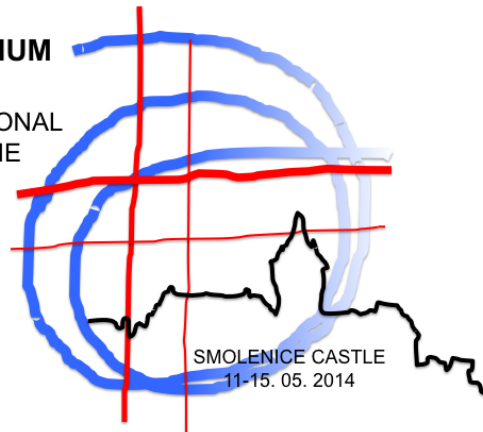


MAGNESIUM
IN
TRANSLATIONAL
MEDICINE



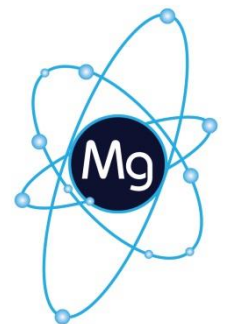
Understanding Magnesium and Magnesium Transporters in Cancer: .. How Far? ...How Close?

Federica I. Wolf

Istituto di Patologia generale

Facoltà di Medicina “A. Gemelli”

Università Cattolica del Sacro Cuore - Roma



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A. Cittadini, **F.I. Wolf**, D. Bossi and G. Calviello *Magnesium in normal and neoplastic cell proliferation: state of the art of in vitro data*, **Magnesium Research**, **1991**, 4, 23-33.

F.I. Wolf, A. Di Francesco, V. Covacci and A. Cittadini () *Regulation of Na-dependent magnesium efflux from intact tumor cells*, Supplement to Magnesium Research: ADVANCES IN MAGNESIUM RESEARCH:1 (R. Smetana ed.) John Libbey, London, **1997**, pp. 490-496.

F.I. Wolf and A. Cittadini () *Magnesium in cell proliferation and differentiation*, **Front. Bioscience**. **1999**, 4, d607-617

F.I. Wolf, A. Sgambato, V. Covacci, B. Faraglia, A. Torsello, R. Ardito and A. Cittadini () *Magnesium in the Control of Cell Proliferation. A metabolic enhancer or a specific regulator?* In: ADVANCES IN MAGNESIUM RESEARCH: NUTRITION AND HEALTH (Y. Rayssiguier, A. Mazur and J. Durlach eds.), **2001**, John Libbey, London, pp.73-81*.

F.I. Wolf, J.A.M. Maier, A. Nasulewicz, C. Feillet-Coudray, A. Mazur, M. Simonacci, and A. Cittadini *Magnesium and Neoplasia: from Carcinogenesis, to Tumor Growth and Progression or Tumor Treatment*. **Arch. Biochem. Biophys.** **2007**, 458:24-32.*

F.I. Wolf, V. Trapani and A. Cittadini *Magnesium and the control of cell proliferation: looking for a needle in a haystack*. **Magnesium Research**, **2008**, 21(2), 1-9.*

F.I. Wolf, A. Cittadini and J.A.M. Maier *Magnesium and Tumors: Ally or Foe?* **Cancer Treatment Reviews**, **2009**, Jun;35(4):378-82.*

