Acidosis

Übersäuerung als Initiator und Motor des Krebs-Geschehens

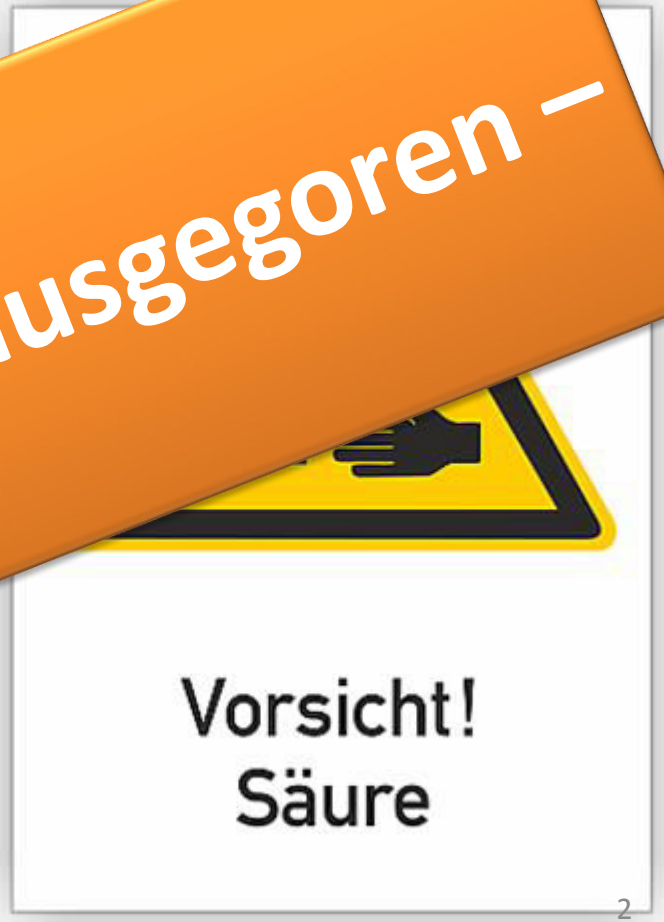
Spannende Studien

Dr.med. Helmut B Retzek

„Azidose: Ursache von Haar-Ausfall, Krebs und Tod“

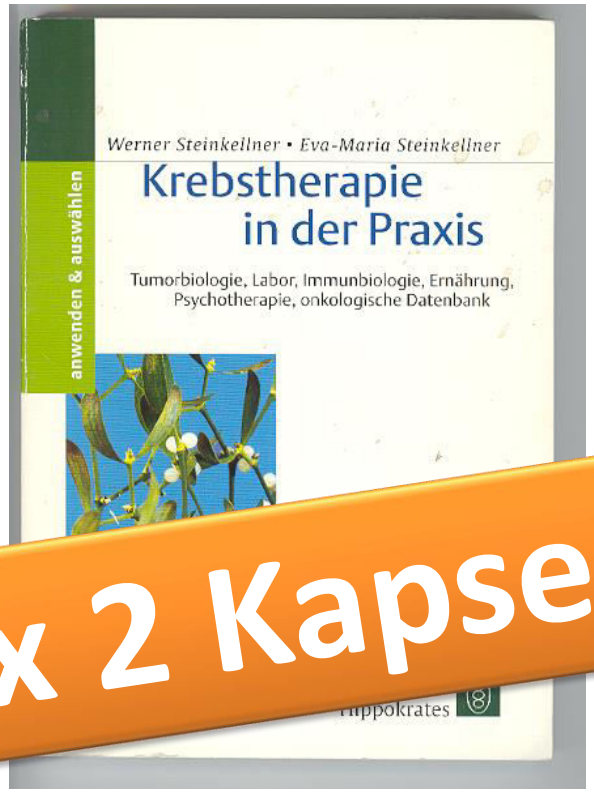
- Verschlackungen
- Gelosen = Lokalüber
- Pischinger
- Ha
- V
- ….

Wirr und Konfus – konzeptionell unausgegoren – widersprüchlich



Werner Steinkellner

1996 Hospitation 2 Wochen

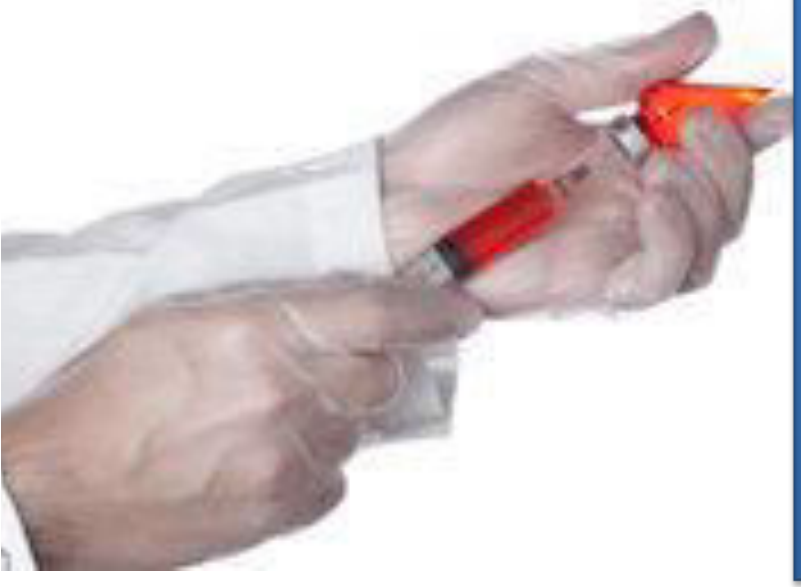


3 x 2 Kapseln Basenpulver

Regel der begrenzten Interventions-Möglichkeit

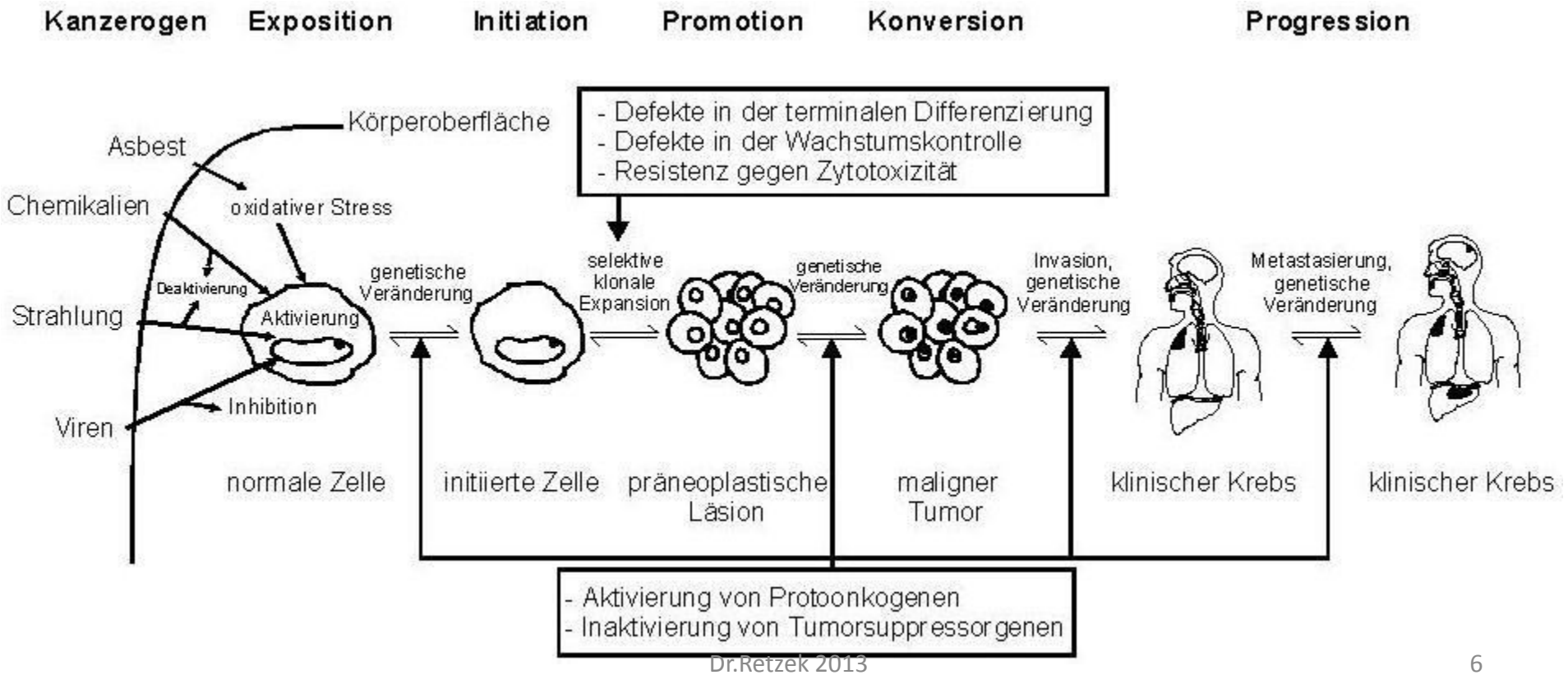
- 5 Items
- € 30 pm
- 2 x täglich
- max 10

Akzeptanz –Wg- Index



- → Infusionen
- → Spritzen
- → Manuell
- → Farbig
- → Einläufe
- → Tropfen
- → Tee
- → Pulver
- → Physikalische Verfahren

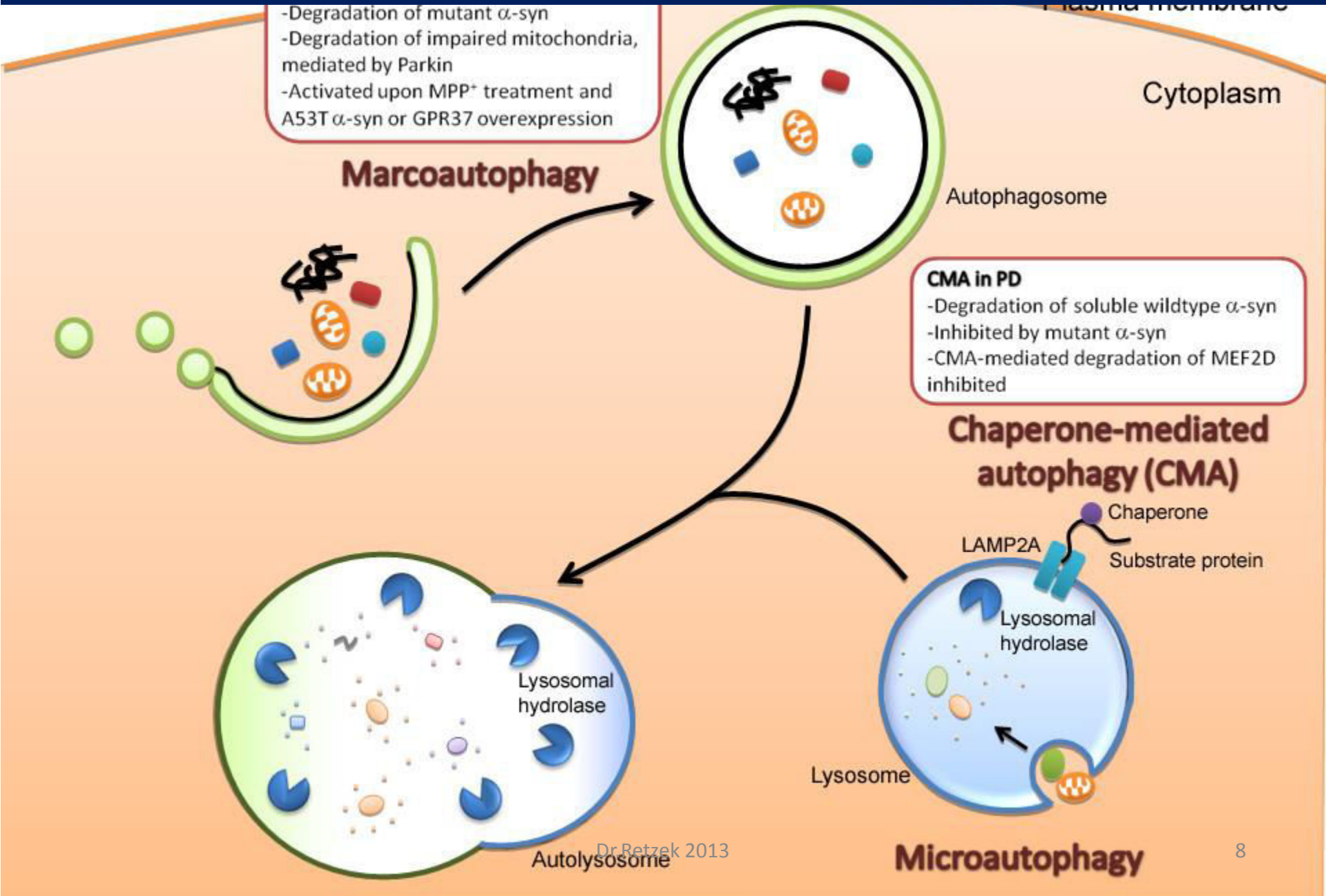
Krebs-Entstehung

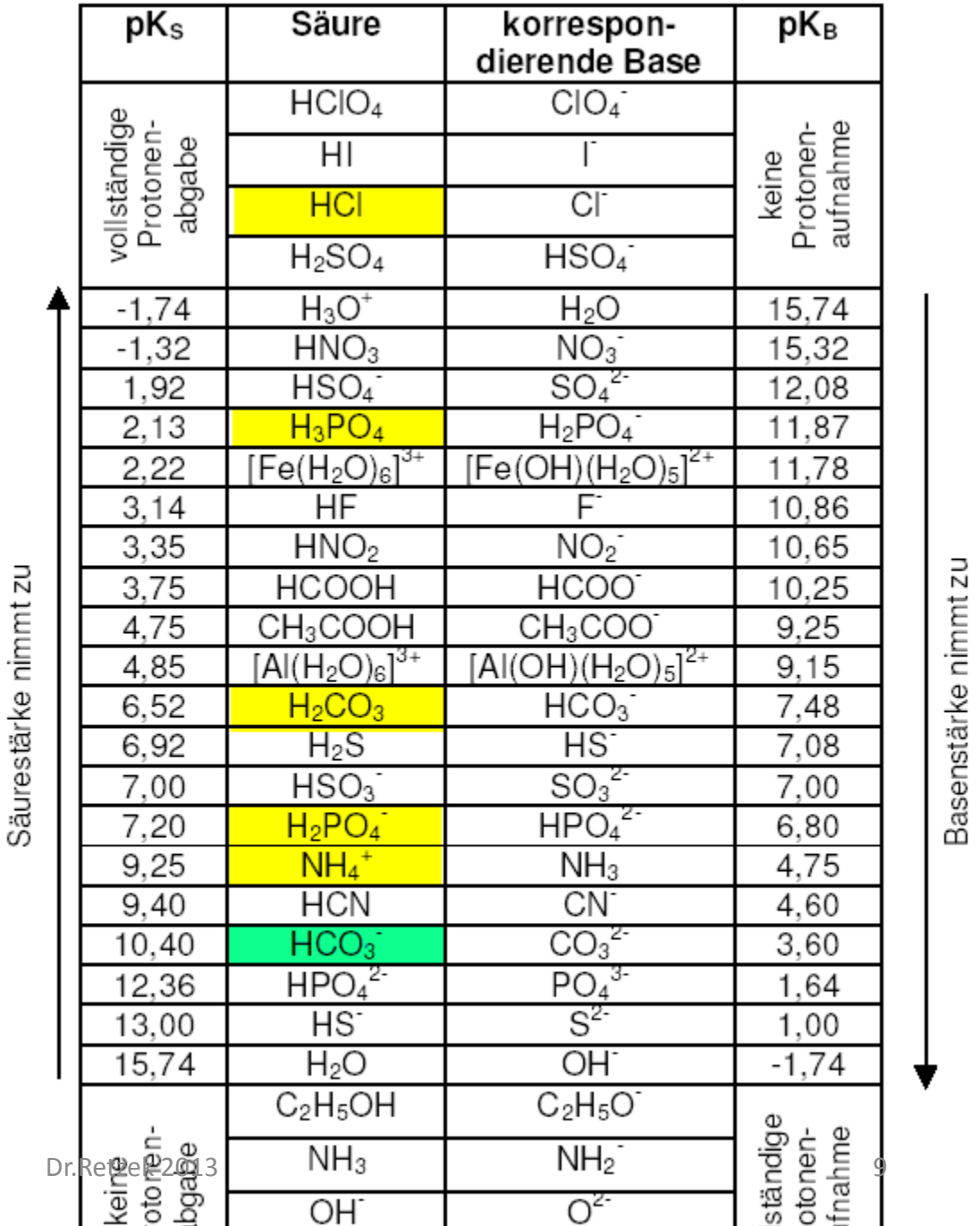


Begriffe zur Azidose / Krebs

- pH
- Hypoxie 20% -- 8% -- 1% -- 0.1%
- HIF-1
- Protonenpumpe, Carb-Anhydrase
- Glykolyse → Glukose-Mangel
- Mikro-Environment
- Laktazidose
- Epidermal-Mesenchymale Transformation, Motilität
- MMP
- Caspase → Apoptose
- Autophagie
- IL 8
- EGF(R)
- CTL – Lytische Granules

Autophagie – „Leben von der Substanz“





pK_S	Säure	korrespondierende Base	pK_B
vollständige Protonenabgabe	$HClO_4$	ClO_4^-	keine Protonenaufnahme
	HI	I^-	
	HCl	Cl^-	
	H_2SO_4	HSO_4^-	
-1,74	H_3O^+	H_2O	15,74
-1,32	HNO_3	NO_3^-	15,32
1,92	HSO_4^-	SO_4^{2-}	12,08
2,13	H_3PO_4	$H_2PO_4^-$	11,87
2,22	$[Fe(H_2O)_6]^{3+}$	$[Fe(OH)(H_2O)_5]^{2+}$	11,78
3,14	HF	F^-	10,86
3,35	HNO_2	NO_2^-	10,65
3,75	HCOOH	$HCOO^-$	10,25
4,75	CH_3COOH	CH_3COO^-	9,25
4,85	$[Al(H_2O)_6]^{3+}$	$[Al(OH)(H_2O)_5]^{2+}$	9,15
6,52	H_2CO_3	HCO_3^-	7,48
6,92	H_2S	HS^-	7,08
7,00	HSO_3^-	SO_3^{2-}	7,00
7,20	$H_2PO_4^-$	HPO_4^{2-}	6,80
9,25	NH_4^+	NH_3	4,75
9,40	HCN	CN^-	4,60
10,40	HCO_3^-	CO_3^{2-}	3,60
12,36	HPO_4^{2-}	PO_4^{3-}	1,64
13,00	HS^-	S^{2-}	1,00
15,74	H_2O	OH^-	-1,74
keine Protonenabgabe	C_2H_5OH	$C_2H_5O^-$	vollständige Protonenaufnahme
	NH_3	NH_2^-	
	OH^-	O^{2-}	

Säurestärke nimmt zu

Basenstärke nimmt zu

Krebs-Entstehung

- Hypoxie → HIF
- Umschaltung in Glykolyse → 8fach
- Lactazidose
- Zell-Zyklus-Arrest (pH 6.8) → Zell-Tod (pH 6.5)
- Klone mit stabilem Phänotypus Dauer-Glykolyse egal welcher pH, Autophagie, Wachstums-Potential bei pH < 6.7
- blockierte Apoptose
- Hemmung der cytotoxischen T-Zellen
- Irreguläre Blutgefässe
- Epidermal-mesenchymale Transformation
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- Tumor-Stammzellen
- pH - Therapie

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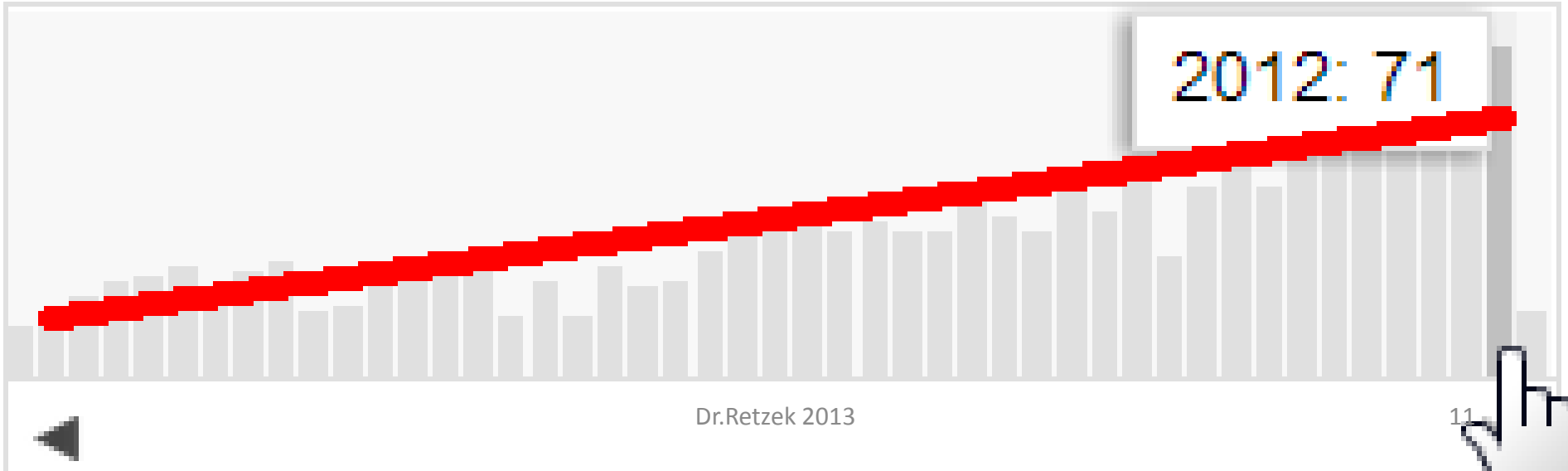

Hypoxie ermöglicht Überleben ….. 2010

- …. weil erst jetzt HIF induziert wird, der viele pH-regulierende Systeme als Expressionsfaktor produziert.
- Erst jetzt ist es möglich mit AZIDOSE zu copen

J Cell Mol Med. 2010 Apr;14(4):771-94.

