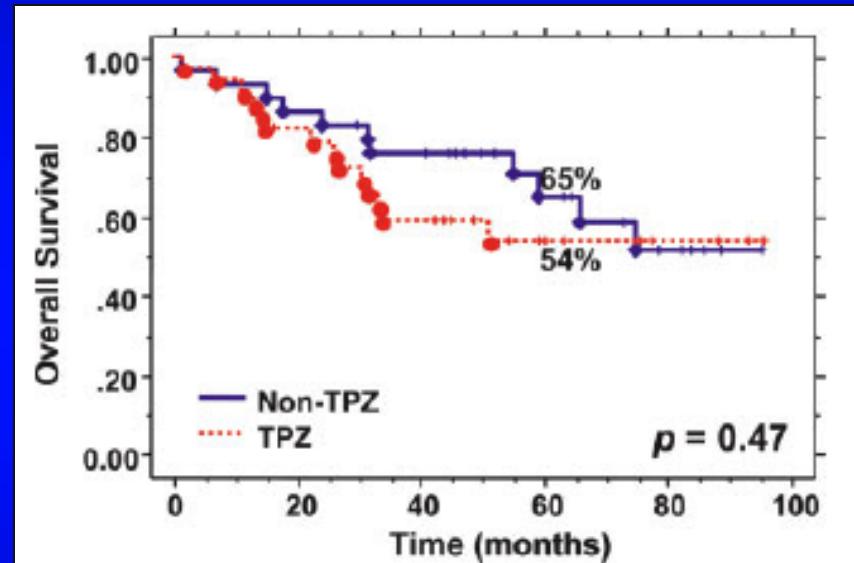


FIGURE 3. Overall survival by treatment arm. TPZ: tirapazamine.

Le et al., Cancer, 2006.