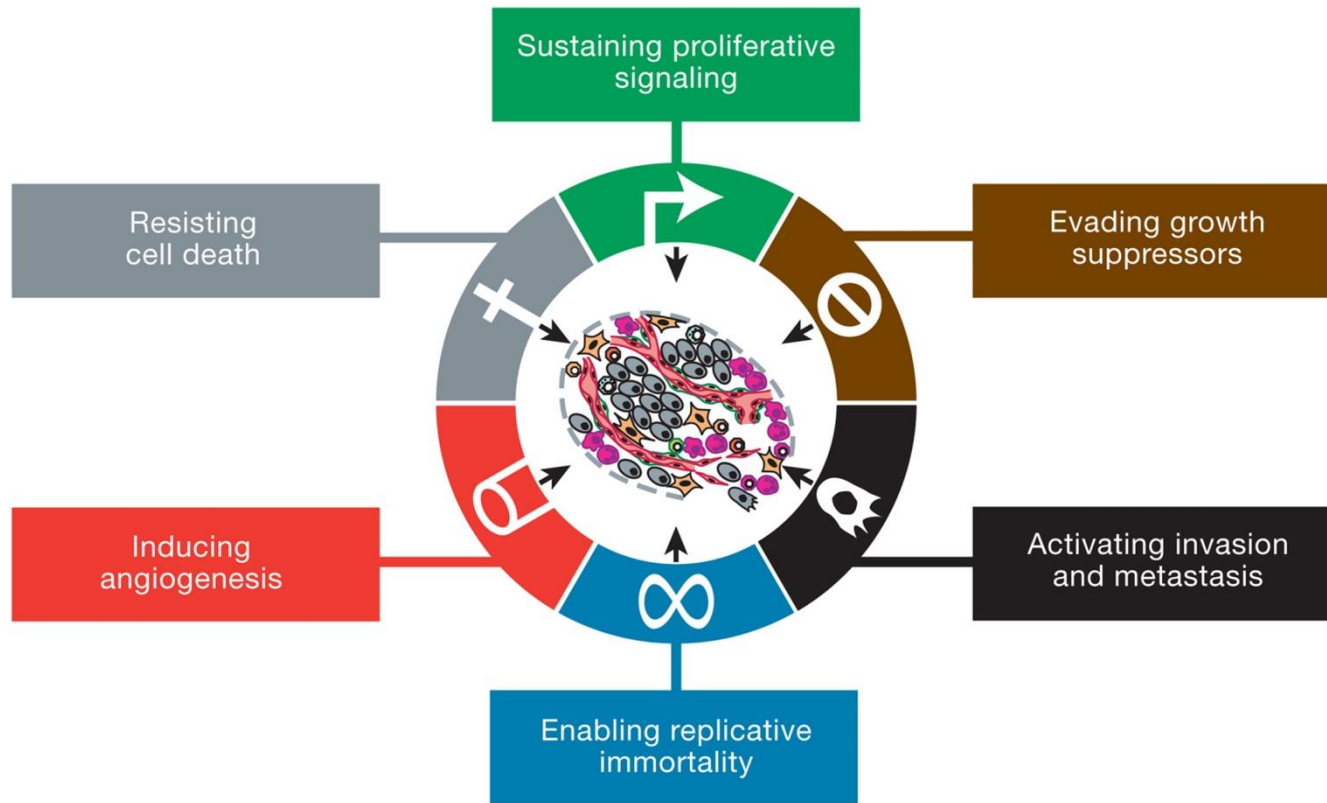
F.I. Wolf, V. Trapani, A. Cittadini and J.A.M. Maier *Hypomagnesaemia in Oncologic Patients: To treat or not to treat?* **Magnesium Research**, 2009, Mar;22(1):5-9.*

V. Trapani, **F.I. Wolf** *Magnesium Transporters in Cancer: a Novel Paradigm in Tumour Development*. **Clin Sci (Lond)**. **2012** Oct;123(7):417-27.*

Trapani V, Arduini D, Cittadini A, **Wolf F.I.** From Magnesium To Magnesium-transporters: Trpm7 As Novel Signature Of Tumour Development **Mag Res**, **2013**