Tumour hypoxia induces a metabolic shift causing acidosis: a common feature in cancer.

Chiche J, Brahimi-Horn MC, Pouysségur J.

Institute of Developmental Biology and Cancer Research, University of Nice, CNRS UMR, Centre A. Lacassagne, Nice, France.

Abstract

Maintenance of cellular pH homeostasis is fundamental to life. A number of key intracellular pH (pHi) regulating systems including the Na(+)/H(+) exchangers, the proton pump, the monocarboxylate transporters, the HCO(3)(-) transporters and exchangers and the membrane-associated and cytosolic carbonic anhydrases cooperate in maintaining a pHi that is permissive for cell survival. A common feature of tumours is acidosis caused by hypoxia (low oxygen tension). In addition to oncogene activation and transformation, hypoxia is responsible for inducing acidosis through a shift in cellular metabolism that generates a high acid load in the tumour microenvironment. However, hypoxia and oncogene activation also allow cells to adapt to the potentially toxic effects of an excess in acidosis. Hypoxia does so by inducing the activity of a transcription factor the hypoxia-inducible factor (HIF), and particularly HIF-1, that in turn enhances the expression of a number of pHi-regulating systems that cope with acidosis. In this review, we will focus on the characterization and function of some of the hypoxia-inducible pH-regulating systems and their induction by hypoxic stress. It is essential to understand the fundamentals of pH regulation to meet the challenge consisting in targeting tumour metabolism and acidosis as an anti-tumour approach. We will summarize strategies that take advantage of intracellular and extracellular pH regulation to target the primary tumour and metastatic growth, and to turn around resistance to chemotherapy and radiotherapy.

Hypoxie ermöglicht Überleben bei Säure

- … Across all cell lines tested, hypoxia (1% O_2) provided protection against acidosis induced cell death compared to normoxia …..

Results: 1 to 20 of 205

Hypoxia promotes tumor cell survival in acidic conditions by preserving ATP levels.

Parks SK, Mazure NM, Counillon L, Pouysségur J.

J Cell Physiol. 2013 Mar 4. doi: 10.1002/jcp.24346. [Epub ahead of print]

Sauerstoff und Azidose

- HYPOXIE (1% O2) ermöglicht es trotz Acidose einen hohen ATP-Spiegel zu halten.
- Erst Hypoxie ermöglicht Zellen bei Acidose UND Medikament-Stress zu Überleben

J Cell Physiol. 2013 Mar 4. doi: 10.1002/jcp.24346. [Epub ahead of print]

Hypoxia promotes tumor cell survival in acidic conditions by preserving ATP levels.

Parks SK, Mazure NM, Counillon L, Pouysségur J.

Institute for Research on Cancer and Aging, Nice (IRCAN), University of Nice-Sophia Antipolis, CNRS UMR7284, INSERM U1081, Centre A. Lacassagne. Scott.Parks@unice.fr.

Abstract

The efficacy of targeting pH disruption to induce cell death in the acidic and hypoxic tumor microenvironment continues to be assessed. Here we analyzed the impact of varying levels of hypoxia in acidic conditions on fibroblasts and tumor cell survival. Across all cell lines tested, hypoxia (1% O_2) provided protection against acidosis induced cell death compared to normoxia. Meanwhile severe hypoxia (0.1% O_2) removed this protection and in some cases exacerbated acidosis-induced cell death. Differential survival between cell types during external acidosis correlated with their respective intracellular pH regulating capabilities. Cellular ATP measurements were conducted to determine their contribution to cell survival under these combined stresses. In general, hypoxia (1% O_2) maintained elevated ATP levels in acidic conditions while severe hypoxia did not. To further explore this interaction we combined acidosis with ATP depletion using 2-Deoxyglucose and observed an enhanced rate of cell mortality. Striking results were also observed with hypoxia providing protection against cell death in spite of a severe metabolic stress induced by a combination of acidosis and oligomycin. Finally, we demonstrated that both HIF1α and HIF2α expression were drastically reduced in hypoxic and acidic conditions indicating a sensitivity of this protein to cellular pH conditions. This knockdown of HIF expression by acidosis has implications for the development of therapies targeting the disruption of cellular pH regulation. Our results reinforce the proof of concept that acidosis and metabolic disruption affecting ATP levels could be exploited as a tumor cell killing strategy. J. Cell. Physiol. © 2013 Wiley Periodicals, Inc.

8 x Glycolyse | ph-Resistenz

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J Theor Biol. 2010 Feb 21;262(4):601-13. doi: 10.1016/j.jtbi.2009.10.031. Epub 2009 Oct 31.

A quantitative theoretical model for the development of malignancy in ductal carcinoma in situ.

Silva AS, Gatenby RA, Gillies RJ, Yunes JA.

Centro Infantil Boldrini, Rua Dr Gabriel Porto 1270, Campinas, SP 13083-210, Brazil. ariosto.silva@moffitt.org

Abstract

Mathematical models and clinical observations have demonstrated that microenvironmental hypoxia and acidosis are important selection factors during the later stages of the somatic evolution of breast cancer. The consequent promotion of constitutive upregulation of glycolysis and resistance to acid-induced cellular toxicity is hypothesized to be critical for the ability of cancer cells to invade host tissue. In this work we developed a 3D fixed lattice cellular automata model to study the role of these two phenotypes in determining morphology and the potential for invasion of ductal carcinoma in situ (DCIS), which in this work is defined as the erosion of a healthy epithelial cell layer and direct contact with the basement membrane. The model was conceived as a 40-cell wide epithelial duct surrounded by blood vessels and composed of a basement membrane and one internal layer of epithelial cells. Our results show that an increment in the order of 8-fold in glucose metabolism and an increase in acid resistance corresponding to pH thresholds of approximately 6.8 and 6.45 for quiescence and death, respectively, are required for the tumor to breach through the layer of healthy epithelial cells and reach the basement membrane as a first step for invasion. Our model also suggests correlations between classic morphologies and different values of hyperglycolytic and acid-resistant phenotypes, indicating that immunohistochemistry studies targeting these genes may improve the predictive power of morphological analyses of biopsies.

J Theor Biol. 2010 Feb

Lactat direkt Wachstums-Promotor

- Milchsäure wirkt direkt stimulierend auf Tumor-Wachstum und Metastasierung ein
- 2012

Curr Pharm Des. 2012;18(10):1319-30.

Multiple biological activities of lactic acid in cancer: influences on tumor growth, angiogenesis and metastasis.

Dhup S, Dadhich RK, Porporato PE, Sonveaux P.

Pole of Pharmacology, Institute of Experimental and Clinical Research-IREC, Université Catholique de Louvain-UCL Medical School, Brussels, Belgium.

Abstract

High rate of glycolysis is a metabolic hallmark of cancer. While anaerobic glycolysis promotes energy production under hypoxia, aerobic glycolysis, the Warburg effect, offers a proliferative advantage through redirecting carbohydrate fluxes from energy production to biosynthetic pathways. To fulfill tumor cell needs, the glycolytic switch is associated with elevated glucose uptake and lactic acid release. Altered glucose metabolism is the basis of positron emission tomography using the glucose analogue tracer [18F]- fluorodeoxyglucose, a widely used clinical application for tumor diagnosis and monitoring. On the other hand, high levels of lactate have been associated with poor clinical outcome in several types of human cancers. Although lactic acid was initially considered merely as an indicator of the glycolytic flux, many evidences originally from the study of normal tissue physiology and more recently transposed to the tumor situation indicate that lactic acid, i.e. the lactate anion and protons, directly contributes to tumor growth and progression. Here, we briefly review the current knowledge pertaining to lactic acidosis and metastasis, lactate shuttles, the influence of lactate on redox homeostasis, lactate signaling and lactate-induced angiogenesis in the cancer context. The monocarboxylate transporters MCT1 and MCT4

1996 - Melanom wird aggressiv durch dauerhafte Zellkulturbedingung pH 6.8

- nur kultivieren bei pH 6.8 → aggressiv
- Kultivieren bei pH 7.4 dann 6.8 → nicht aggr.

Clin Exp Metastasis. 1996 Mar;14(2):176-86.

Acidic pH enhances the invasive behavior of human melanoma cells.

Martínez-Zaguilán R, Seftor EA, Seftor RE, Chu YW, Gillies RJ, Hendrix MJ.

Department of Biochemistry, University of Arizona Health Sciences Center, Tucson, USA.

Abstract

As a consequence of poor perfusion and elevated acid production, the extracellular pH (pHex) of tumors is generally acidic. Despite this, most in vitro experiments are still performed at the relatively alkaline pHex of 7.4. This is significant, because slight changes in pHex can have profound effects on cell phenotype. In this study we examined the effects of mildly acidic conditions on the in vitro invasive potential of two human melanoma cell lines; the highly invasive C8161, and poorly invasive A375P. We observed that culturing of either cell line at acidic pH (6.8) caused dramatic increases in both migration and invasion, as measured with the Membrane Invasion Culture System (MICS). This was not due to a direct effect of pH on the invasive machinery, since cells cultured at normal pH (7.4) and tested at acidic pH did not exhibit increased invasive potential. Similarly, cells cultured at acidic pH were more aggressive than control cells when tested at the same medium pH. These data indicate that culturing of cells at mildly acidic pH induces

Melanom: Azidose selektiert aggressiven Phenotypus - 2008

- Azidose → Zelltot
- wenige überleben, gut adaptiert
- stabil über viele Generationen: AGGRESSIVER + MOBILER → Azidose-Effekt über Selektion nicht über reversible Adaption (→ TRAMP-Mäuse)

Clin Exp Metastasis. 2008;25(4):411-25. doi: 10.1007/s10585-008-9145-7. Epub 2008 Feb 27.

Acid treatment of melanoma cells selects for invasive phenotypes.

Moellering RE, Black KC, Krishnamurty C, Baggett BK, Stafford P, Rain M, Gatenby RA, Gillies RJ.

Arizona Cancer Center, Arizona Health Sciences Center, Tucson, AZ , USA.

Abstract

Solid tumors become acidic due to hypoxia and upregulated glycolysis. We have hypothesized that this acidosis leads to more aggressive invasive behavior during carcinogenesis (Nature Reviews Cancer 4:891-899, 2004). Previous work on this subject has shown mixed results. While some have observed an induction of metastasis and invasion with acid treatments, others have not. To investigate this, human melanoma cells were acclimated to low pH growth conditions. Significant cell mortality occurred during acclimation, suggesting that acidosis selected for resistant phenotypes. Cells maintained under acidic conditions exhibited a greater range of motility, a reduced capacity to form flank tumors in SCID mice and did not invade more rapidly in vitro, compared to non-selected control cells. However, re-acclimation of these selected cells to physiological pH gave rise to stable populations with significantly higher in vitro invasion. These re-acclimated cells maintained higher invasion and higher motility for multiple generations. Transcriptomic analyses of these three phenotypes revealed significant differences, including upregulation of relevant pathways important for tissue remodeling, cell cycle control and proliferation. These results reinforce the hypothesis that acidosis promotes selection of stable, more invasive phenotypes, rather than inductive changes, which would be reversible.

Lacat-azidose ermöglicht erst Tumorzellen Zucker-Deprivation zu überleben

- - Glukose: 90% Zelltot / 24h
- - Zucker + Laktazidose: 10 → 64d !!!!

J Pathol. 2012 Jun;227(2):189-99. doi: 10.1002/path.3978. Epub 2012 Feb 17.

Central role of lactic acidosis in cancer cell resistance to glucose deprivation-induced cell death.

Wu H, Ding Z, Hu D, Sun F, Dai C, Xie J, Hu X.

Cancer Institute (Key Laboratory for Cancer Intervention and Prevention, China National Ministry of Education, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang Province, China.

Abstract

Solid tumours are dependent on glucose, but are generally glucose-deprived due to poor vascularization. Nevertheless, cancer cells can generally survive glucose deprivation better than their normal counterparts. Thus, to render cancer cells sensitive to glucose depletion may potentially provide effective strategy for cancer intervention. We propose that lactic acidosis, a tumour microenvironment factor, may allow cancer cells to develop resistance to glucose deprivation-induced death, and that disruption of lactic acidosis may resume cancer cells' sensitivity to glucose depletion. Lactic acidosis, lactosis, or acidosis was generated by adding pure lactic acid, sodium lactate, or HCl to the culture medium. Cell death, cell cycle, autophagy, apoptosis, and gene expression profiling of the surviving cancer cells under glucose deprivation with lactic acidosis were determined. Under glucose deprivation without lactic acidosis, 90% of 4T1 cancer cells died within a single day; in a sharp contrast, under lactic acidosis, 90% 4T1 cells died in a period of 10 days, with viable cells identified even 65 days after glucose was depleted. Upon glucose restoration, surviving cells resumed proliferation. Lactic acidosis also significantly extended survival of other cancer cells under glucose deprivation. G1/G0 arrest, autophagy induction, and apoptosis inhibition were tightly associated with lactic acidosis-mediated resistance to glucose deprivation. Lactosis alone had no effect on cell survival under glucose deprivation; acidosis alone can prolong cell survival time but is not as potent as lactic acidosis. Thus, the ability cancer cells to resist glucose deprivation-induced cell death is conferred, at least in part, by lactic acidosis, and we envision that disrupting the lacti acidosis may resume the sensitivity of cancer cells to glucose deprivation.

Krebs-Entstehung - AZIDOSE

- ☑ Hypoxie → HIF
- ☑ Umschaltung in Glykolyse → 8fach
- ☑ Lactazidose
- ☑ Zell-Zyklus-Arrest (6.8) → Zell-Tod (6.5) → KLONE
- ☑ Klone mit stabilem Phänotypus Dauer-Glykolyse egal welcher pH, Autophagie, Wachstums-Potential bei pH < 6.7
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- Hemmung der cytotoxischen T-Zellen
- Irreguläre Blutgefässe
- Epidermal-mesenchymale Transformation
- MMP Expression
- Metastasierung
- MDR, Chemo-Resistenz, Radio-Resistenz
- Tumor-Reversion
- Tumor-Stammzellen
- pH - Therapie

2004 – Konzept vollständig

- Hypoxie führt zur !!! Glykolyse → Lactat
- Azidose d. Mikro-Umgebung
- Selektiert aggressive Klone: Wachstum, Mobilität → Metastasierung

Nat Rev Cancer. 2004 Nov;4(11):891-9.

Why do cancers have high aerobic glycolysis?

Gatenby RA, Gillies RJ.

Department of Radiology, University of Arizona, Tucson, Arizona 85721, USA. rgatenby@radiology.arizona.edu

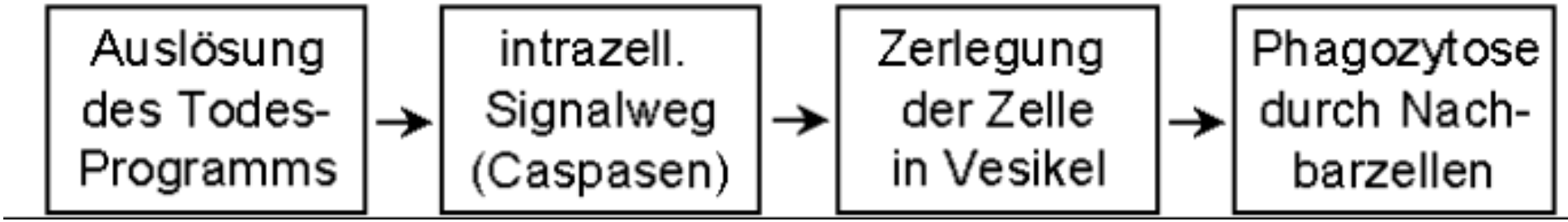
Abstract

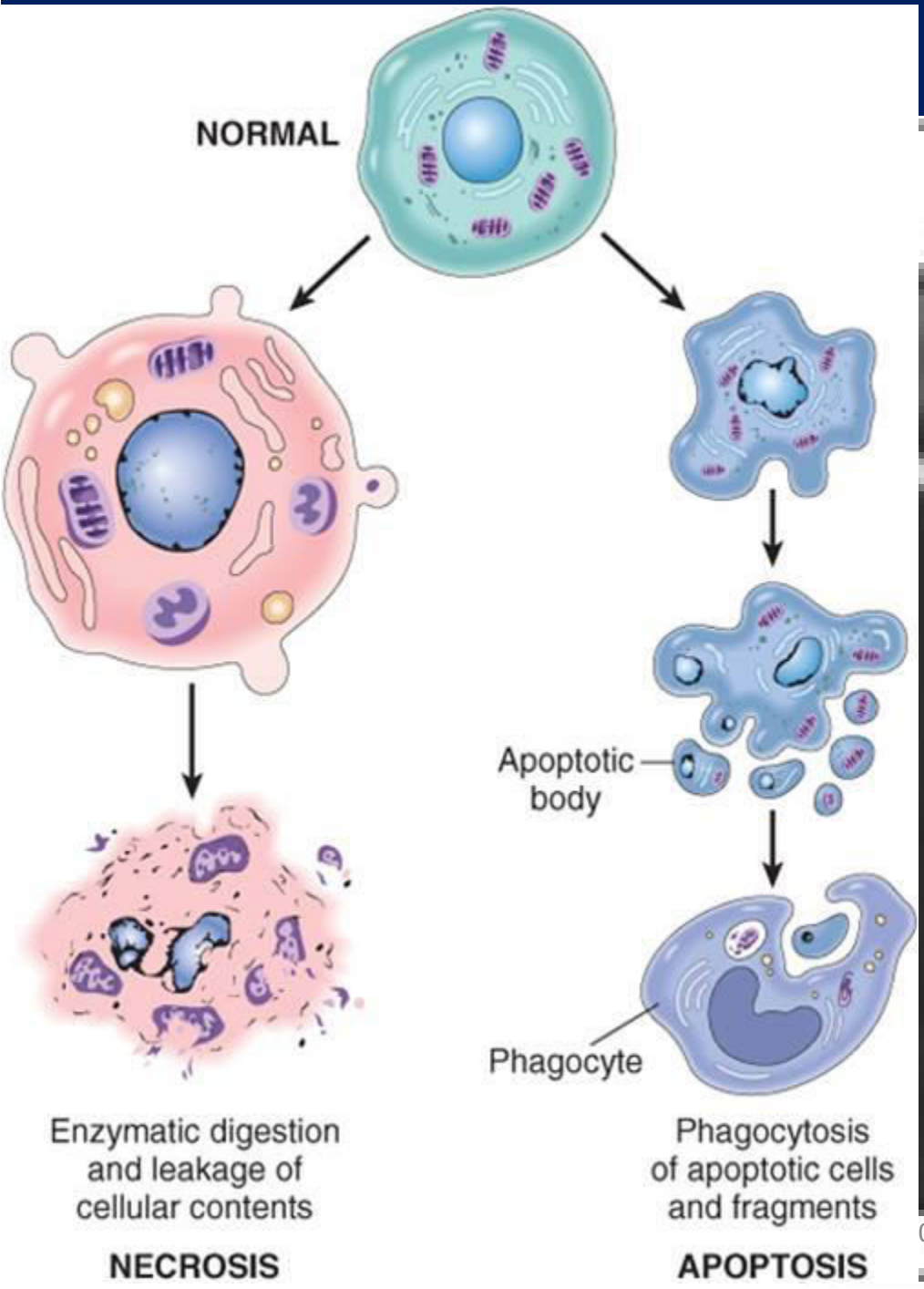
If carcinogenesis occurs by somatic evolution, then common components of the cancer phenotype result from active selection and must, therefore, confer a significant growth advantage. A near-universal property of primary and metastatic cancers is upregulation of glycolysis, resulting in increased glucose consumption, which can be observed with clinical tumour imaging. We propose that persistent metabolism of glucose to lactate even in aerobic conditions is an adaptation to intermittent hypoxia in pre-malignant lesions. However, upregulation of glycolysis leads to microenvironmental acidosis requiring evolution to phenotypes resistant to acid-induced cell toxicity. Subsequent cell populations with upregulated glycolysis and acid resistance have a powerful growth advantage, which promotes unconstrained proliferation and invasion.