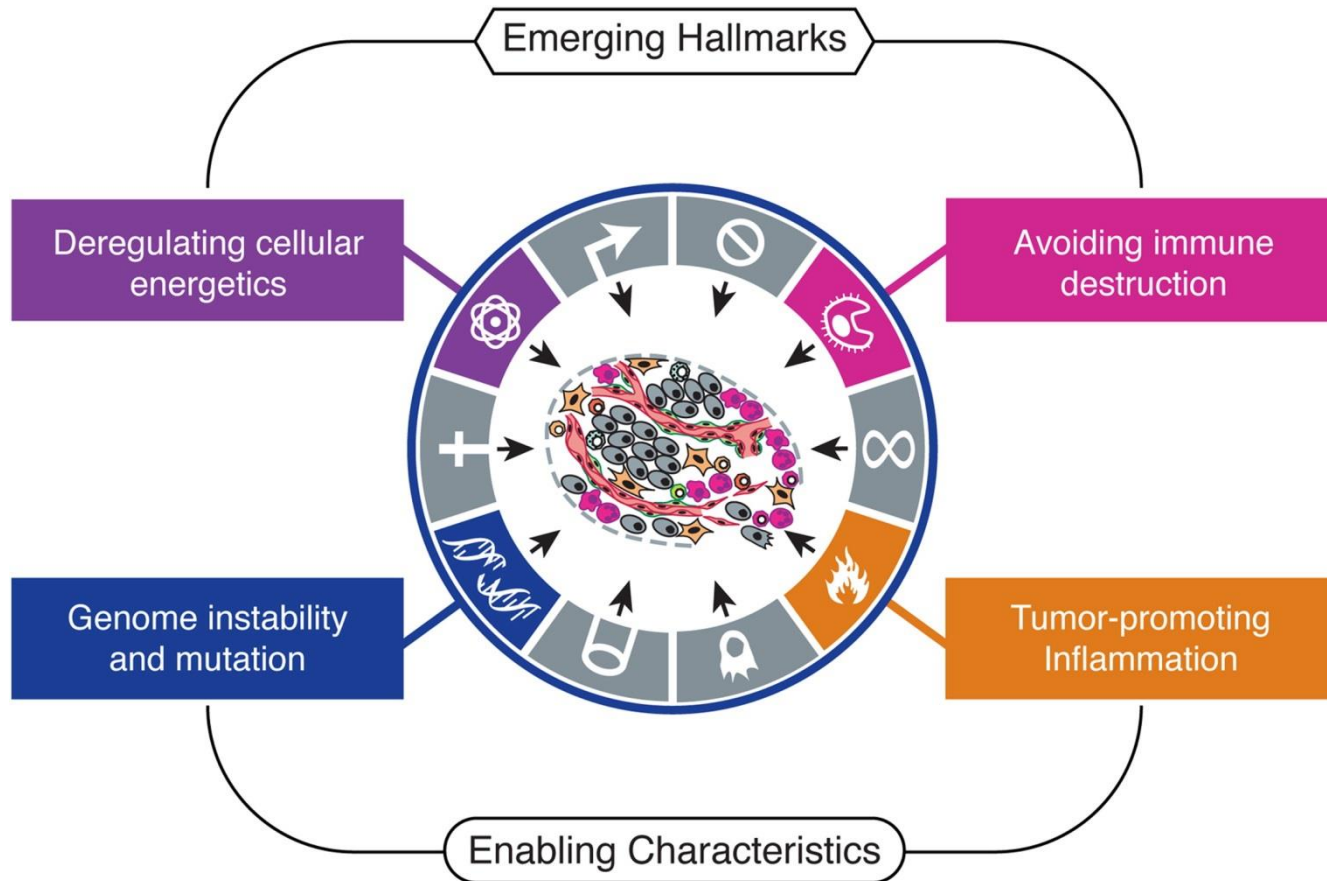


The Hallmarks of Cancer



Hanahan and Weinberg, Cell, 2000

Hanahan and Weinberg, Cell, 2011





COMPLICATIONS OF TREATMENT

Magnesium and tumors: Ally or foe?

Federica I. Wolf^{a,*}, Achille R.M. Cittadini^{a,c}, Jeanette A.M. Maier^{b,d}^aUniversità Cattolica del Sacro Cuore, Istituto di Patologia generale e Centro di Ricerche Oncologiche Giovanni XXIII, Facoltà di Medicina "A. Gemelli", Largo Francesco Vito 1, 00168 Roma, Italy^bUniversità di Milano, Dipartimento di Scienze Precliniche IITA Mulba, Via G.B. Grassi 74, 20157 Milano, Italywww.sdrmsociety.org**Carcinogenesis:**

Oxidative stress
DNA damage repair

< Mg²⁺ ↑

Tumour growth and spreading:

Proliferation, Metabolism
Angiogenesis

< Mg²⁺ ↓

Invasion
Metastasis

< Mg²⁺ ↑

Inflammation



Tumour treatment:

Neprototoxic agents
Therapeutical outcome ?

< Mg²⁺ ↑

Magnesium in Carcinogenesis

In Vitro mechanisms

Oxidative stress 
DNA damage repair 

< Mg^{2+}

< Mg^{2+}



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G Model
DNAREP-1929; No. of Pages 13

ARTICLE IN PRESS

DNA Repair xxx (2014) xxx–xxx



Contents lists available at ScienceDirect

DNA Repair

journal homepage: www.elsevier.com/locate/dnarepair



The cutting edges in DNA repair, licensing, and fidelity: DNA and RNA repair nucleases sculpt DNA to measure twice, cut once

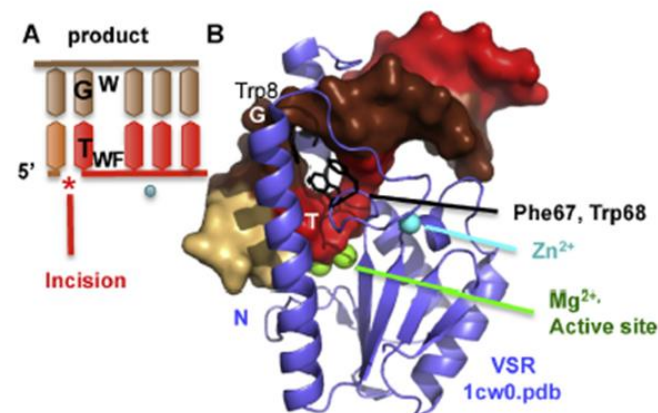
Susan E. Tsutakawa^{a,*}, Julien Lafrance-Vanasse^a, John A. Tainer^{a,b,*}