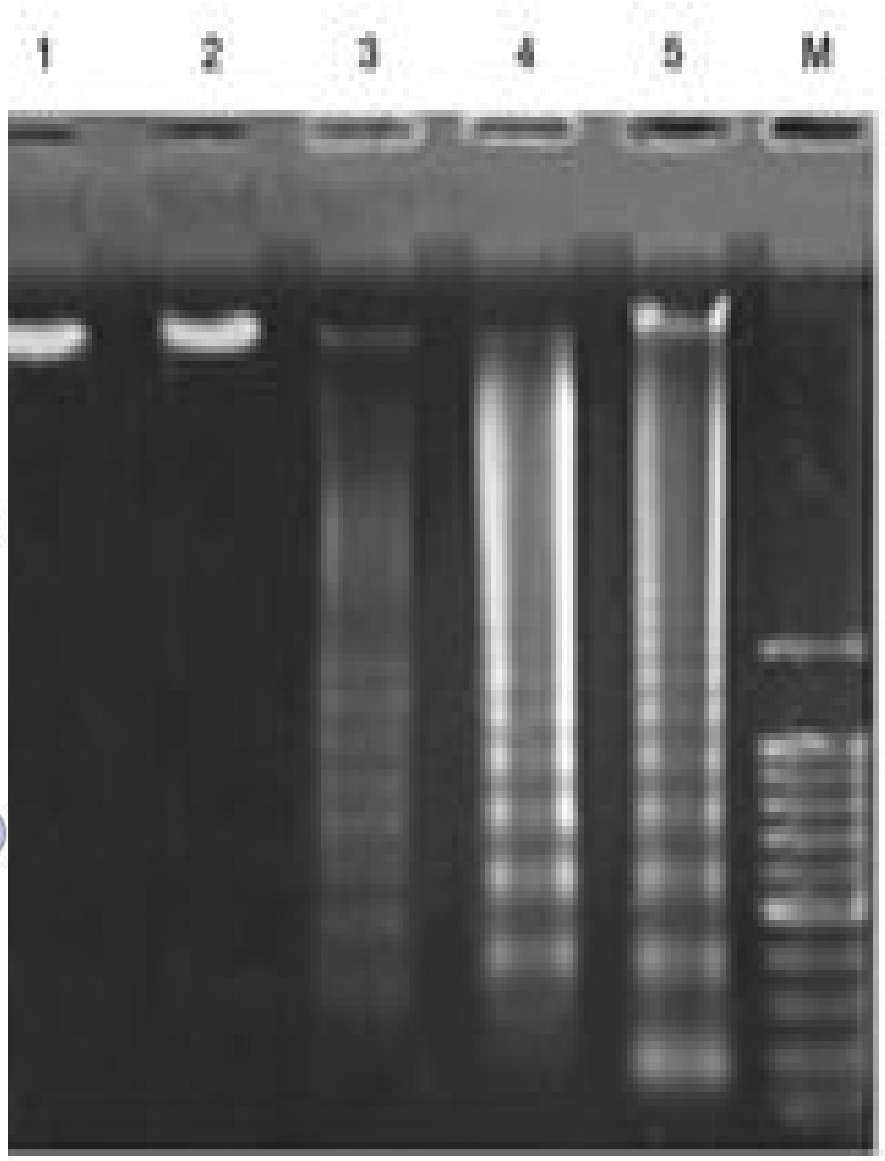
Apoptose – programmierter SM d Zelle

Apoptose: aktive Selbstzerstörung

betrifft: isolierte Einzelzelle




NORMAL
Apoptotic body
Phagocyte
Enzymatic digestion and leakage of cellular contents
NECROSIS
Phagocytosis of apoptotic cells and fragments
APOPTOSIS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Azidose blockiert direkt APOPTOSE

J Biol Chem. 2012 Aug 10;287(33):27863-75. doi: 10.1074/jbc.M112.384685. Epub 2012 Jun 8.

Acidosis promotes Bcl-2 family-mediated evasion of apoptosis: involvement of acid-sensing G protein-coupled receptor Gpr65 signaling to Mek/Erk.

Ryder C, McColl K, Zhong F, Distelhorst CW.

Department of Pharmacology, Case Western Reserve University School of Medicine, Case Comprehensive Cancer Center, and University Hospitals Case Medical Center, Cleveland, Ohio 44106, USA.

Abstract

Acidosis arises in solid and lymphoid malignancies secondary to altered nutrient supply and utilization. Tumor acidosis correlates with therapeutic resistance, although the mechanism behind this effect is not fully understood. Here we show that incubation of lymphoma cell lines in acidic conditions (pH 6.5) blocks apoptosis induced by multiple cytotoxic metabolic stresses, including deprivation of glucose or glutamine and treatment with dexamethasone. We sought to examine the role of the Bcl-2 family of apoptosis regulators in this process. Interestingly, we found that acidic

Krebs-Entstehung - AZIDOSE

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- Tumor-Stammzellen
- pH - Therapie

Sofortige Hemmung T-Zellen 2012

- **Zytotoxische T-Zellen** komplett blockiert durch **Lact-Azidose** im MicroEnv
- Funktionell, reversibel durch pH ↑

Int J Cancer. 2012 Aug 1;131(3):633-40. doi: 10.1002/ijc.26410. Epub 2011 Oct 5.

Tumor lactic acidosis suppresses CTL function by inhibition of p38 and JNK/c-Jun activation.

Mendler AN, Hu B, Prinz PU, Kreutz M, Gottfried E, Noessner E.

Helmholtz Zentrum München-Germany Research Center for Environmental Health, Institute of Molecular Immunology, Munich, Germany.

Abstract

Lactic acidosis is common to most solid tumors and has been found to affect infiltrating immune cells. Here we document effector phase inhibition of cytotoxic T cells (CTLs) involving complete blockage of cytokine production and partial impairment of lytic granule exocytosis. Lactic acidosis impaired TCR-triggered phosphorylation of JNK, c-Jun and p38, while not affecting MEK1 and ERK. The select targeting of signaling proteins involved in IFNγ production (JNK/c-Jun, p38) without affecting those jointly used in cytokine regulation and granule exocytosis (MEK1/ERK) explains the observed split effect of lactic acidosis on the CTL responses. CTL inhibition by lactic acidosis showed fast dynamics with immediate onset and reversion. Functional recovery by neutralizing the extracellular pH despite continuous presence of lactate holds promise that CTL activity can be improved in the milieu of solid tumors with appropriate anti-acidosis treatment, thereby increasing the efficacy of adoptive T cell therapy.

Dendritische Zellen aktiviert d Azidose

- Dendriten = „Meisterzellen d Immunsystems“
- Aktiviert durch Azidose

Crit Rev Immunol. 2004;24(5):363-84.

The impact of extracellular acidosis on dendritic cell function.

Vermeulen ME, Gamberale R, Trevani AS, Martínez D, Ceballos A, Sabatte J, Giordano M, Geffner JR.

Institute of Hematologic Research, National Academy of Medicine, Department of Microbiology, Buenos Aires University School of Medicine, Buenos Aires, Argentina.

Abstract

Dendritic cells (DCs) are the most efficient antigen-presenting cells. They are activated in the periphery by conserved pathogen molecules and by inflammatory mediators produced by a variety of cell types in response to danger signals. It is widely appreciated that inflammatory responses in peripheral tissues are usually associated with the development of acidic microenvironments. Surprisingly, there are relatively few studies directed to analyze the effect of extracellular acidosis on the immune response. We focus on the influence of extracellular acidosis on the function of immature DCs. The results presented here show that acidosis activates DCs. It increases the acquisition of extracellular antigens for MHC class I-restricted presentation and the ability of antigen-pulsed DCs to induce both specific CD8+ CTL and B-cell responses. These findings may have important implications to our understanding of the mechanisms through which DCs sense the presence of infection or inflammation in nonlymphoid tissues.

Krebs-Entstehung - AZIDOSE

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- MMP Expression
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- MDR, Chemo-Resistenz, Radio-Resistenz
- Tumor-Reversion
- Tumor-Stammzellen
- pH - Therapie

IL-8 – Motor der Angiogenese

- 2003: Azidose produziert IL-8
- IL-8 für Angiogenes zuständig

Clin Cancer Res. 2003 Jul;9(7):2786-97.

Nuclear factor-kappaB mediates angiogenesis and metastasis of human bladder cancer through the regulation of interleukin-8.

Karashima T, Sweeney P, Kamat A, Huang S, Kim SJ, Bar-Eli M, McConkey DJ, Dinney CP.

Departments of Cancer Biology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030, USA.

Abstract

PURPOSE: Interleukin (IL)-8 is an important mediator of angiogenesis, tumorigenicity, and metastasis in transitional cell carcinoma (TCC) of the bladder. Nuclear factor kappaB (NF-kappaB)/relA regulates IL-8 expression in several neoplasms. The purpose of this study was to determine whether the organ microenvironment (hypoxia, acidosis) regulates the expression of IL-8 in TCC via NF-kappaB, and whether inhibition of NF-kappaB function by mutant IkappaB-alpha prevents induction of IL-8 expression.

EXPERIMENTAL DESIGN: IL-8 mRNA expression and protein production by human TCC cell lines (UM-UC-14, HTB-9, RT-4, KU-7 and 253J B-V) were measured by Northern blot analysis and ELISA under acidic (pH 7.35-6.0) and hypoxic (1.0% O(2)) conditions. The involvement of NF-kappaB

Ovarial-Karzinom | IL-8 Achse

Oncol Res. 2000;12(2):97-106.

Interleukin 8: an autocrine growth factor for human ovarian cancer.

Xu L, Fidler IJ.

Department of Cancer Biology, The University of Texas M. D. Anderson Cancer Center, Houston 77030, USA.

Cancer Res. 2000 Aug 15;60(16):4610-6.

Acidic pH-induced elevation in interleukin 8 expression by human ovarian carcinoma cells

Xu L, Fidler IJ.

Department of Cancer Biology, The University of Texas M.D. Anderson Cancer Center, Houston 77030, USA.

Cancer Res. 1999 Nov 15;59(22):5822-9.

Hypoxia-induced elevation in interleukin-8 expression by human ovarian carcinoma cells.

Xu L, Xie K, Mukaida N, Matsushima K, Fidler IJ.

Department of Cancer Biology, The University of Texas M.D. Anderson Cancer Center, Houston 77030, USA.

IL-8 und Melanom - 1998

- Blutgefäss-Einsprossung
- MMP-Expression
- Invasiver & metastasierender
- Hypoxie

Pathobiology. 1999;67(1):12-8.

Role of interleukin-8 in tumor growth and metastasis of human melanoma.

Bar-Eli M.

Department of Cell Biology, The University of Texas M.D. Anderson Cancer Center, Houston, Tex. 77030, USA. mbareli@notes.mdacc.tmc.edu

IL-8 durch Anti-RNA §§§

Science News

Protein That Fue
Researchers

Feb. 28, 2008 — A pro
vessel growth worsens
production can be stifle
wrapped in a fatty nanop
by scientists at The Unive
Anderson Cancer Center
National Cancer Institute.

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IL-8 Wachstumsfaktor für OvCa

Übersäuerung treibt an,

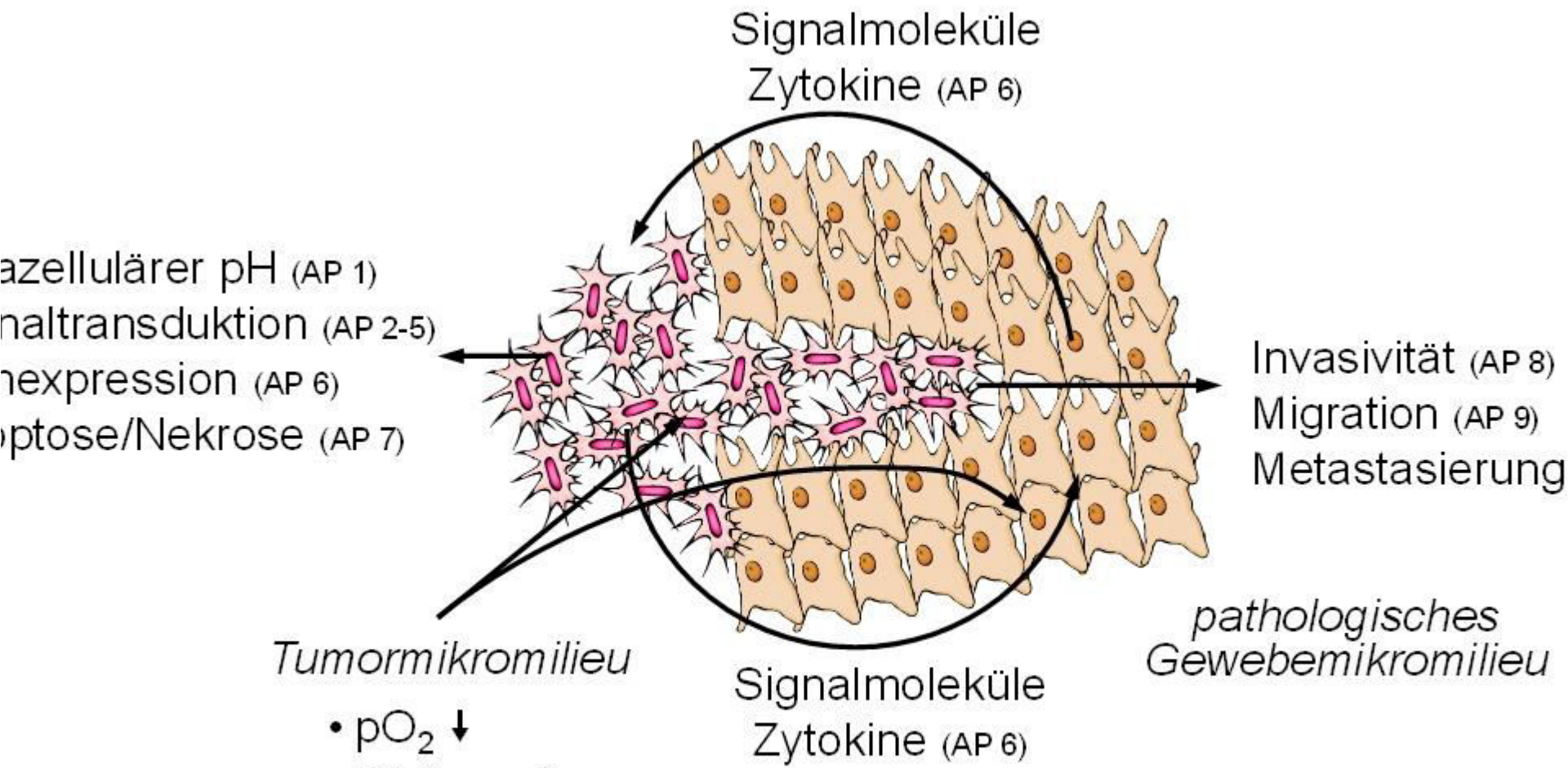
HYPOXIE aggr

Aktuell: Experimente mit Anti-Sense RNA

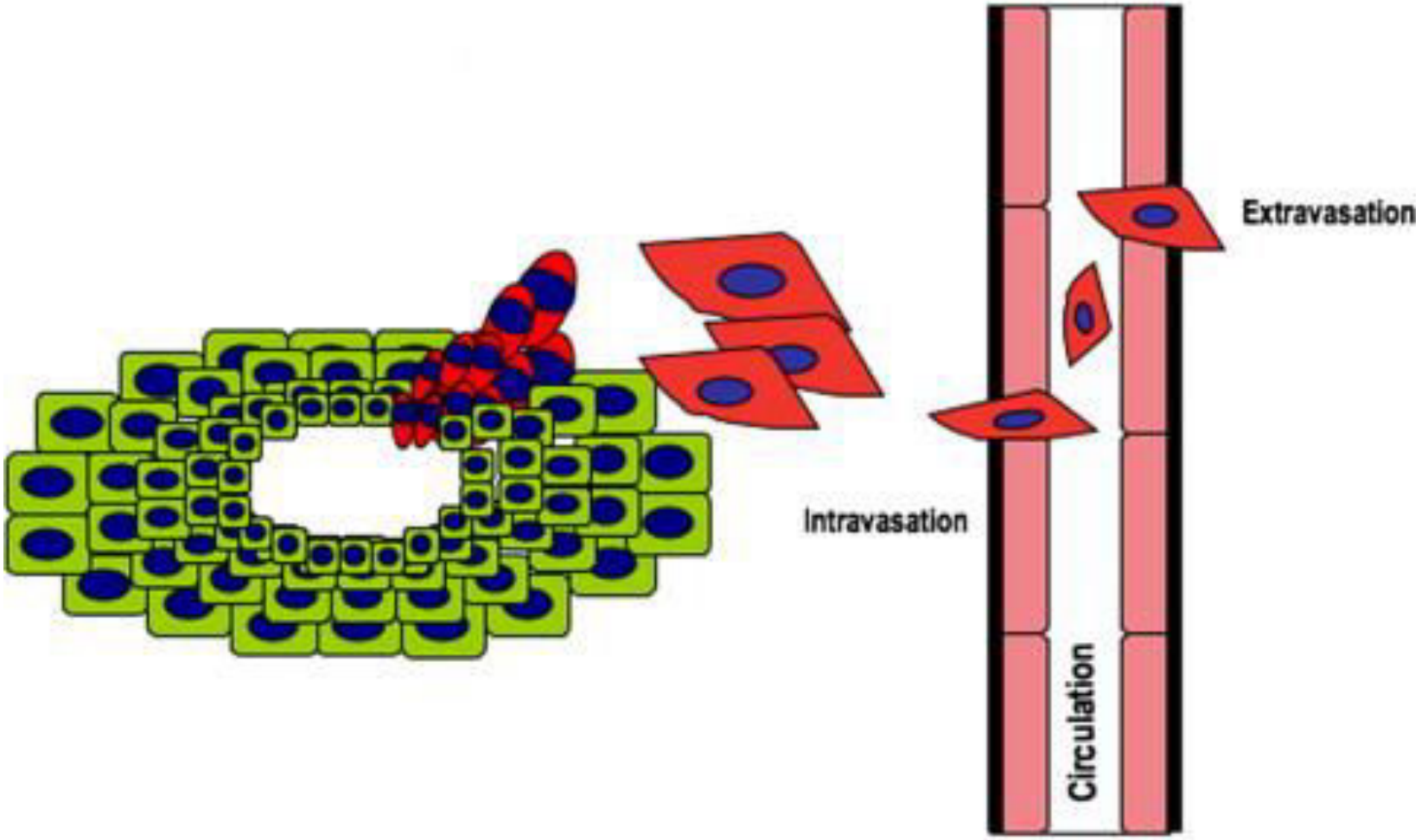
Krebs-Entstehung - AZIDOSE

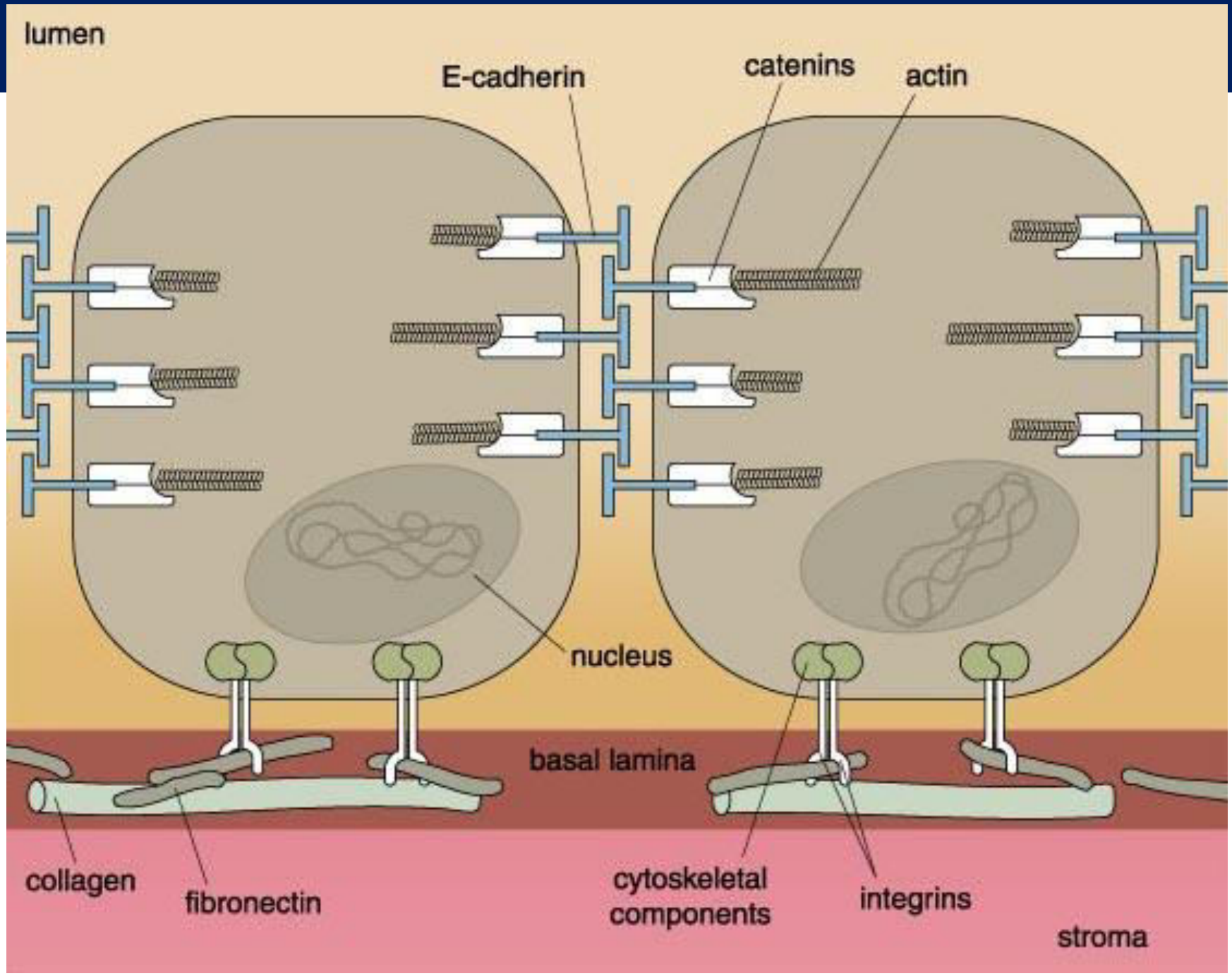
- ☑ Hypoxie → HIF
- ☑ Umschaltung in Glykolyse → 8fach
- ☑ Lactazidose
- ☑ Zell-Zyklus-Arrest (6.8) → Zell-Tod (6.5) → KLONE
- ☑ Klone mit stabilem Phänotypus Dauer-Glykolyse egal welcher pH, Autophagie, Wachstums-Potential bei pH < 6.7
- ☑ blockierte Apoptose
- ☑ Hemmung der cytotoxischen T-Zellen
- **☑ Irreguläre Blutgefässe – IL8**
- Epidermal-mesenchymale Transformation
- MMP Expression
- Metastasierung
- MDR, Chemo-Resistenz, Radio-Resistenz
- Tumor-Reversion
- Tumor-Stammzellen
- pH - Therapie

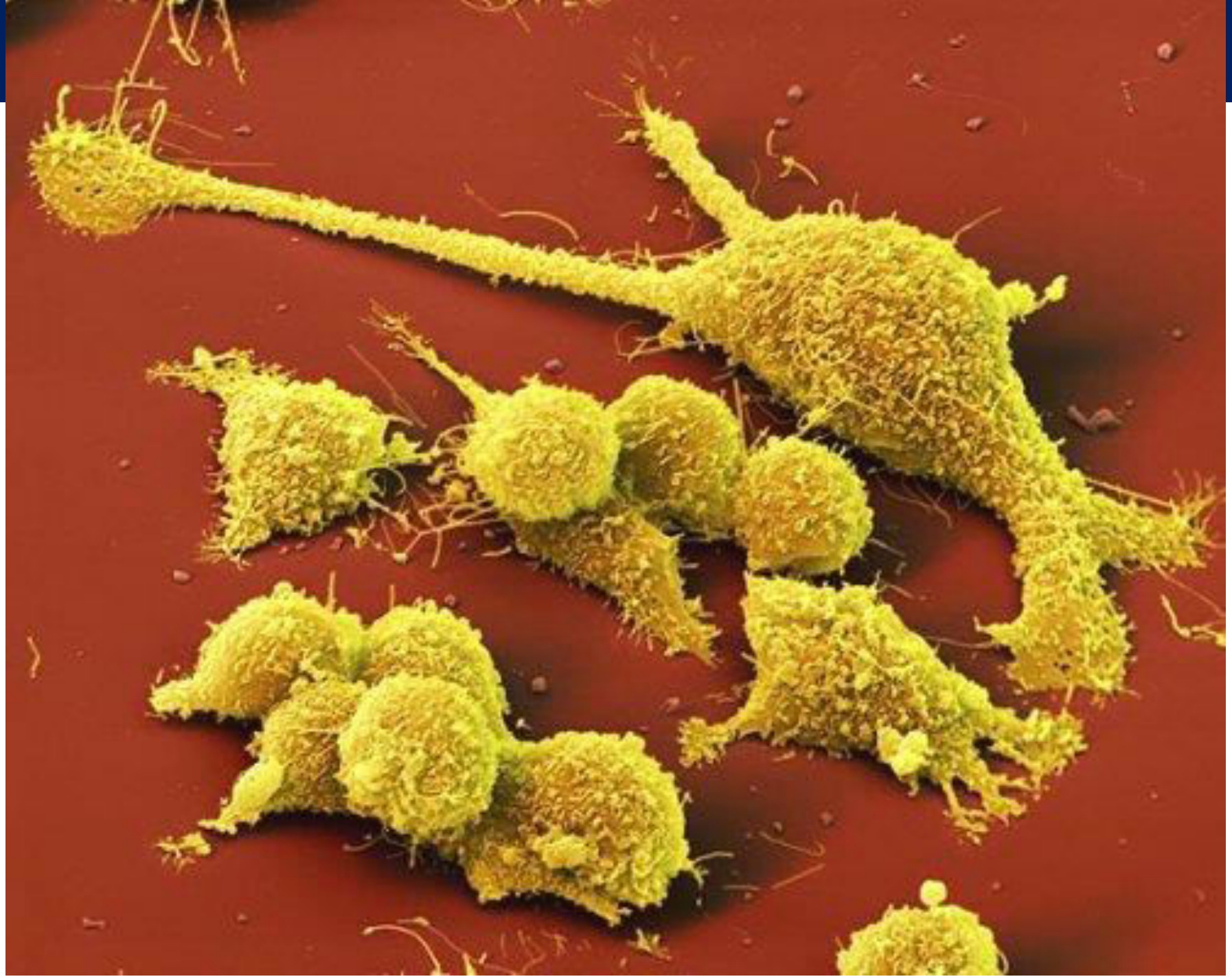
Krebs-Entstehung → Metastasen

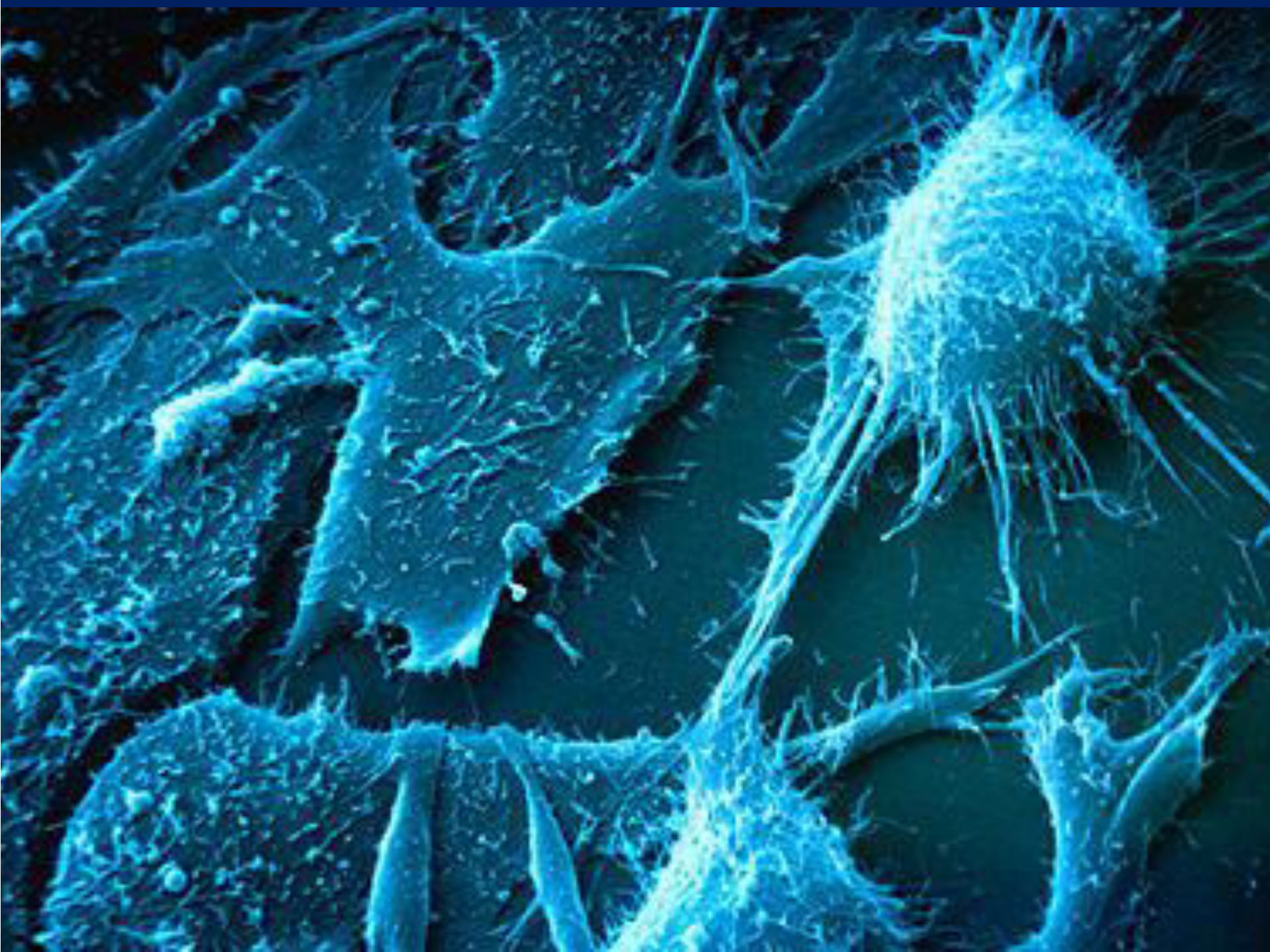


Epidermal-mesenchymal Transition




lumen
E-cadherin
catenins
actin
nucleus
basal lamina
collagen
fibronectin
cytoskeletal components
integrins
stroma





Carbanhydrase – Motor der EMT

- 85% geringeres Tu-Wachstum im Xeno-Transplantat durch Blockade der CarbAnhydrase
- Diese antagonisiert die Acidose und ermöglicht Tumor-Überleben

Cancer Res. 2009 Jan 1;69(1):358-68. doi: 10.1158/0008-5472.CAN-08-2470.

Hypoxia-inducible carbonic anhydrase IX and XII promote tumor cell growth by counteracting acidosis through the regulation of the intracellular pH.

Chiche J, Ilc K, Laferrière J, Trottier E, Dayan F, Mazure NM, Brahimi-Horn MC, Pouysségur J.

Institute of Developmental Biology and Cancer Research University of Nice, Centre National de la Recherche Scientifique UMR 6543, Centre A. Lacassagne, 33 Avenue Valombrose, Nice, France.

Abstract

Acidosis of the tumor microenvironment is typical of a malignant phenotype, particularly in hypoxic tumors. All cells express multiple isoforms of carbonic anhydrase (CA), enzymes catalyzing the reversible hydration of carbon dioxide into bicarbonate and protons. Tumor cells express membrane-bound CAIX and CAXII that are controlled via the hypoxia-inducible factor (HIF). Despite the recognition that tumor expression of HIF-1alpha and CAIX correlates with poor patient survival, the role of CAIX and CAXII in tumor growth is not fully resolved. To understand the advantage that tumor cells derive from expression of both CAIX and CAXII, we set up experiments to either force or invalidate the expression of these enzymes. In hypoxic LS174Tr tumor cells expressing either one or both CA isoforms, we show that (a) in response to a "CO(2) load," both CAs contribute to extracellular acidification and (b) both contribute to maintain a more alkaline resting intracellular pH (pH(i)), an action that preserves ATP levels and cell survival in a range of acidic outside pH (6.0-6.8) and low bicarbonate medium. In vivo experiments show that ca9 silencing alone leads to a 40% reduction in xenograft tumor volume with up-regulation of ca12 mRNA levels, whereas invalidation of both CAIX and CAXII gives an impressive 85% reduction. Thus, hypoxia-induced CAIX and CAXII are major tumor prosurvival pH(i)-regulating enzymes, and their combined targeting shows that they hold potential as anticancer targets.

Epidermal-mesenchymale-Transition

- Anoxie – Reoxigenierung → Faktor der EMT

Oncol Rep. 2013 Jun;29(6):2311-2317. doi: 10.3892/or.2013.2401. Epub 2013 Apr 10.

Anoxia/reoxygenation induces epithelial-mesenchymal transition in human colon cancer cell lines.

Okajima M, Kokura S, Ishikawa T, Mizushima K, Tsuchiya R, Matsuyama T, Adachi S, Okayama T, Sakamoto N, Kamada K, Katada K, Uchiyama K, Handa O, Takagi T, Yagi N, Naito Y, Yoshikawa T.

Department of Molecular Gastroenterology and Hepatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto 602-8566, Japan.

Abstract

Epithelial-mesenchymal transition (EMT) is considered to be a crucial event in the development of cancer metastasis. Anoxia/reoxygenation (A/R) is known to occur in cancer tissues due to angiogenesis and changes in tissue pressure that occur during tumor growth. We investigated whether A/R induces EMT in the human colon cancer cell line HT-29. Colon cancer cells were exposed to anoxia (2 h) followed by reoxygenation (4-22 h) and evaluated for EMT changes using immunofluorescence and western blot analyses. We also investigated the expression of EMT-related transcription factors (Snail and ZEB1) using RT-PCR and evaluated the expression of NF-κB using ELISA. To determine whether NF-κB is involved in A/R-induced EMT, HT-29 cells were treated with proteasome inhibitors. Colon cancer cells exposed to A/R underwent EMT morphological changes; the cancer cells acquired a spindle-shaped phenotype. The expression of E-cadherin on the cell surface and the total amount of E-cadherin proteins were

1996 - Melanom wird aggressiv durch dauerhafte Zellkulturbedingung pH 6.8

- nur kultivieren bei pH 6.8 → aggressiv
- Kultivieren bei pH 7.4 dann 6.8 → nicht aggr.

Clin Exp Metastasis. 1996 Mar;14(2):176-86.

Acidic pH enhances the invasive behavior of human melanoma cells.

Martínez-Zaguilán R, Seftor EA, Seftor RE, Chu YW, Gillies RJ, Hendrix MJ.

Department of Biochemistry, University of Arizona Health Sciences Center, Tucson, USA.

Abstract

As a consequence of poor perfusion and elevated acid production, the extracellular pH (pHex) of tumors is generally acidic. Despite this, most in vitro experiments are still performed at the relatively alkaline pHex of 7.4. This is significant, because slight changes in pHex can have profound effects on cell phenotype. In this study we examined the effects of mildly acidic conditions on the in vitro invasive potential of two human melanoma cell lines; the highly invasive C8161, and poorly invasive A375P. We observed that culturing of either cell line at acidic pH (6.8) caused dramatic increases in both migration and invasion, as measured with the Membrane Invasion Culture System (MICS). This was not due to a direct effect of pH on the invasive machinery, since cells cultured at normal pH (7.4) and tested at acidic pH did not exhibit increased invasive potential. Similarly, cells cultured at acidic pH were more aggressive than control cells when tested at the same medium pH. These data indicate that culturing of cells at mildly acidic pH induces

Epidermal-mesenchymale Transformation durch Azidose

J Urol. 2012 Aug;188(2):624-31. doi: 10.1016/j.juro.2012.03.113. Epub 2012 Jun 15.

Systemic buffers inhibit carcinogenesis in TRAMP mice.

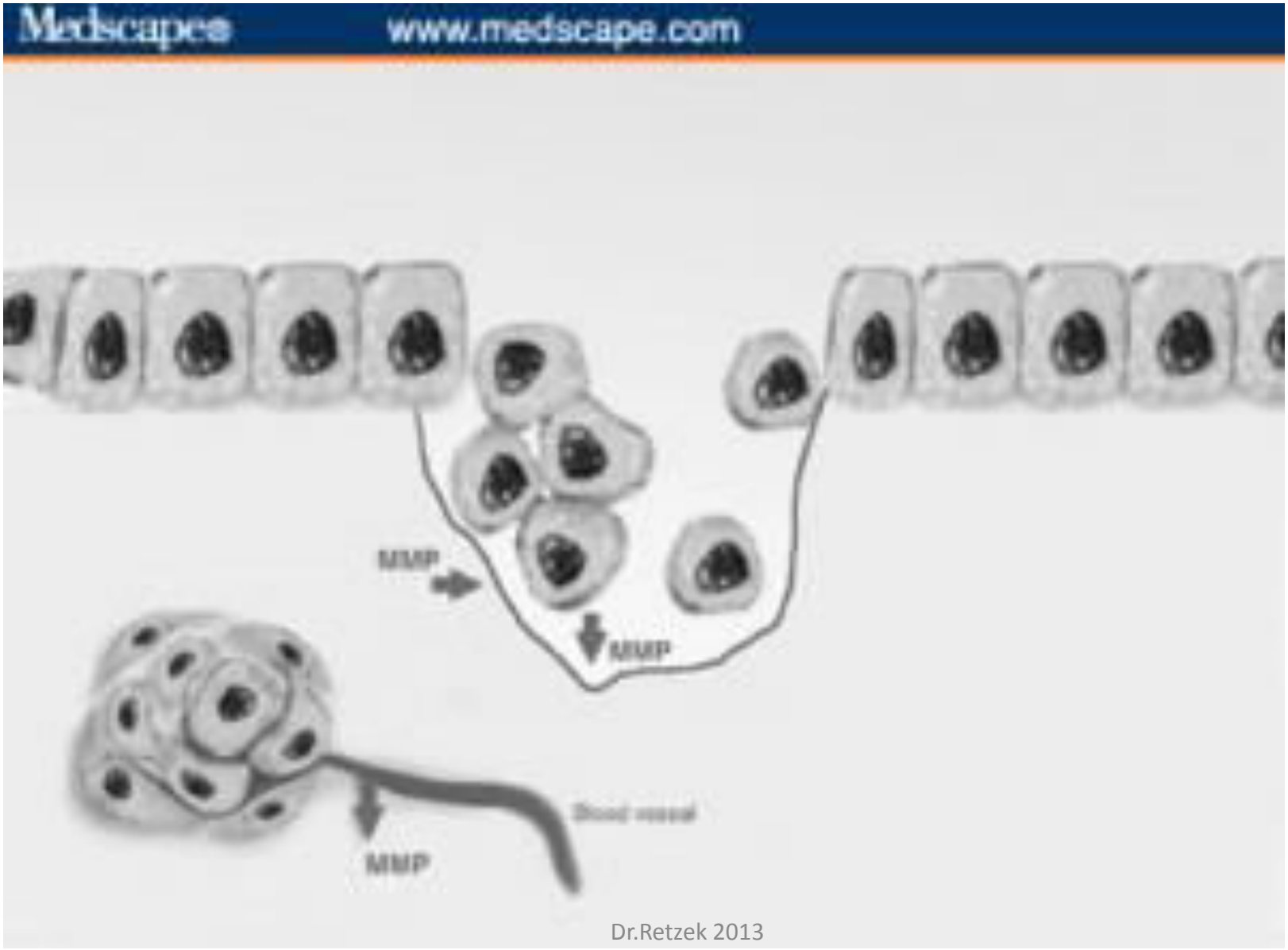
Ibrahim-Hashim A, Cornnell HH, Abrahams D, Lloyd M, Bui M, Gillies RJ, Gatenby RA.

Department of Radiology, H. Lee Moffitt Cancer Center, Tampa, Florida 33612, USA.