^a Life Science Division, 1 Cyclotron Road, Berkeley, CA 94720, USA

^b The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA 92037, USA

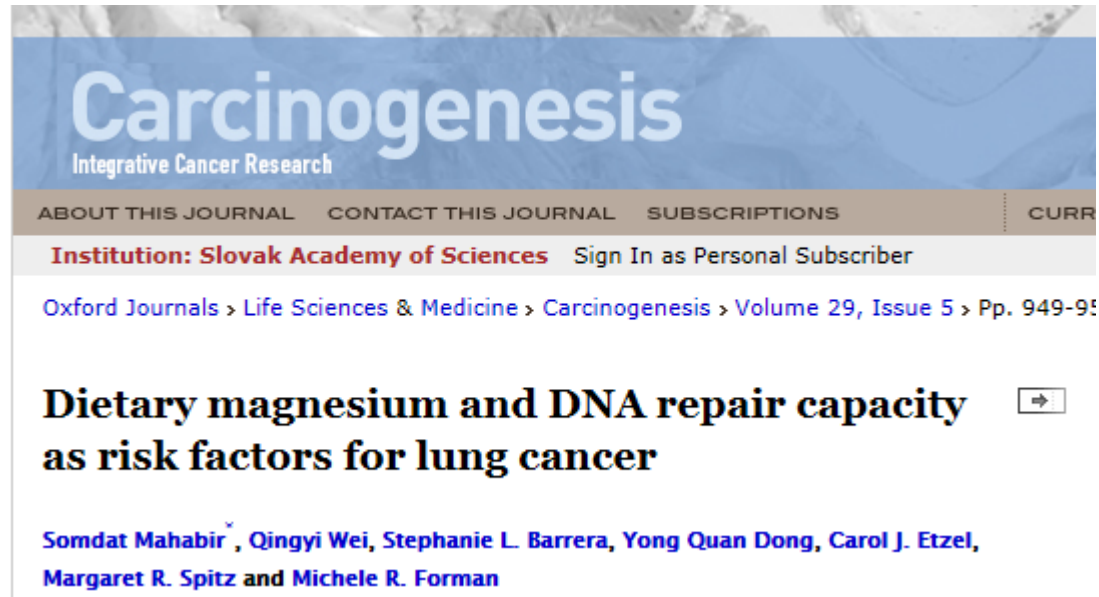
6

S.E. Tsutakawa et al. / DNA R



Magnesium in Carcinogenesis

in vivo data



1139 cases and 1210 matched healthy controls with data on both diet and DNA repair capacity (DRC), measured using the host cell reactivation assay to assess repair in lymphocyte cultures .

Low dietary Mg intake was associated with poorer DRC and increased risk of lung cancer. The effects were more pronounced among older subjects (>60 years), current or heavier smokers, drinkers, those with a family history of cancer.

Magnesium in carcinogenesis

Epidemiological data

OPEN ACCESS Freely available online



Blood Magnesium, and the Interaction with Calcium, on the Risk of High-Grade Prostate Cancer

Qi Dai^{1*}, Saundra S. Motley¹, Joseph A. Smith Jr.², Raoul Concepcion^{2,3}, Daniel Barocas², Susan Byerly¹, Jay H. Fowke¹

¹ Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Vanderbilt University School of Medicine, Nashville, Tennessee, United States of America, ² Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, Tennessee, United States of America, ³ Urology Associates, Nashville, Tennessee, United States of America

The American Journal of CLINICAL NUTRITION

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Institution: UNIV CATTOLICA DEL SACRO CUORE Sign In as M

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Magnesium intake and colorectal tumor risk: a case-control study and meta-analysis^{1,2,3,4}

Petra A Wark, Rosa Lau, Teresa Norat, and Ellen Kampman

Carcinogenesis: in vivo data

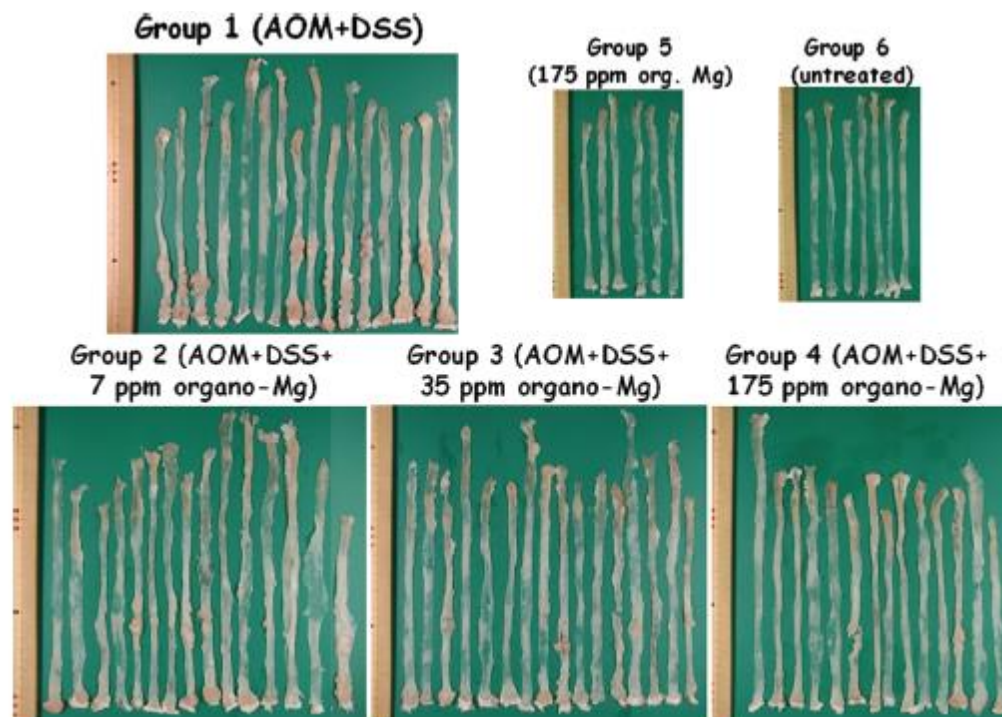
Carcinogenesis vol.34 no.2 pp.361–369, 2013
doi:10.1093/carcin/bgs348
Advance Access publication November 3, 2012