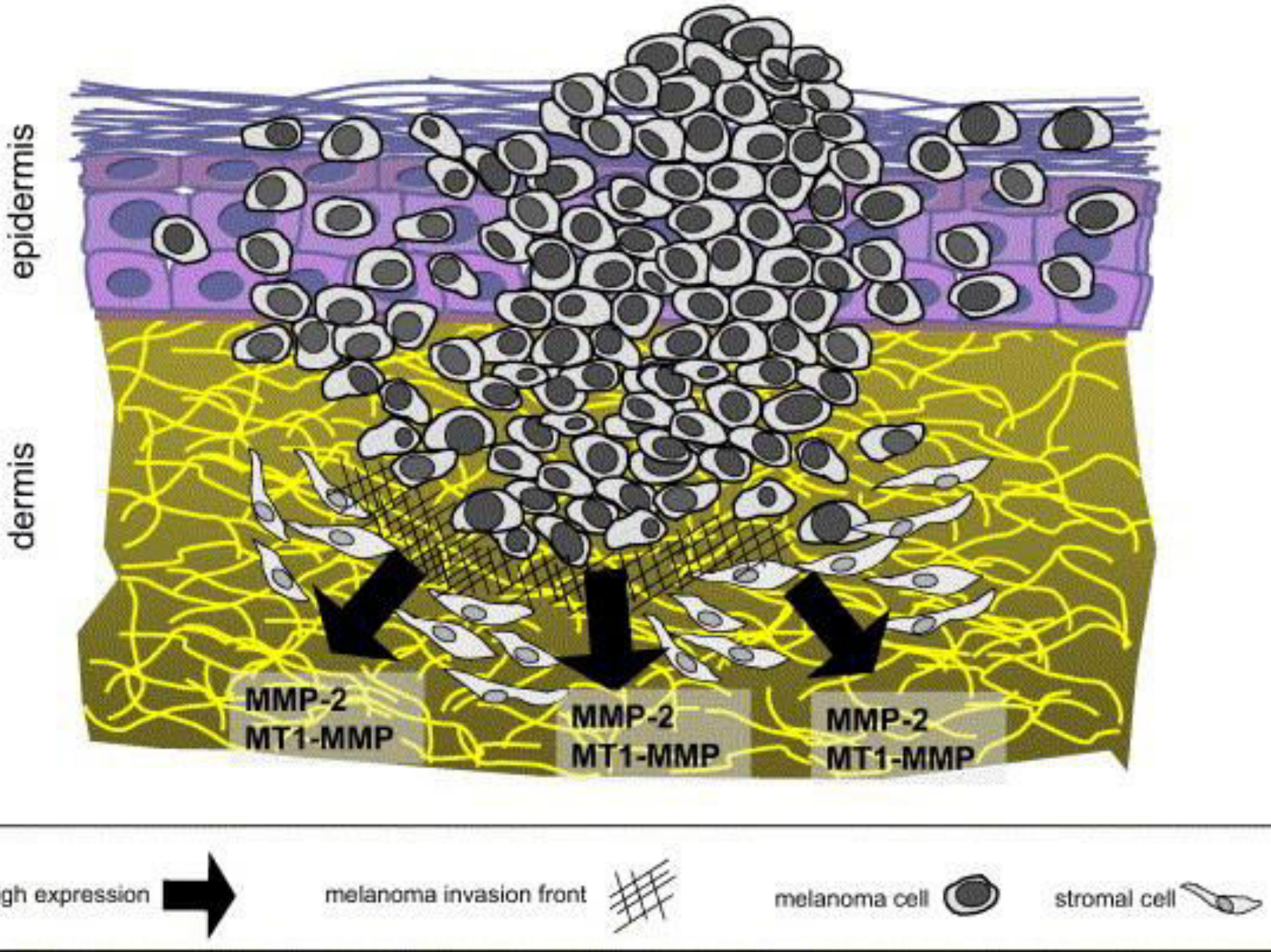
Abstract

PURPOSE: Hypoxia and acidosis develop in in situ tumors as cellular expansion increases the diffusion distance of substrates and metabolites from blood vessels deep to the basement membrane. Prior studies of breast and cervical cancer revealed that cellular adaptation to microenvironmental hypoxia and acidosis is associated with the transition from in situ to invasive cancer. We hypothesized that decreased acidosis in intraductal tumors would alter environmental selection pressures for acid adapted phenotypes and delay or prevent evolution to invasive cancer.

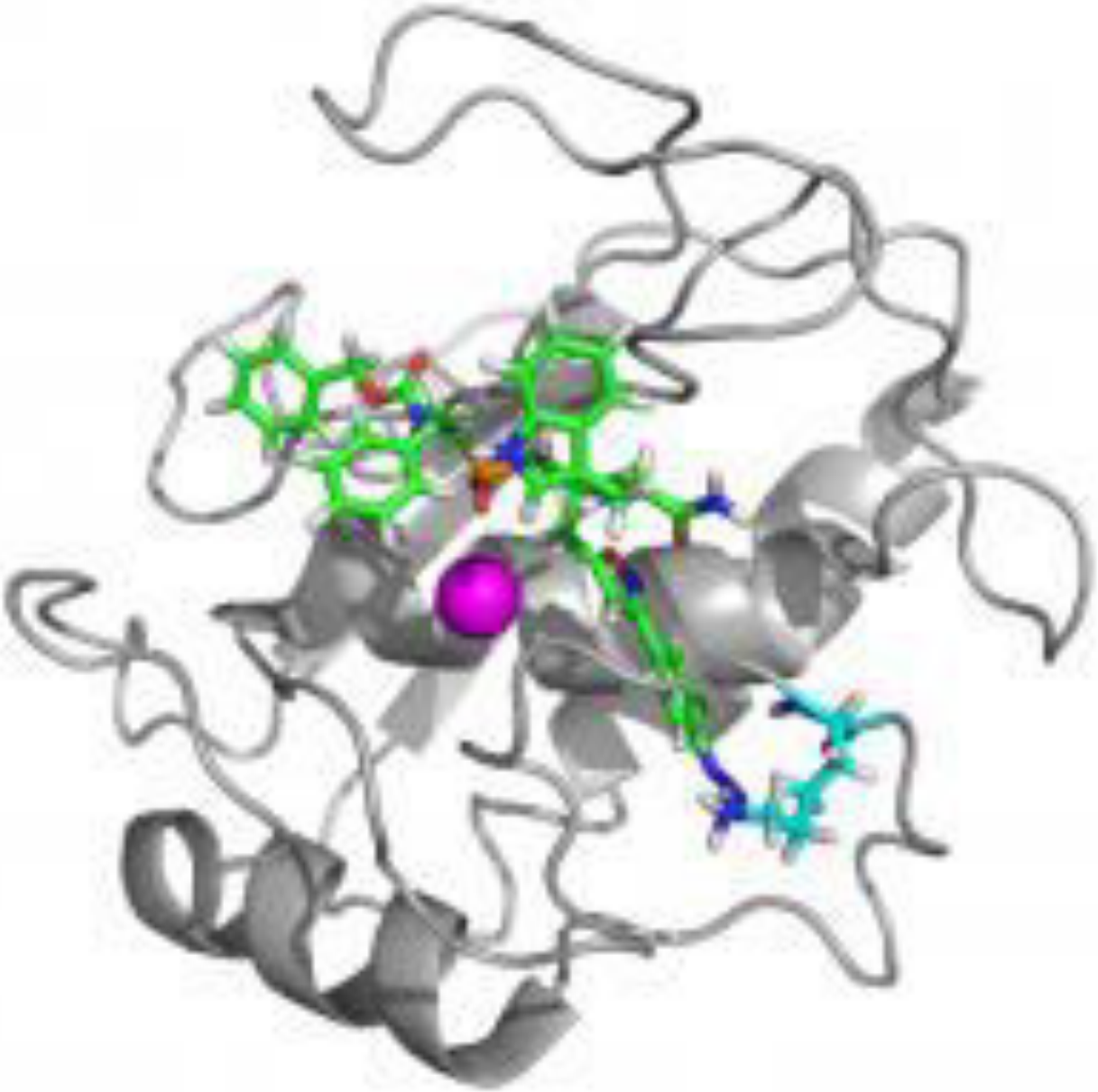
MMP als Motoren der Metastasierung



Invasive primary melanoma



MMP – Kollagenasen / Gelatinasen



Cranberry hemmt MMP in PCa

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J Cell Biochem. 2010 Oct 15;111(3):742-54. doi: 10.1002/jcb.22761.

Proanthocyanidins from the American Cranberry (Vaccinium macrocarpon) inhibit matrix metalloproteinase-2 and matrix metalloproteinase-9 activity in human prostate cancer cells via alterations in multiple cellular signalling pathways.

Déziel BA, Patel K, Neto C, Gottschall-Pass K, Hurta RA.

Department of Biology, University of Prince Edward Island, Prince Edward Island, Canada.

Abstract

Prostate cancer is one of the most common cancers in the Western world, and it is believed that an individual's diet affects his risk of developing cancer. There has been an interest in examining phytochemicals, the secondary metabolites of plants, in order to determine their potential anti-cancer activities in vitro and in vivo. In this study we document the effects of proanthocyanidins (PACs) from the American

Plasma matrix metalloproteinase (**MMP**)-9 levels are reduced following low-calorie supplementation in men.

Ruel G, Pomerleau S, Couture P, Lemieux S, Lamarche B, Couillard C.

J Am Coll Nutr. 2009 Dec;28(6):694-701.

PMID: 20516270 [PubMed - indexed for MEDLINE] **Free Article**

Related citations

Cranberry proanthocyanidins inhibit **MMP** production and activity.

La VD, Howell AB, Grenier D.

J Dent Res. 2009 Jul;88(7):627-32. doi: 10.1177/0022034509339487.

PMID: 19641150 [PubMed - indexed for MEDLINE]

Related citations

Inhibition of host extracellular matrix destructive enzyme production and activity by molecular-weight **cranberry** fraction.

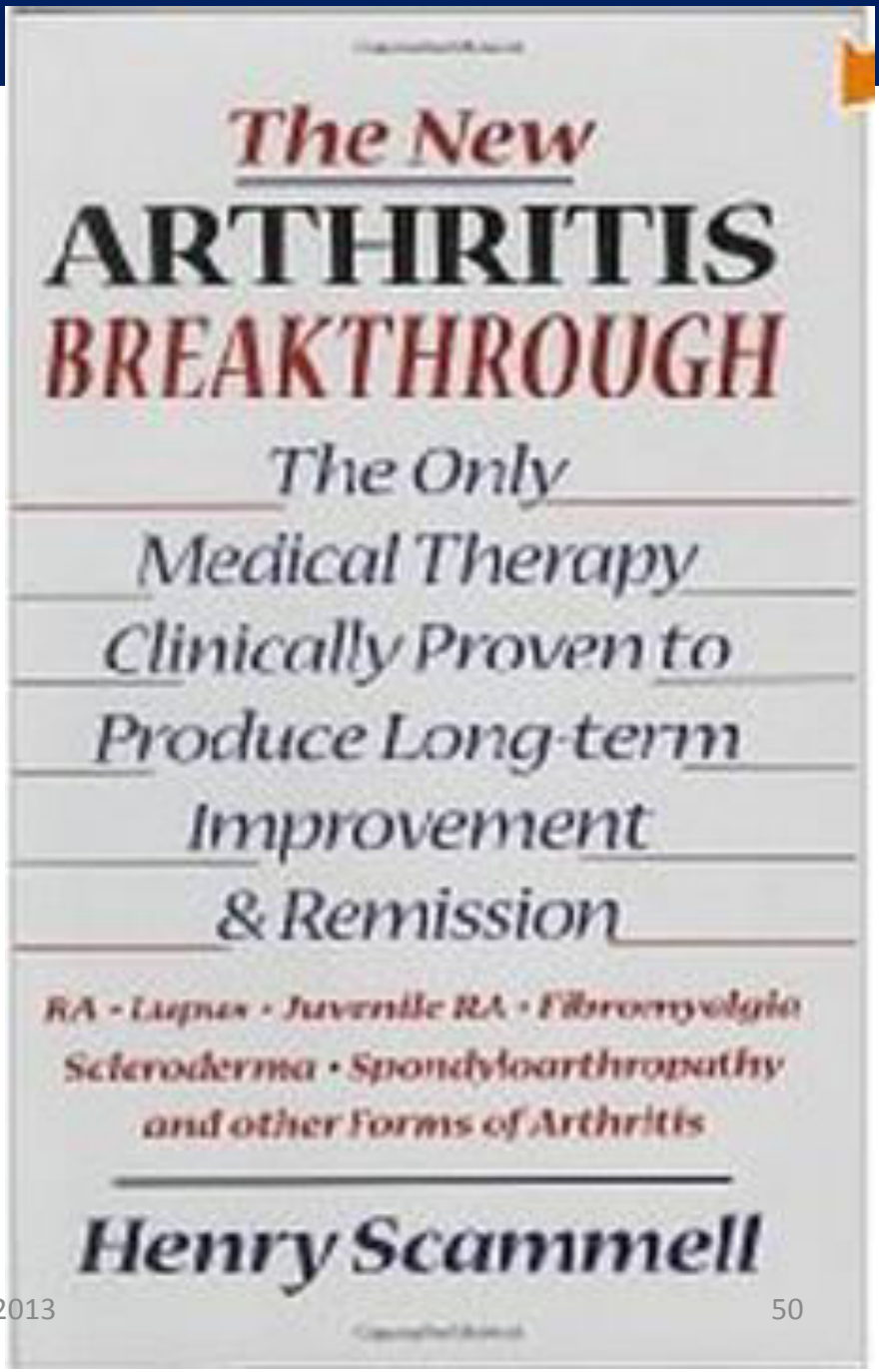
Bodet C, Chandad F, Grenier D.

J Periodontal Res. 2007 Apr;42(2):159-68.

PMID: 17305875 [PubMed - indexed for MEDLINE]

Related citations

MMP Hemmung


The New
ARTHRITIS
BREAKTHROUGH
The Only
Medical Therapy
Clinically Proven to
Produce Long-term
Improvement
& Remission
RA · Lupus · Juvenile RA · Fibromyalgia
Scleroderma · Spondyloarthropathy
and other Forms of Arthritis
Henry Scammell

Carbanhydrase

- CarbAnhydratase → induziert durch HIF / Hypoxie
- Reguliert MicroEnvir im Tumor
- AKTIV beteiligt bei **Epidermal-mesenchymal-Transition** und **MOTILITÄT**

Cell Adh Migr. 2013 Mar-Apr;7(2):226-31. doi: 10.4161/cam.23257. Epub 2013 Jan 9.

Carbonic anhydrase IX: a hypoxia-controlled "catalyst" of cell migration.

Svastova E, Pastorekova S.

Department of Molecular Medicine, Institute of Virology, Slovak Academy of Sciences, Bratislava, Slovak Republic.

Abstract

Cell migration can be principally viewed as a chain of well-orchestrated morphological events that lead to dynamic reshaping of the cell body. However, behind the scene of such a "morphological theater" there are very complex, interrelated molecular and physiological processes that drive the cell movement. Among them, ion transport and pH regulation play a key role, with carbonic anhydrase IX (CA IX) emerging as one of the important "molecular actors." CA IX is a highly active cell surface enzyme expressed in a broad range of solid tumors in response to hypoxia and explored as a clinically useful biomarker of hypoxia and as a therapeutic target. Its biological role is to protect tumor cells from hypoxia and acidosis in the tumor microenvironment. The study published recently by our group showed that CA IX actively contributes to cell migration and invasion. For the first time, we demonstrated CA IX accumulation in lamellipodia of migrating cells and its direct in situ interaction with bicarbonate transporters. Our findings indicate that tumor cells need CA IX not only as a pro-survival factor in hypoxia and acidosis, but also as a pro-migratory component of the cellular apparatus driving epithelial-mesenchymal transition.

Glioblastom – erst in Azidose aggressiv

Oncogene. 2009 Jan 8;28(1):9-19. doi: 10.1038/onc.2008.355. Epub 2008 Sep 22.

Promotion of glioma cell survival by acyl-CoA synthetase 5 under extracellular acidosis conditions.

Mashima T, Sato S, Sugimoto Y, Tsuruo T, Seimiya H.

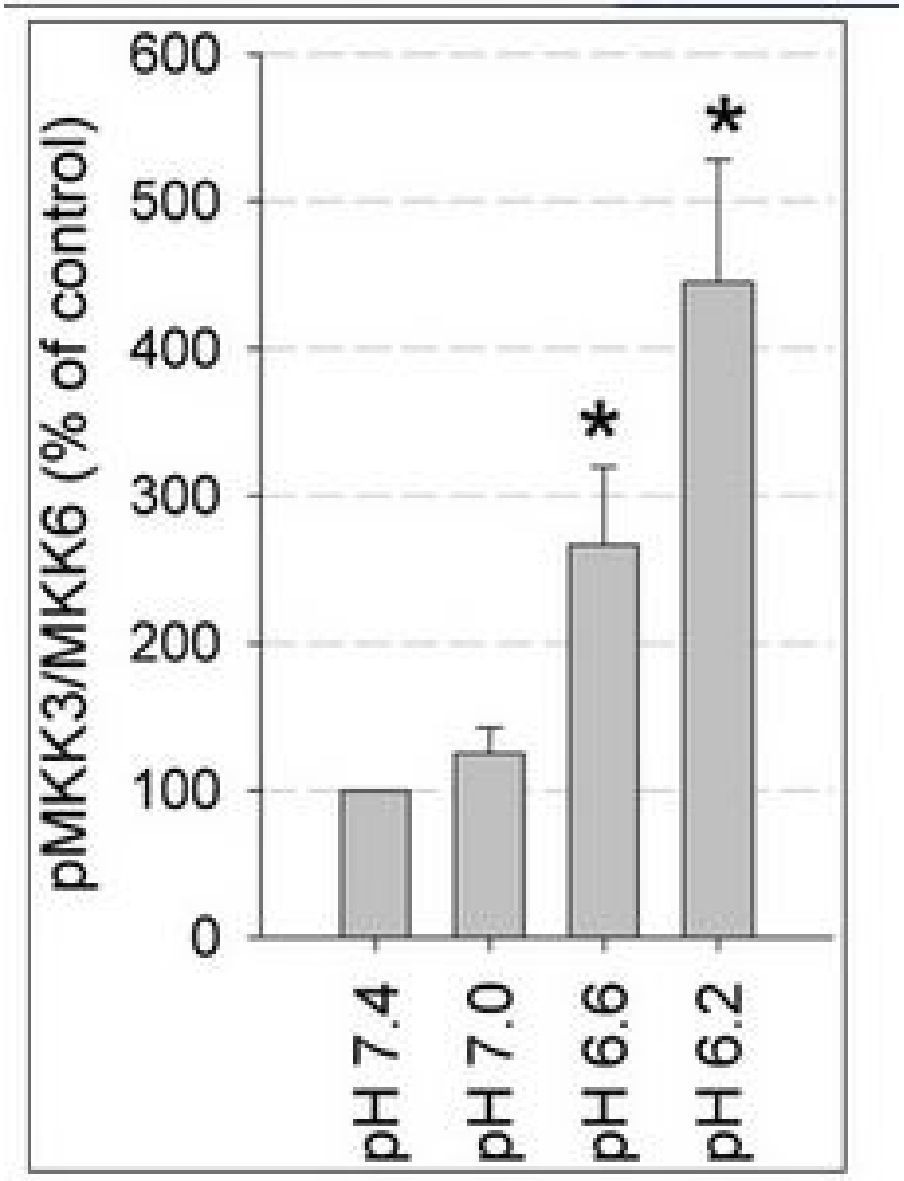
Division of Molecular Biotherapy, Cancer Chemotherapy Center, Japanese Foundation for Cancer Research, Tokyo, Japan.

Abstract

Extracellular acidosis (low pH) is a tumor microenvironmental stressor that has a critical function in the malignant progression and metastatic dissemination of tumors. To survive under stress conditions, tumor cells must evolve resistance to stress-induced toxicity. Acyl-CoA synthetase 5 (ACSL5) is a member of the ACS family, which converts fatty acid to acyl-CoA. ACSL5 is frequently overexpressed in malignant glioma, whereas its functional significance is still unknown. Using retrovirus-mediated stable gene transfer (gain of function) and small interfering RNA-mediated gene silencing (loss of function), we show here that ACSL5 selectively promotes human glioma cell survival under extracellular acidosis. ACSL5 enhanced cell survival through its ACS catalytic activity. To clarify the genome-wide changes in cell signaling pathways by ACSL5, we performed cDNA microarray analysis and identified an ACSL5-dependent gene expression signature. The analysis revealed that ACSL5 was critical to the expression of tumor-related factors including midkine (MDK), a heparin-binding growth factor frequently overexpressed in cancer. Knockdown of MDK expression significantly attenuated ACSL5-mediated survival under acidic state. These results indicate that ACSL5 is a critical factor for survival of glioma cells under acidic tumor microenvironment, thus providing novel molecular basis for cancer therapy.