Organomagnesium suppresses inflammation-associated colon carcinogenesis in male Crj: CD-1 mice

Toshiya Kuno¹, Yuichiro Hatano¹, Hiroyuki Tomita¹,
Akira Hara¹, Yachinobu Hirose¹, Akihito Hirata²

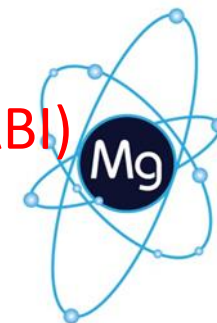
There has been a marked increase in the understanding of cell and molecular mechanisms underlying a variety of carcinogenic pro-

Azoxymetane
Dextran
Sulphate

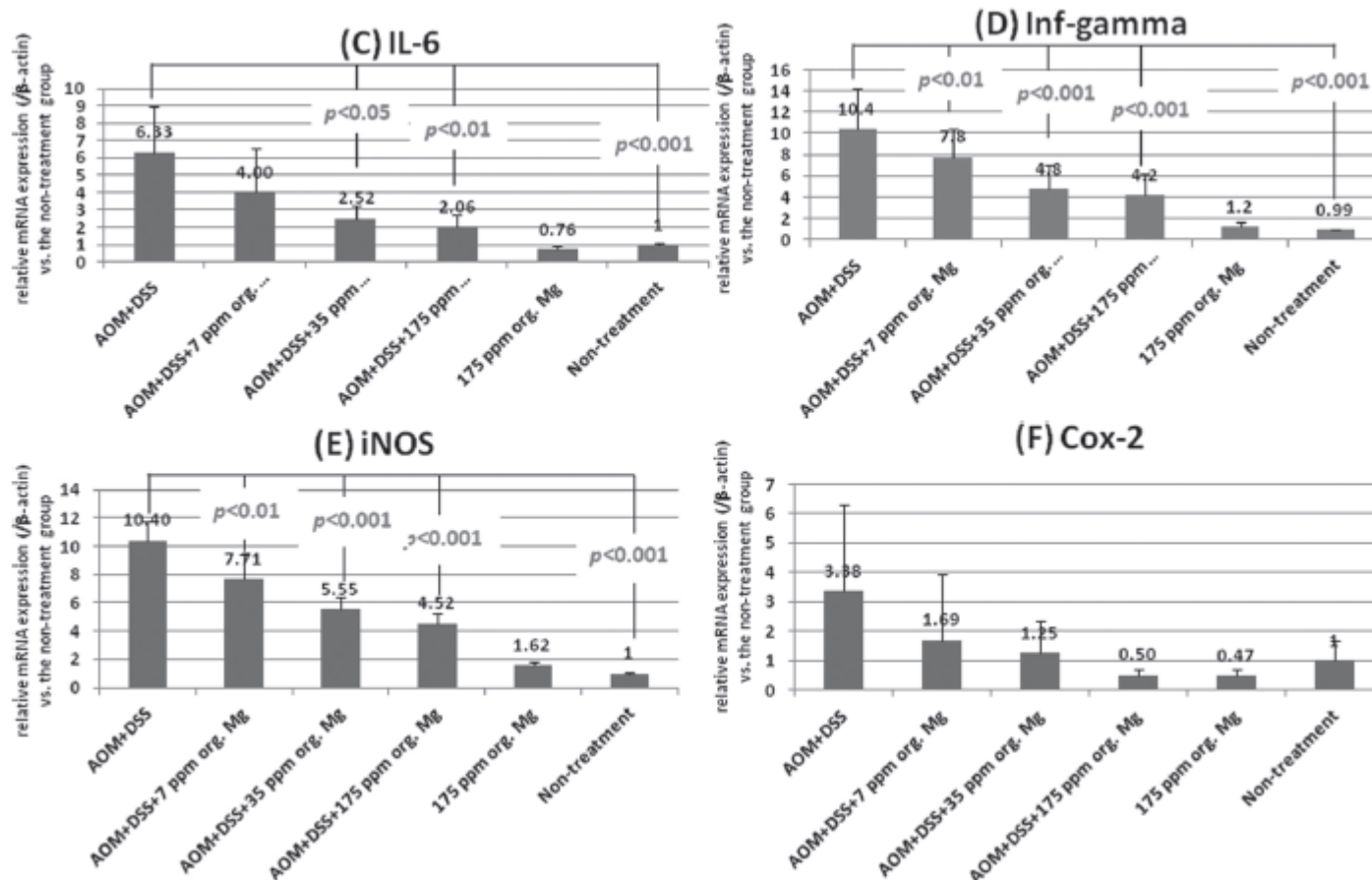


- Inflammation score
- Mitotic index (AI)
- **Inflammatory cytokines:**
- *TNF α* , *IL-1 β* , *IL-6*, *INF- γ* ,

- MCM2-positive index
- Anaphase Bridging Index (ABI)
- *iNOS*, *Cox-2*



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Conclusion



- **Organo-Mg inhibits inflammation-related mouse colon carcinogenesis by modulating**
 - the proliferative activities
 - chromosomal instability of CRC and
 - suppressing colonic inflammation
- *Results may suggest potential use of*
- *organo-Mg for clinical chemoprevention trials of CRC in the inflamed colon.*
 - *Toshiya K, Carcinogenesis, 2013*

Tumour growth and spreading:



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- $< \text{Mg}^{2+}$

- Proliferation,