PMID: 18806831 [PubMed - indexed for MEDLINE]

Azidose ↑↑ Tu-Wachstum



PLoS One. 2011;6(7):e22445. doi: 10.1371/journal.pone.0022445. Epub 2011 Jul 26.

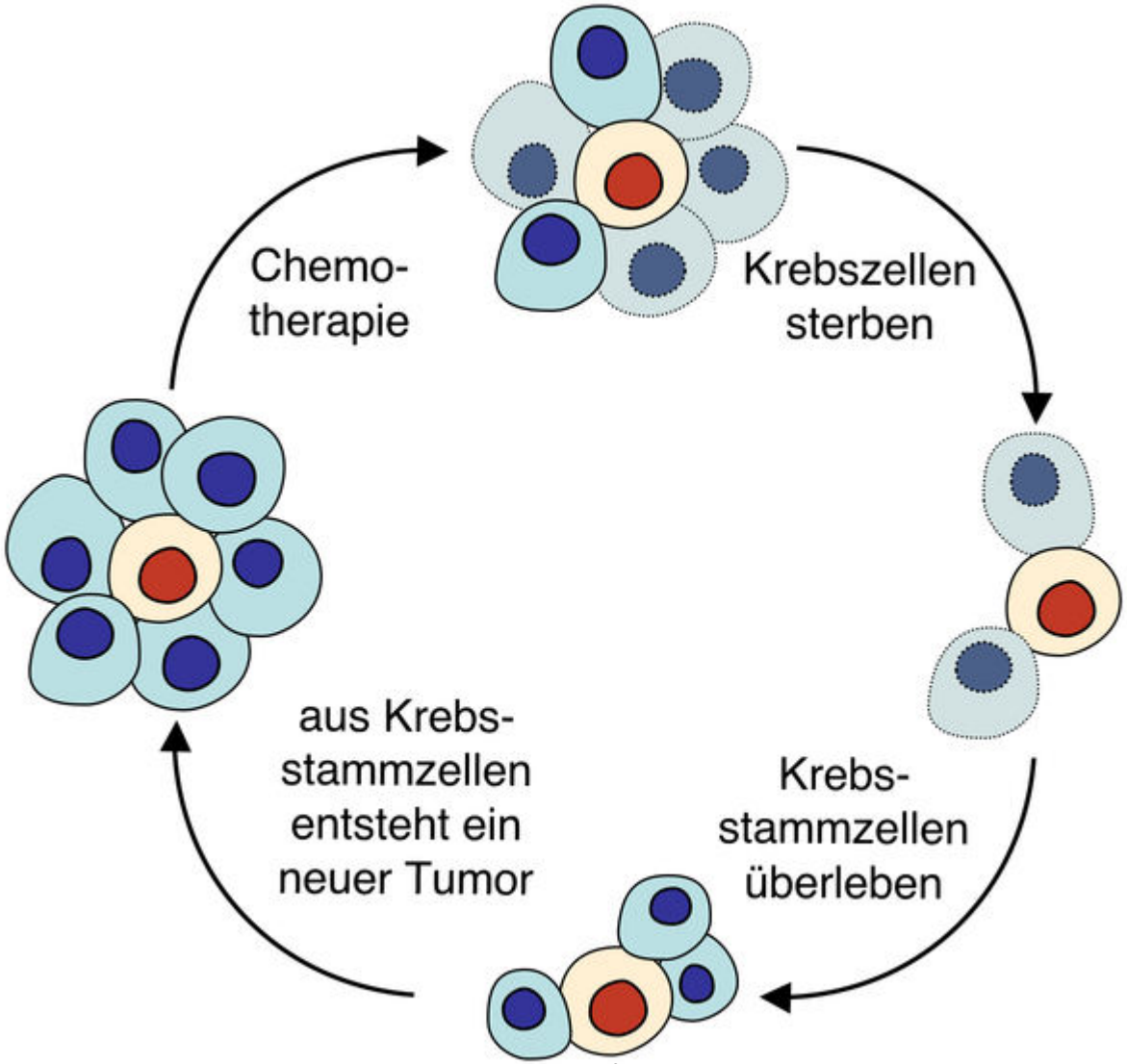
Acidic environment leads to ROS-induced MAPK signaling in cancer cells.

Riemann A, Schneider B, Ihling A, Nowak M, Sauvant C, Thews O, Gekle M.
Julius-Bernstein-Institut für Physiologie der Universität Halle-Wittenberg, Halle, Germany.

Krebs-Entstehung - AZIDOSE

- ☑ Hypoxie → HIF
- ☑ Umschaltung in Glykolyse → 8fach
- ☑ Lactazidose
- ☑ Zell-Zyklus-Arrest (6.8) → Zell-Tod (6.5) → KLONE
- ☑ Klone mit stabilem Phänotypus Dauer-Glykolyse egal welcher pH, Autophagie, Wachstums-Potential bei pH < 6.7
- ☑ blockierte Apoptose
- ☑ Hemmung der cytotoxischen T-Zellen
- ☑ Irreguläre Blutgefässe – IL8
- ☑ **Epidermal-mesenchymale Transformation**
- ☑ **MMP Expression**
- ☑ **Metastasierung**
- MDR, Chemo-Resistenz, Radio-Resistenz
- Tumor-Reversion
- Tumor-Stammzellen
- pH - Therapie

Krebs-Stammzellen | Chemoresistent



Chemo-Resistenz

- Extrazelluläre **Acidose verursacht die Chemo-Resistenz**

Hypoxia-induced extracellular **acidosis** increases p-glycoprotein activity and chemoresistance in tumors in vivo via p38 signaling pathway.

Thews O, Nowak M, Sauvant C, Gekle M.

Adv Exp Med Biol. 2011;701:115-22. doi: 10.1007/978-1-4419-7756-4_16.

PMID: 21445777 [PubMed - indexed for MEDLINE]

Related citations

MicroEnv als Quelle Resistenz

- **… Brustkrebs hypoxisch und der gestörte Metabolismus führt zu Resistenz gegen Bestrahlung und Chemo …..**

Cancer Treat Rev. 2013 Apr;39(2):171-9. doi: 10.1016/j.ctrv.2012.08.004. Epub 2012 Oct 12.

New strategies for targeting the hypoxic tumour microenvironment in breast cancer.

Ward C, Langdon SP, Mullen P, Harris AL, Harrison DJ, Supuran CT, Kunkler IH.

Breakthrough Breast Unit and Division of Pathology, Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK. cward@staffmail.ed.ac.uk

Abstract

Radiation and drug resistance remain major challenges and causes of mortality in the treatment of locally advanced, recurrent and metastatic breast cancer. Metabolic reprogramming is a recently recognised hallmark of cancer with the hypoxic acidic extracellular environment as a major driver of invasion and metastases. Nearly 40% of all breast cancers and 50% of locally advanced breast cancers are hypoxic and their altered metabolism is strongly linked to resistance to radiotherapy and systemic therapy. The dependence of metabolically adapted breast cancer cells on alterations in cell function presents a wide range of new therapeutic targets such as carbonic anhydrase IX (CAIX). This review highlights preclinical approaches to evaluating an array of targets against tumour metabolism in breast cancer and early phase clinical studies on efficacy.

Adv Pharmacol. 2012;65:63-107. doi: 10.1016/B978-0-12-397927-8.00004-X.

Targeting the metabolic microenvironment of tumors.

Bailey KM, Wojtkowiak JW, Hashim AI, Gillies RJ.

Department of Imaging and Metabolism, H. Lee Moffitt Cancer Center, Tampa, FL, USA.

Glioblastom Stammzelle durch Azidose

- UNABHÄNGIG von HIF / Hypoxie
- Nur durch Acidose
- Aktivierung der Gliom-Stammzellen in Glioblastom-Zellen

Cell Death Differ. 2011 May;18(5):829-40. doi: 10.1038/cdd.2010.150. Epub 2010 Dec 3.

Acidic stress promotes a glioma stem cell phenotype.

Hjelmeland AB, Wu Q, Heddleston JM, Choudhary GS, MacSwords J, Lathia JD, McLendon R, Lindner D, Sloan A, Rich JN.

Departments of Stem Cell Biology and Regenerative Medicine, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA. hjelmea@ccf.org

Abstract

Malignant gliomas are lethal cancers that display cellular hierarchies with cancer stem cells at the apex. Glioma stem cells (GSCs) are not uniformly distributed, but rather located in specialized niches, suggesting that the cancer stem cell phenotype is regulated by the tumor microenvironment. Indeed, recent studies show that hypoxia and its molecular responses regulate cancer stem cell maintenance. We now demonstrate that acidic conditions, independent of restricted oxygen, promote the expression of GSC markers, self-renewal and tumor growth. GSCs exert paracrine effects on tumor growth through elaboration of angiogenic factors, and low pH conditions augment this expression associated with induction of hypoxia inducible factor 2α (HIF2α), a GSC-specific regulator. Induction of HIF2α and other GSC markers by acidic stress can be reverted by elevating pH in vitro, suggesting that raising intratumoral pH may be beneficial for targeting the GSC phenotype. Together, our results suggest that exposure to low pH promotes malignancy through the induction of a cancer stem cell phenotype, and that culturing cancer cells at lower pH reflective of endogenous tumor conditions may better retain the cellular heterogeneity found in tumors.

Je Laktazidotischer – desto Metastasen

- Je mehr Laktazidose im Tumor
- desto mehr Metastasen
- desto schlechter die Kaplan-Meier - Überlebenskurve

Nuklearmedizin. 2010;49 Suppl 1:S16-20.

[Metabolic micromilieu in tumours].

[Article in German]
Mueller-Klieser W.

Institut für Physiologie und Pathophysiologie, Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Duesbergweg 6, 55128 Mainz. mue-kli@uni-mainz.de

Abstract

Solid malignant tumours are characterized by a heterogeneous metabolic micromilieu with the intra-individual variability within single tumours being substantially smaller than the inter-individual differences between tumours. Despite this variability, there are some hallmarks which are characteristic for the majority of malignancies. They include hypoxia, tissue acidosis, and abnormal microcirculation. Peculiarities of the carbohydrate metabolism and specifically of glycolysis in tumours receive increasing attention in experimental and clinical research. As shown by our research with induced bioluminescence, different tumours from various entities exhibit a large spectrum of lactate accumulation. Interestingly, primary lesions with metastasis contain significantly higher amounts of lactate as compared to non-metastatic tumours. Classification into high and low lactate tumours according to the median lactate concentration in combination with a Kaplan-Meier analysis reveals that survival of patients with high lactate tumours is significantly worse than that with low lactate carcinomas. Furthermore, there is a positive correlation between tumour lactate content and radio-resistance. Conclusion: High lactate tumours are characterized by a higher degree of malignancy and therapeutic resistance.

Acidose = Ionenfalle, daher kommen Chemotherapeutika gar nicht an

Mol Pharm. 2011 Dec 5;8(6):2032-8. doi: 10.1021/mp200292c. Epub 2011 Oct 26.

Drug resistance and cellular adaptation to tumor acidic pH microenvironment.

Wojtkowiak JW, Verduzco D, Schramm KJ, Gillies RJ.

Department of Radiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida 33612, United States.

Abstract

Despite advances in developing novel therapeutic strategies, a major factor underlying cancer related death remains resistance to therapy. In addition to biochemical resistance, mediated by xenobiotic transporters or binding site mutations, resistance can be physiological, emerging as a consequence of the tumor's physical microenvironment. This review focuses on extracellular acidosis, an end result of high glycolytic flux and poor vascular perfusion. Low extracellular pH, pHe, forms a physiological drug barrier described by an "ion trapping" phenomenon. We describe how the acid-outside plasmalemmal pH gradient negatively impacts drug efficacy of weak base chemotherapies but is better suited for weakly acidic therapeutics. We will also explore the physiologic changes tumor cells undergo in response to extracellular acidosis which contribute to drug resistance including reduced apoptotic potential, genetic alterations, and elevated activity of a multidrug transporter, p-glycoprotein, pGP. Since low pHe is a hallmark of solid tumors, therapeutic strategies designed to overcome or exploit this condition can be developed.

PMID: 21981633 [PubMed - indexed for MEDLINE] PMCID: PMC3230683 Free PMC Article

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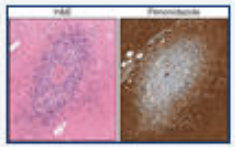
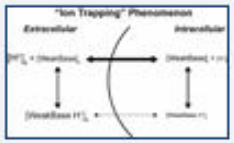
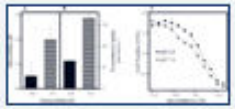
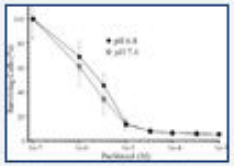
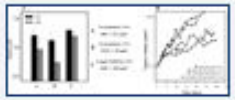
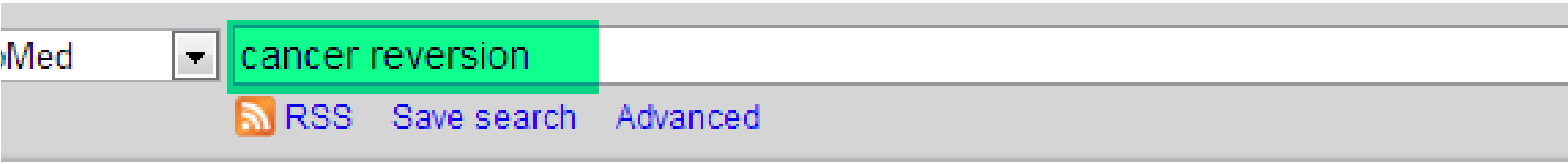






Krebs-Entstehung - AZIDOSE

- ☑ Hypoxie → HIF
- ☑ Umschaltung in Glykolyse → 8fach
- ☑ Lactazidose
- ☑ Zell-Zyklus-Arrest (6.8) → Zell-Tod (6.5) → KLONE
- ☑ Klone mit stabilem Phänotypus Dauer-Glykolyse egal welcher pH, Autophagie, Wachstums-Potential bei pH < 6.7
- ☑ blockierte Apoptose
- ☑ Hemmung der cytotoxischen T-Zellen
- ☑ Irreguläre Blutgefässe – IL8
- ☑ Epidermal-mesenchymale Transformation
- ☑ MMP Expression
- ☑ Metastasierung
- ☑ **MDR, Chemo-Resistenz, Radio-Resistenz**
- Tumor-Reversion
- Tumor-Stammzellen
- pH - Therapie

Verbesserung des pH – Bringts was?

Cancer Reversion



Results: 1 to 20 of 1712

1. Tomatidine inhibits invasion of human lung adenocarcinoma cell A549 by reducing matrix metalloproteinases expression.
Yan KH, Lee LM, Yan SH, Huang HC, Li CC, Lin HT, Chen PS.
Chem Biol Interact. 2013 Apr 6.

2. Normal mammary fibroblasts induce **reversion** of the malignant phenotype in human primary breast **cancer**.
Römer AM, Lühr I, Klein A, Friedl A, Sebens S, Rösel F, Arnold N, Strauss A, Jonat W, Baue
Anticancer Res. 2013 Apr;33(4)

Wie korrigieren wir Azidose - 2009

- Tumor-Wachstum u Metastasierung stark v Azidose abhängig
- **Na-Bicarb erhöht Tu-pH ohne Gewebe u Blut-pH zu stören in den bewährten Mengen**

→ nicht ganz optimal, besser wäre Puffer pk(a) 7

Cancer Res. 2009 Mar 15;69(6):2677-84. doi: 10.1158/0008-5472.CAN-08-2394. Epub 2009 Mar 10.

The potential role of systemic buffers in reducing intratumoral extracellular pH and acid-mediated invasion.

Silva AS, Yunes JA, Gillies RJ, Gatenby RA.

Laboratório de Biologia Molecular, Centro Infantil Boldrini, Campinas, Sao Paulo, Brazil and Departments of Radiology and Integrative Mathematical Oncology, Moffitt Cancer Center, Tampa, Florida.

Abstract

A number of studies have shown that the extracellular pH (pHe) in cancers is typically lower than that in normal tissue and that an acidic pHe promotes invasive tumor growth in primary and metastatic cancers. Here, we investigate the hypothesis that increased systemic concentrations of pH buffers reduce intratumoral and peritumoral acidosis and, as a result, inhibit malignant growth. Computer simulations are used to quantify the ability of systemic pH buffers to increase the acidic pHe of tumors in vivo and investigate the chemical specifications of an optimal buffer for such purpose. We show that increased serum concentrations of the sodium bicarbonate (NaHCO(3)) can be achieved by ingesting amounts that have been used in published clinical trials. Furthermore, we find that consequent reduction of tumor acid concentrations significantly reduces tumor growth and invasion without altering the pH of blood or normal tissues. The simulations also show that the critical parameter governing buffer effectiveness is its pK(a). This indicates that NaHCO(3), with a pK(a) of 6.1, is not an ideal intratumoral buffer and that greater intratumoral pHe changes could be obtained using a buffer with a pK(a) of approximately 7. The simulations support the hypothesis that systemic pH buffers can be used to increase the tumor pHe and inhibit tumor invasion.

Meilenstein-Studie – Pca Xeno-Tr

- Mäuse bekommen vor der Implantation der Krebszellen für 3d einen Puffer

Clin Exp Metastasis. 2011 Dec;28(8):841-9. doi: 10.1007/s10585-011-9415-7. Epub 2011 Aug 23.

Reduction of metastasis using a non-volatile buffer.

Ibrahim Hashim A, Cornnell HH, Coelho Ribeiro Mde L, Abrahams D, Cunningham J, Lloyd M, Martinez GV, Gatenby RA, Gillies RJ.

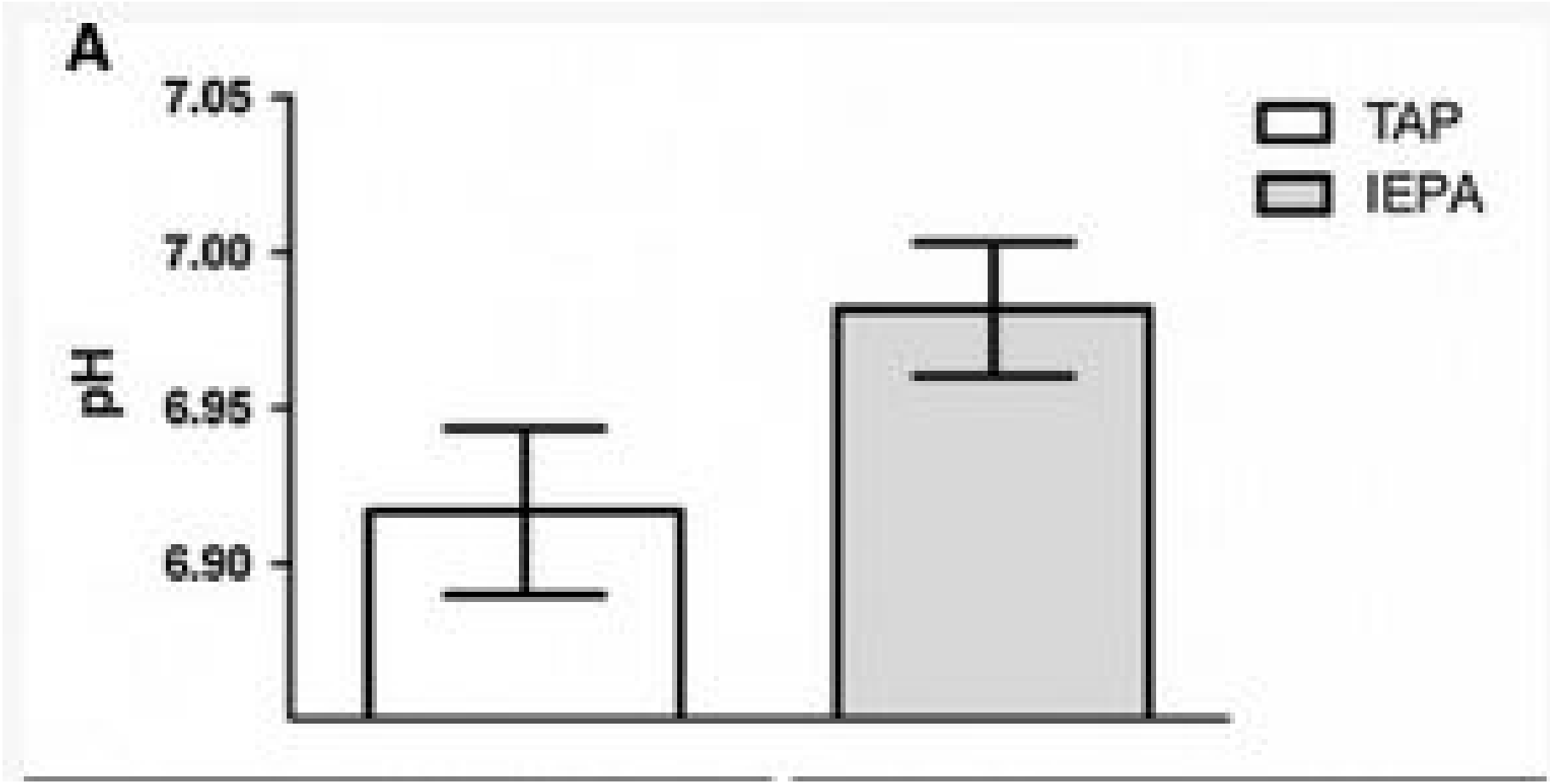
Department of Cancer Imaging Research, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Dr, Tampa, FL 33612, USA. arig.ibrahimhashim@moffitt.org

Abstract

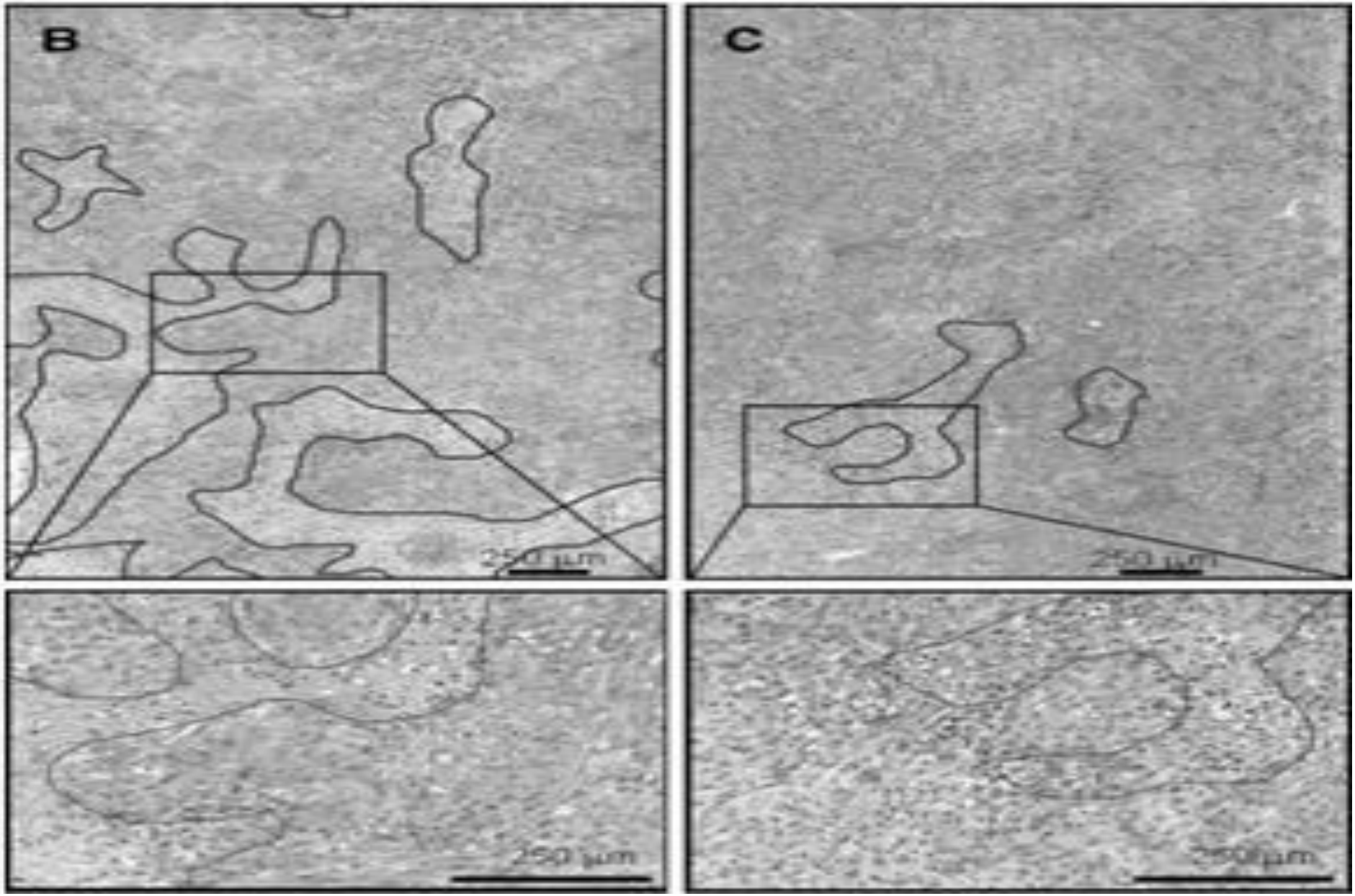
The tumor microenvironment is acidic as a consequence of upregulated glycolysis and poor perfusion and this acidity, in turn, promotes invasion a metastasis. We have recently demonstrated that chronic consumption of sodium bicarbonate increased tumor pH and reduced spontaneous and experimental metastases. This occurred without affecting systemic pH, which was compensated. Additionally, these prior data did not rule out the possibility that bicarbonate was working though effects on carbonic anhydrase, and not as a buffer per se. Here, we present evidence that chronic

Xeno-Transplantat PCa

- Mäuse 3d vorher IEPA-Puffer im Trinkwasser



Puffer reduziert Metastasierung u Tu-W



Meilenstein-Studie 2013

- Je niederer pH, desto mehr Tumor-Invasion
- Bereiche normalen pH‘s KEINE Invasion
- **Bicarbonat Gabe hebt pH und hemmt Tu-Wachstum und lokale Invasion**

Cancer Res. 2013 Mar 1;73(5):1524-35. doi: 10.1158/0008-5472.CAN-12-2796. Epub 2013 Jan 3.

Acidity generated by the tumor microenvironment drives local invasion.

Estrella V, Chen T, Lloyd M, Wojtkowiak J, Cornnell HH, Ibrahim-Hashim A, Bailey K, Balagurunathan Y, Rothberg JM, Sloane BF, Johnson J, Gatenby RA, Gillies RJ.

Departments of Cancer Imaging and Metabolism, Radiology, and Analytic Microscopy Laboratory, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612, USA.

Abstract

The pH of solid tumors is acidic due to increased fermentative metabolism and poor perfusion. It has been hypothesized that acid pH promotes local invasive growth and metastasis. The hypothesis that acid mediates invasion proposes that H(+) diffuses from the proximal tumor microenvironment into adjacent normal tissues where it causes tissue remodeling that permits local invasion. In the current work, tumor invasion and peritumoral pH were monitored over time using intravital microscopy. In every case, the peritumoral pH was acidic and heterogeneous and the regions of highest tumor invasion corresponded to areas of lowest pH. Tumor invasion did not occur into regions with normal or near-normal extracellular pH. Immunohistochemical analyses revealed that cells in the invasive edges expressed the glucose transporter-1 and the sodium-hydrogen exchanger-1, both of which were associated with peritumoral acidosis. In support of the functional importance of our findings, oral administration of sodium bicarbonate was sufficient to increase peritumoral pH and inhibit tumor growth and local invasion in a preclinical model, supporting the acid-mediated invasion hypothesis. Cancer Res; 73(5); 1524-35. ©2012 AACR.

2011 – auf der Suche nach Medikamenten

- Carbanhydratasen, Protonenpumpe …. sollte gehemmt werden.

Nat Rev Drug Discov. 2011 Sep 16;10(10):767-77. doi: 10.1038/nrd3554.

Interfering with pH regulation in tumours as a therapeutic strategy.

Neri D, Supuran CT.

Institute of Pharmaceutical Sciences, Department of Chemistry and Applied Biosciences, Swiss Federal Institute of Technology Zürich, Wolfgang Pauli Strasse 10, CH-8093, Zürich, Switzerland.

Abstract

The high metabolic rate of tumours often leads to acidosis and hypoxia in poorly perfused regions. Tumour cells have thus evolved the ability to function in a more acidic environment than normal cells. Key pH regulators in tumour cells include: isoforms 2, 9 and 12 of carbonic anhydrase, isoforms of anion exchangers, Na+/HCO3- co-transporters, Na+/H+ exchangers, monocarboxylate transporters and the vacuolar ATPase. Both small molecules and antibodies targeting these pH regulators are currently at various stages of clinical development. These antitumour mechanisms are not exploited by the classical cancer drugs and therefore represent a new anticancer drug discovery strategy.

CURCUMIN – Antikrebs u.a. wegen Azidose - Kontrolle

Toxicol Appl Pharmacol. 2011 May 1;252(3):298-306. doi: 10.1016/j.taap.2011.03.002. Epub 2011 Mar 11.

Role of curcumin-dependent modulation of tumor microenvironment of a murine T cell lymphoma in altered regulation of tumor cell survival.

Vishvakarma NK, Kumar A, Singh SM.

School of Biotechnology, Banaras Hindu University, Varanasi-221 005, U.P., India.

Abstract

Using a murine model of a T cell lymphoma, in the present study, we report that tumor growth retarding action of curcumin involves modulation of some crucial parameters of tumor microenvironment regulating tumor progression. Curcumin-administration to tumor-bearing host caused an altered pH regulation in tumor cells associated with alteration in expression of cell survival and apoptosis regulatory proteins and genes. Nevertheless, an alteration was also observed in biophysical parameters of tumor microenvironment responsible for modulation of tumor growth pertaining to hypoxia, tumor acidosis, and glucose metabolism. The study thus sheds new light with respect to the antineoplastic action of curcumin against a tumor-bearing host with progressively growing tumor of hematological origin. This will help in optimizing application of the drug and anticancer research and therapy.

PPI – selber Effekt?

- Esomeprazole (Nexium ®) : **DRAMATISCHE Überlebenszeit-Verlängerung** von **Melanom** - Mäusen, durch pH Regulation

Int J Cancer. 2010 Jul 1;127(1):207-19. doi: 10.1002/ijc.25009.

pH-dependent antitumor activity of proton pump inhibitors against human melanoma is mediated by inhibition of tumor acidity.

De Milito A, Canese R, Marino ML, Borghi M, Iero M, Villa A, Venturi G, Lozupone F, Iessi E, Logozzi M, Della Mina P, Santinami M, Rodolfo M, Podo F, Rivoltini L, Fais S.

Department of Therapeutic Research and Medicines Evaluation, Unit of Antitumor Drugs, Istituto Superiore di Sanità, Rome, Italy. angelo.demilito@iss.it

Abstract

Metastatic melanoma is associated with poor prognosis and still limited therapeutic options. An innovative treatment approach for this disease is represented by targeting acidosis, a feature characterizing tumor microenvironment and playing an important role in cancer malignancy. Proton pump inhibitors (PPI), such as esomeprazole (ESOM) are prodrugs functionally activated by acidic environment, fostering pH neutralization by inhibiting proton extrusion. We used human melanoma cell lines and xeno-transplated SCID mice to provide preclinical evidence of ESOM antineoplastic activity. Human melanoma cell lines, characterized by different mutation and signaling profiles, were treated with ESOM in different pH conditions and evaluated for proliferation, viability and cell death. SCID mice engrafted with human melanoma were used to study ESOM administration effects on tumor growth and tumor pH by magnetic resonance spectroscopy (MRS). ESOM inhibited proliferation of melanoma cells in vitro and induced a cytotoxicity strongly boosted by low pH culture conditions. ESOM-induced tumor cell death occurred via rapid intracellular acidification and activation of several caspases. Inhibition of caspases activity by pan-caspase inhibitor z-vad-fmk completely abrogated the ESOM-induced cell death. ESOM administration (2.5 mg kg(-1)) to SCID mice engrafted with human melanoma reduced tumor growth, consistent with decrease of proliferating cells and clear reduction of pH gradients in tumor tissue. Moreover, systemic ESOM administration dramatically increased survival of human melanoma-bearing animals, in absence of any relevant toxicity. These data show preclinical evidence supporting the use of PPI as novel therapeutic strategy for melanoma, providing the proof of concept that PPI target human melanoma modifying tumor pH gradients.

Sport = kurzfristige Azidose

- Kurzfristige systemische Azidose durch Sport antagonisiert die Ausbildung eines malignen Phänotyps

Biol Direct. 2010 Apr 20;5:22. doi: 10.1186/1745-6150-5-22.

Episodic, transient systemic acidosis delays evolution of the malignant phenotype: Possible mechanism for cancer prevention by increased physical activity.

Smallbone K, Maini PK, Gatenby RA.

Manchester Centre for Integrative Systems Biology, Manchester Interdisciplinary Biocentre, 131 Princess Street, Manchester, M1 7DN, UK. kieran.smallbone@manchester.ac.uk

Abstract

BACKGROUND: The transition from premalignant to invasive tumour growth is a prolonged multistep process governed by phenotypic adaptation to changing microenvironmental selection pressures. Cancer prevention strategies are required to interrupt or delay somatic evolution of the malignant invasive phenotype. Empirical studies have consistently demonstrated that increased physical activity is highly effective in reducing the risk of breast cancer but the mechanism is unknown.

CAVE: Blasen-Ca

- Nitrosamin-induziertes Ca
- Unter Basenpulver: ↑↑

Food Chem Toxicol. 1999 Dec;37(12):1159-66.

Effect of urinary pH on the progression of urinary bladder tumours.

Lina BA, van Garderen-Hoetmer A.

TNO Nutrition and Food Research Institute, AJ, Zeist, The Netherlands.

Abstract

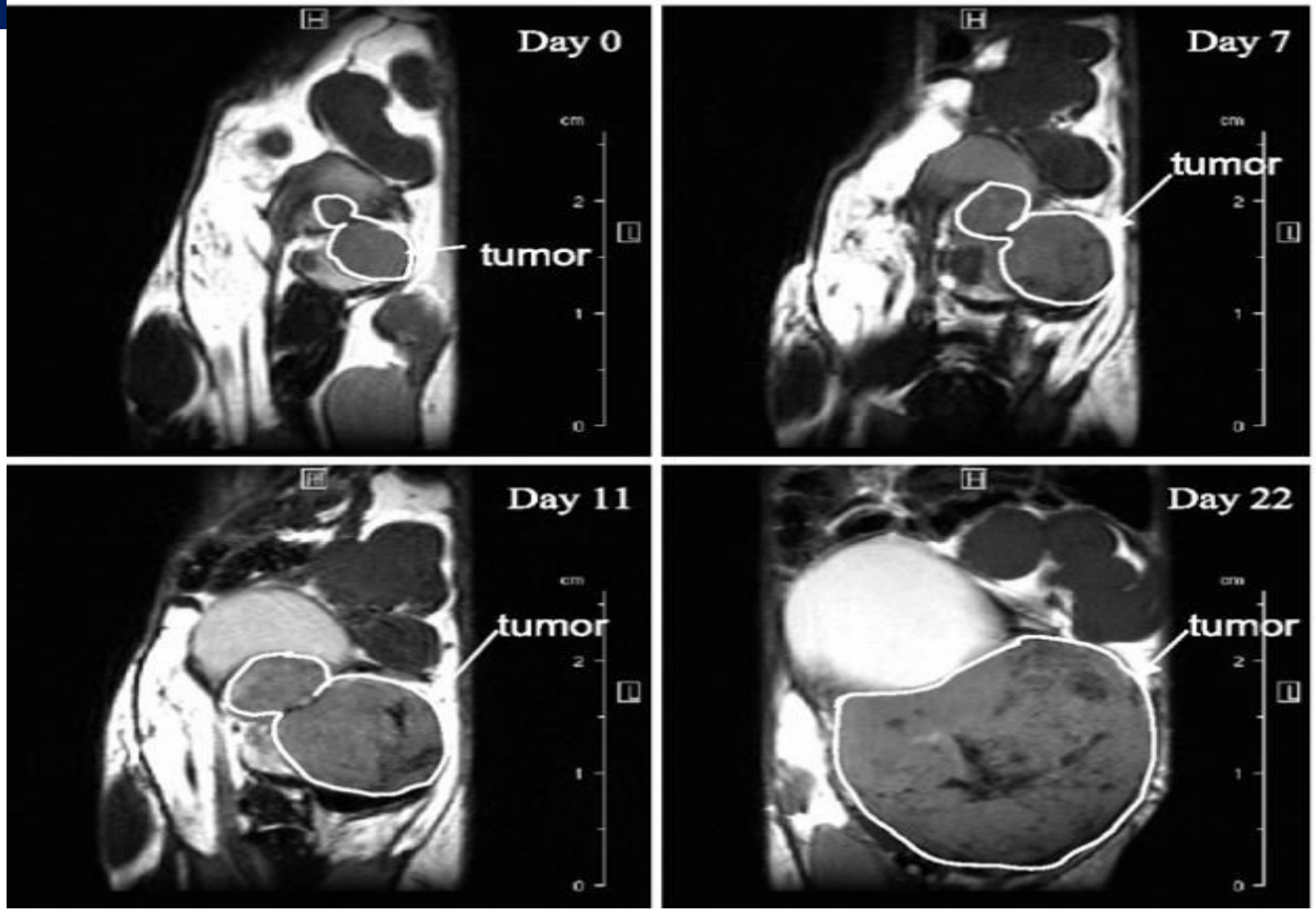
Systemic alkalosis has been postulated to enhance tumorigenesis, whereas systemic acidosis has been implicated to exert a favourable influence on tumour control and regression. In the present study the urinary pH was influenced by feeding acid-forming or base-forming diets, and the effect of alkaline or acid urine on the early and late progression phase of urinary bladder carcinogenicity was investigated in male Wistar rats. Bladder lesions were initiated by N-butyl-N-(4-hydroxybutyl) nitrosamine (0.05% BBN in the drinking water during 4 weeks) and promoted by sodium bicarbonate (3.4% NaHCO3 in the diet during 15 or 25 weeks). After short- (15 week) and more long-term (25 week) promotion with NaHCO3, groups of 20 rats were fed a diet containing the acidifying salt ammonium chloride (2.1% NH4Cl) or the control diet. All surviving rats were killed after a total study duration of 52 weeks. Additional control groups were, after initiation, fed diets containing NaHCO3 and killed after 15 wk or 25 wk of promotion, or at the end of the study. In rats fed diets with added salts, water intake and the amount of urine produced were increased and the urinary density was decreased compared to rats fed control diet. During NaHCO3 feeding, urinary pH and sodium concentration were increased. During NH4Cl feeding, urinary pH was decreased and urinary chloride and calcium concentrations were increased. Initiation by BBN followed by treatment with NaHCO3 caused a high incidence of papillary/nodular hyperplasia, papillomas and carcinomas of the bladder epithelium. These lesions progressed with time or longer duration of NaHCO3 promotion. A tumour protective effect of urinary acidification by NH4Cl was not found. In fact, both acidification and prolonged alkalinization tended to aggravate the malignancy of bladder carcinomas.

TRAMP-MÄUSE

- Prostata Krebs 37 W
- sterben 37 Woche

TRAMP-Mi

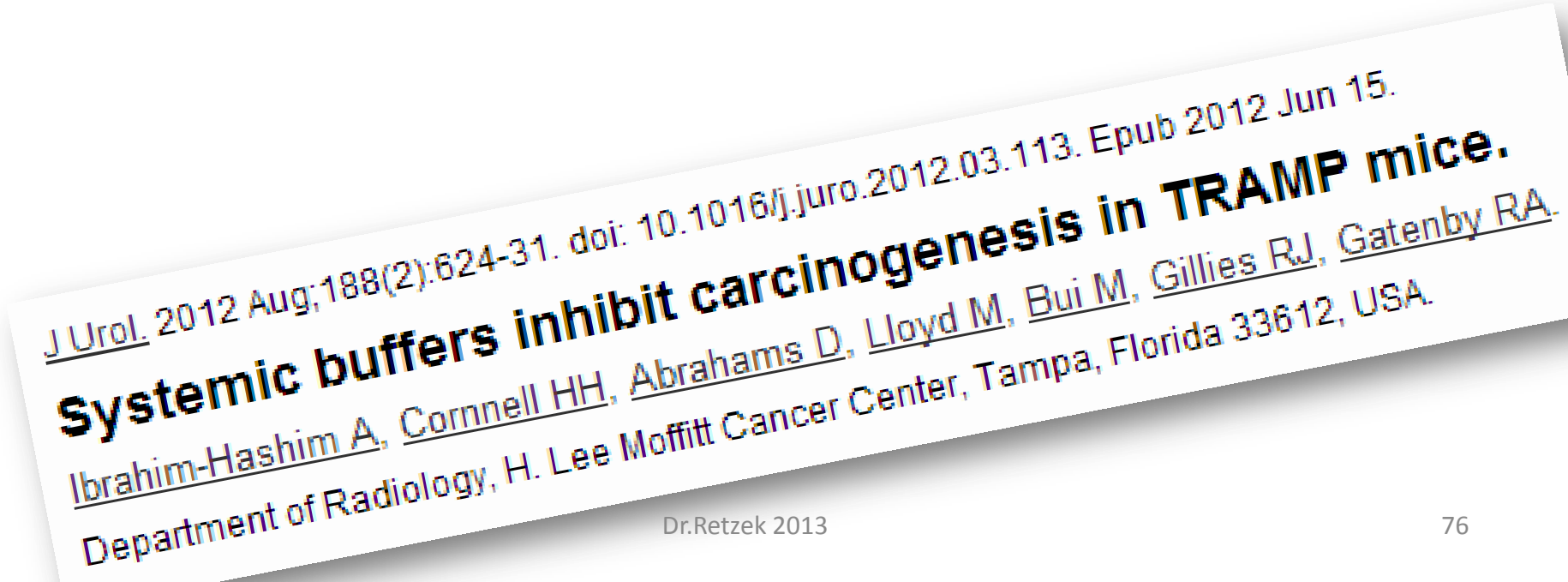
Control



TRAMP-Mäuse

In all 18 controls prostate cancer developed that was visible on 3-dimensional ultrasound at a mean age of **13 weeks.**

They **died** within 52 weeks (median **37 weeks**).



J Urol. 2012 Aug;188(2):624-31. doi: 10.1016/j.juro.2012.03.113. Epub 2012 Jun 15.

Systemic buffers inhibit carcinogenesis in TRAMP mice.

Ibrahim-Hashim A, Cornnell HH, Abrahams D, Lloyd M, Bui M, Gillies RJ, Gatenby RA.

Department of Radiology, H. Lee Moffitt Cancer Center, Tampa, Florida 33612, USA.

TRAMP-MÄUSE

Sodium bicarbonate were added to drinking water starting between ages 4 and 10 weeks. When sodium bicarbonate therapy commenced before age 6 weeks in 10 mice, **all reached senescence (age 76 weeks)** without radiographic evidence of prostate cancer.


J Urol. 2012 Aug;188(2):624-31. doi: 10.1016/j.juro.2012.03.113. Epub 2012 Jun 15.

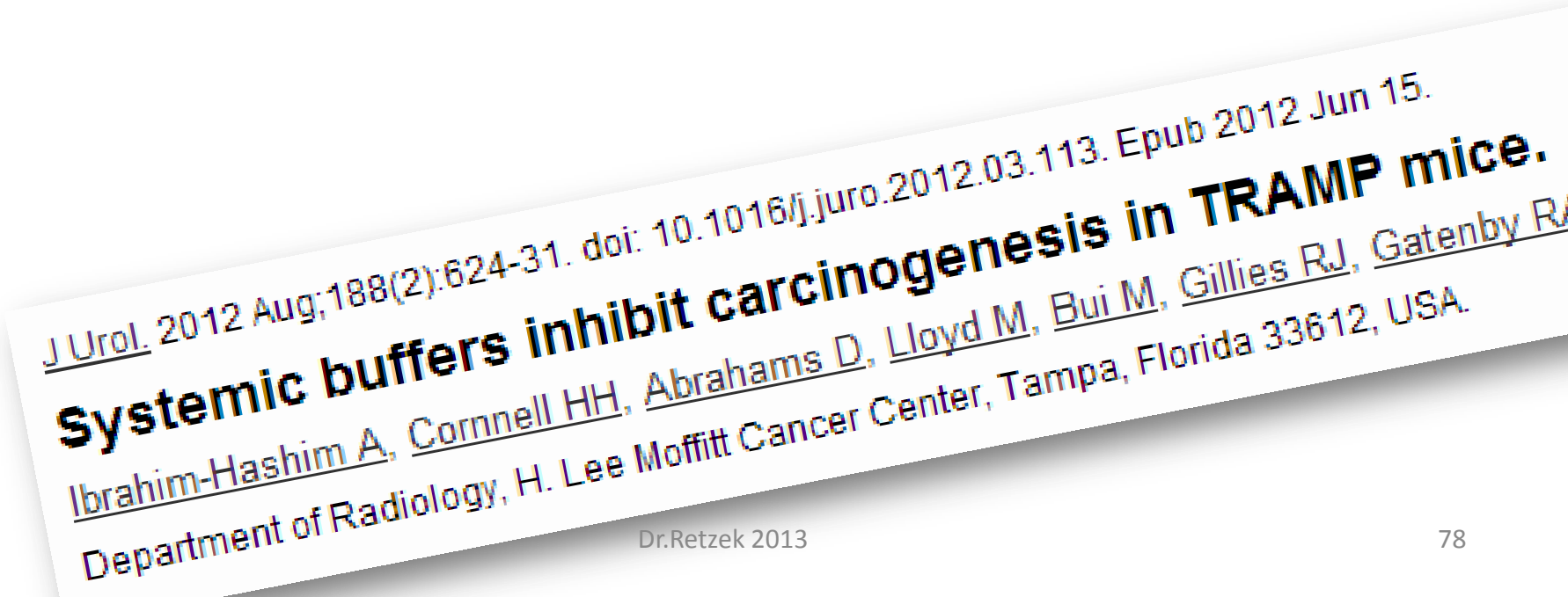
Systemic buffers inhibit carcinogenesis in TRAMP mice

Ibrahim-Hashim A, Cornnell HH, Abrahams D, Lloyd M, Bui M, Gillies RJ, Gatenby

Department of Radiology, H. Lee Moffitt Cancer Center, Tampa, Florida 33612, USA.

Tramp II

Histological sections of the prostates in this cohort showed **hyperplasia but no cancer in 70%** of mice and **minimal well differentiated cancer in the remainder**.


J Urol. 2012 Aug;188(2):624-31. doi: 10.1016/j.juro.2012.03.113. Epub 2012 Jun 15.

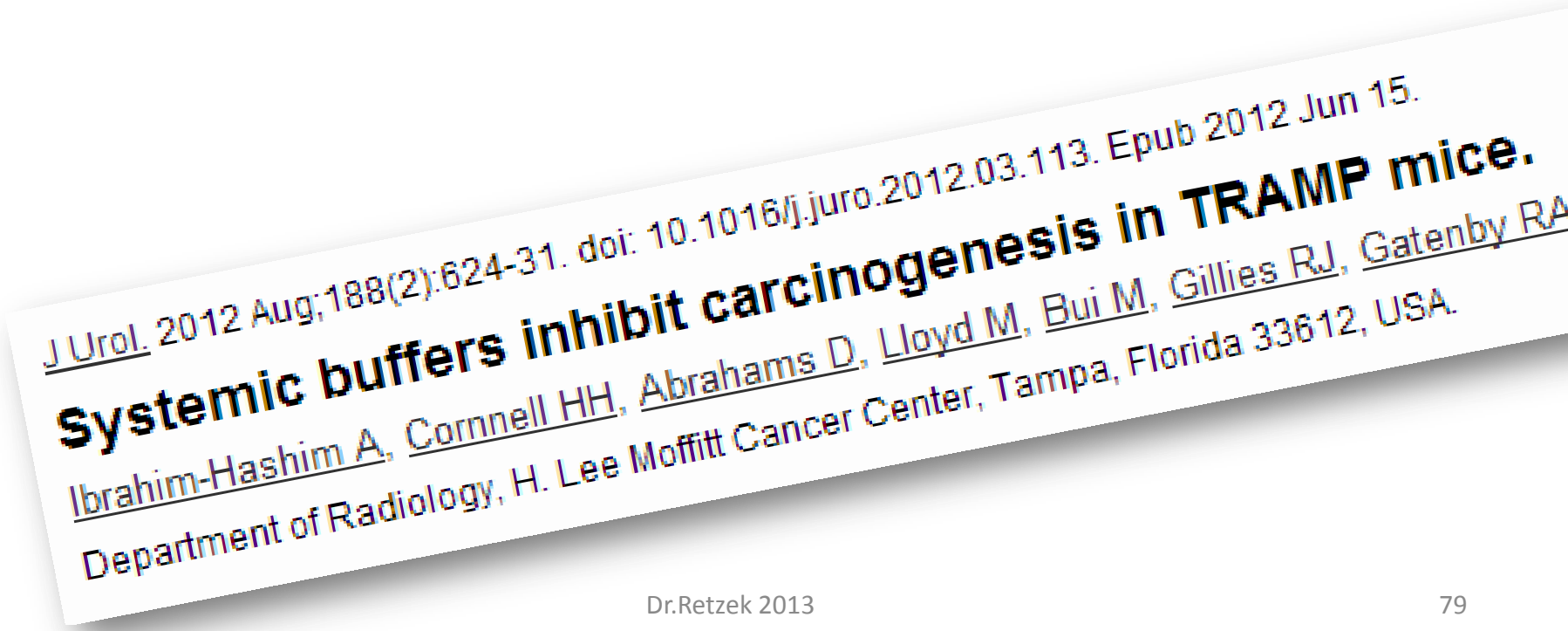
Systemic buffers inhibit carcinogenesis in TRAMP mice.

Ibrahim-Hashim A, Cornnell HH, Abrahams D, Lloyd M, Bui M, Gillies RJ, Gatenby RA

Department of Radiology, H. Lee Moffitt Cancer Center, Tampa, Florida 33612, USA.

TRAMP III

- When *Bicarbonat* therapy commenced after age 6 weeks in 9 mice, prostate cancer development was no different from that in controls.


J Urol. 2012 Aug;188(2):624-31. doi: 10.1016/j.juro.2012.03.113. Epub 2012 Jun 15.

Systemic buffers inhibit carcinogenesis in TRAMP mice.

Ibrahim-Hashim A, Cornnell HH, Abrahams D, Lloyd M, Bui M, Gillies RJ, Gatenby RA

Department of Radiology, H. Lee Moffitt Cancer Center, Tampa, Florida 33612, USA.

BEDEUTUNG TRAMP 2012

- Beim Prostatakrebs: **selbst bei stärkster genetischer Disposition** kann Krebs **nur bei Übersäuerung** entstehen.

- Ist der Krebs entstanden, kann er durch Entsäuerung nicht mehr eliminiert werden

- (bei Studienbedingungen)

TRAMP mice: Prostata Krebs

- TRAMP-Mäuse sind ein experiemental-Modell für Prostatakrebs, da sie alle Prostata-Krebs entwickeln. Im nachfolgend beschriebenen Experiment bekamen alle 18 Kontroll-Mäuse durchschnittlich in der 13 Lebenswoche Prostatakrebs und starben daran in der 37 Lebenswoche.
- Bekamen die Mäuse jedoch Bicarbonat (=Basenpulver) in ihr Trinkwasser, noch vor der 6. Lebenswoche (also bevor der Tumor manifest wurde), erreichten sie alle das normale Lebensalter von 76 Wochen.
- Wenn die Mäuse nach ihrem Ableben untersucht wurden, fand man zwar in der Prostata von 70% der Mäusen "Hyperplasien" (Vergrösserungen), jedoch keinen Krebs.
- In den verbleibenden 30% der Mäusen fand sich ein kleiner, aber relativ gutartiger Krebs.
- Wurde jedoch das Basenpulver nach Entstehung der Tumore verabreicht, war die Entwicklung des Prostatakrebs nicht unterschiedlich zu den Mäusen, die kein Basenpulver bekommen hatten.
- Systemic buffers inhibit carcinogenesis in TRAMP mice. / J Urol. 2012 Aug;188(2):624-31. doi: 10.1016/j.juro.2012.03.113. Epub 2012 Jun 15.

Dr. Tullio SIMONCINI

Krebs = PILZ | Bicarbonat = Lösung

DR. SIMONCINI'S THERAPY WITH SODIUM BICARBONATE

CANCERFUNGUS

Behandel Krebs mit Natriumbikarbonat

VIDEO DR. SIMONCINI

Interview Dr. Simoncini

In diesem Interview erklärt Dr. Simoncini die Therapie durch das Beantworten von Fragen und das Zeigen von videogesamtlänge von einigen behandelten Patienten.

POPULAR LINKS

- The Fungal Hypothesis
- Interview Doug Kaufmann
- Interview Dr. Apsley
- Emails to Dr. Simoncini

cancerfungus.com - das Deutsche Portal von Dr. Simoncini Therapie vom Behandeln des Krebses mit Natriumhydrogencarbonat

ein neues Jahr • die Therapie • donation

IMPORTANT

Watch this video before enter the site

Simoncini krebstherapie - Der Grundgedanke der Theorie besteht darin, dass Krebs keine geheimnisvollen Ursachen hat (also keine genetischen, immunologischen oder auto-immunologischen Gründe, wie sie die offizielle Onkologie annimmt). Krebs wird schlicht von einer Pilzinfektion ausgelöst, deren zerstörerische Kraft in den tiefen Gewebeschichten unterschätzt wird.

die Therapie und klinische Fälle
www.curenaturalicancro.com

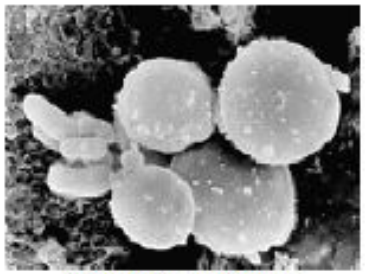
das Buch "cancer is a fungus"
www.cancerisafungus.com

DR. SIMONCINI

Dr. Tullio Simoncini lebt und arbeitet in Rom. Er ist Arzt und Chirurg, spezialisiert auf Onkologie, Diabetologie und Stoffwechsel störungen.

NATIONAL LINKS

- Zentrum der Gesundheit
- Nexus Magazine



candida albicans

Fragwürdige Persönlichkeit

- Verspricht 80% Heilung
- Heftige Werbung übers Internet
- 2003 wegen Todschlag verurteilt
  - Patient mit Darmkrebs im Endstadium +
  - Patient mit Glioblastom, €28.000,- +
- Seither über NL tätig

PSIRAM.COM

- Penible Auflistung verschiedenster Todesfälle von Simoncini-Patienten
- Enorme Honorare

wurde er nicht verurteilt, in diesen Fällen wurde ihm nur Betrug angelastet.[4]

Unbekannte Opfer

Ein weiteres Opfer war ein US-Amerikaner, bei dem ein wahrscheinliches Glioblastom (ein bösartiger Hirntumor) diagnostiziert wurde. Seine Verwandten bezahlten ca. 28.000 Euro an Simoncini. Während der Behandlung traten schwere Hirnblutungen und ein Herzanfall auf. Als Folge wurde er für hirntot erklärt und die Lebenserhaltung abgeschaltet.[5][6]

Sylvia Trachsler

In den Niederlanden kam es am 8. Oktober 2007 zu einem weiteren Todesfall im Zusammenhang mit der Bikarbonat-Therapie nach Simoncini. Auch dort fand seine Theorie, dass Krebs eine Mykose sei (*kanker is een schimmel*), Anhänger. Laut niederländischen Presseberichten starb eine 58-jährige Brustkrebspatientin namens Sylvia Trachsler[7] in einer alternativmedizinischen Klinik namens *Kliniek voor Preventieve Geneeskunde Berg en Bosch (KPG)* in Bilthoven.[8][9][10] An dieser Klinik wurde nicht nur die umstrittene Chelattherapie angewendet, sondern auch die Bikarbonat-Therapie nach Simoncini. Der Lebenspartner der Patientin, Peter M., berichtete in einem niederländischen Forum für Krebskranke, dass Sylvia täglich mit Bikarbonaten behandelt wurde und rief im Internet zu weiteren Zeugenberichten von Patienten und Angehörigen auf.[11] Die als "nicht natürlich" deklarierte Todesursache der 58-jährigen Krebspatientin ist nicht abschliessend geklärt. Ihr Herzstillstand ist entweder auf die Bikarbonat-Injektionen zurückzuführen oder auf Kaliumgaben, die gegeben werden mussten, um einen therapiebedingten Kaliummangel auszugleichen. Die niederländische Gesundheitsbehörde schritt ein und untersagte diese Therapie.[12]

Sylvia Trachsler (Bild: netwerk.tv)

Marjolein Bouwman

Bei der Holländerin Marjolein Bouwman wurde Eierstockkrebs diagnostiziert und ihr zur einer konventionellen Therapie geraten. Sie entschied sich stattdessen für Simoncinis Therapie. Nach einigen Injektionen mit Natriumbicarbonat erklärte Simoncini sie für geheilt. Sie begann danach leidenschaftlich für ihn Werbung zu machen. Einige Monate später fand Marjolein heraus, dass Simoncini sie betrogen hatte und dass sie mitnichten geheilt war. Zu diesem Zeitpunkt hatte der Krebs bereits beträchtliche Metastasen gebildet. Sie starb am 2. November 2008. Marjolein war 25 Jahre alt und Mutter eines kleinen Buben.[13]

Marjolein Bouwman 02-01-1983 – 02-11-2008

Aysha

Bei einer jungen Italienerin namens Aysha wurde 2006 Krebs in der rechten Brust (sie litt bereits 2004 an Krebs in der linken Brust und erhielt damals eine konventionelle Behandlung) diagnostiziert und sie entschied sich für eine Behandlung bei Simoncini. Sie trat einem Simoncini gewidmeten Alternativmedizin-Forum bei und wurde zuerst nett behandelt. Aber als ihr Gesundheitszustand sich verschlechterte, als sie Hautentzündungen und offene Wunden bekam, ("I see no improvement at all, the whole area is red and it reaches almost to the left side.") und begann, an der Behandlung zu zweifeln, begegnete sich die Ärzte

Krebs-Entstehung - AZIDOSE

- ☑ Hypoxie → HIF
- ☑ Umschaltung in Glykolyse → 8fach
- ☑ Lactazidose
- ☑ Zell-Zyklus-Arrest (6.8) → Zell-Tod (6.5) → KLONE
- ☑ Klone mit stabilem Phänotypus Dauer-Glykolyse egal welcher pH, Autophagie, Wachstums-Potential bei pH < 6.7
- ☑ blockierte Apoptose
- ☑ Hemmung der cytotoxischen T-Zellen
- ☑ Irreguläre Blutgefässe – IL8
- ☑ Epidermal-mesenchymale Transformation
- ☑ MMP Expression
- ☑ Metastasierung
- ☑ MDR, Chemo-Resistenz, Radio-Resistenz

- ☑ **Tumor-Reversion**
- ☑ **Tumor-Stammzellen**
- ☑ **pH - Therapie**

Zusammenfassend

- Hypoxie → Warburg , Milchsäure, Gewebsübersäuerung
- Mikro-Environment als Hauptpromotions-Faktor
- Epidermal-Mesenchymale Transformation
- Metastasierung
- Überlebenszeit ↑↑↑
- Simoncini | Braun v. Gladis u.a. m.

Danke für Aufmerksamkeit

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Banerji Protocols

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Oncol Rep. 2008 Jul;20(1):69-74.

Cancer patients treated with the Banerji protocols utilising homoeopathic medicine: a Best Case Series Program of the National Cancer Institute USA.

Banerji P, Campbell DR, Banerji P.

PBH Research Foundation, Kolkata 700020, West Bengal, India. pbhrfindia@dataone.in

Abstract

Although many studies have been conducted on the role of alternative medicine in the treatment of cancer, only a few reports have been published regarding the total regression of malignant tumors. At the PBH Research Foundation (PBHRF), two of the authors have used homoeopathic therapy to treat many patients with various malignant tumors. The objective of the present study was to have their treatment procedures evaluated and validated by the United States (US) National Cancer Institute (NCI) Best Case Series (BCS) Program. Lung and oesophageal carcinoma patients were treated with homoeopathic remedies at the PBHRF according to Banerji's protocol until there was complete regression of the tumors. Case records including pathology and radiology reports for 14 patients were submitted for review by the US NCI BCS Program. Four of these cases had an independent confirmation of the diagnosis and radiographic response and were accepted as sufficient information for the NCI to initiate further investigation. These four cases are presented in detail in this report along with follow-up and outcome information. This study describes the process and outcome of a selected case series review through the NCI BCS Program. The results of the review were deemed to be sufficient to warrant NCI-initiated prospective research follow-up in the form of an observational study.

PMID: 18575720 [PubMed - indexed for MEDLINE]

MeSH Terms

LinkOut - more resources

Glioblastom Therapie

Hirntumoren behandeln wir mit Ruta graveolens C6 und Calcium phosphoricum D3

ohne Chemotherapie und Strahlentherapie

hervorragende Ergebnisse.

Diese Ruta-Behandlung wird jetzt in vielen Fällen auf der ganzen Welt mit großem Erfolg angewendet, zusammen mit und nach Chemo- und Strahlentherapie und Rückfällen.

1) Ruta graveolens C6, Globuli Nr. 40 oder 5 mm Durchmesser, 2 Globuli pro Gabe, 2 Gaben täglich morgens und abends.

2) Calcium phosphoricum D3 in Tablettenform, 2 Tabletten pro Gabe, 2 Gaben täglich mittags und nachts

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