- Metabolism

- Angiogenesis



Primary tumou growth

- $< \text{Mg}^{2+}$

- Invasion



- Metastasis

- $< \text{Mg}^{2+}$



- Inflammation

Metastatization

Magnesium and cell cycle regulation

Magnesium Depletion Causes Growth Inhibition, Reduced Expression of Cyclin D1, and Increased Expression of P27^{KIP1} in Normal But Not in Transformed Mammary Epithelial Cells

ALESSANDRO SGAMBATO,* FEDERICA I. WOLF, BEATRICE FARAGLIA,
AND ACHILLE CITTADINI

ARTICLE

Journal of Cellular Biochemistry 112:3563–3572 (2011)

Journal of **Cellular
Biochemistry**

Magnesium Deficiency Suppresses Cell Cycle Progression Mediated by Increase in Transcriptional Activity of p21^{Cip1} and p27^{Kip1} in Renal Epithelial NRK-52E Cells

Akira Ikari,^{1*} Hayato Sawada,¹ Ayumi Sanada,¹ Chie Tonegawa,¹ Yasuhiro Yamazaki,¹ and Junko Sugatani^{1,2}

¹Department of Pharmaco-Biochemistry, School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan

²Global Center of Excellence for Innovation in Human Health Sciences, School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan

Magnesium and angiogenesis

In vitro data

Circulation
Research

JOURNAL OF THE AMERICAN HEART ASSOCIATION



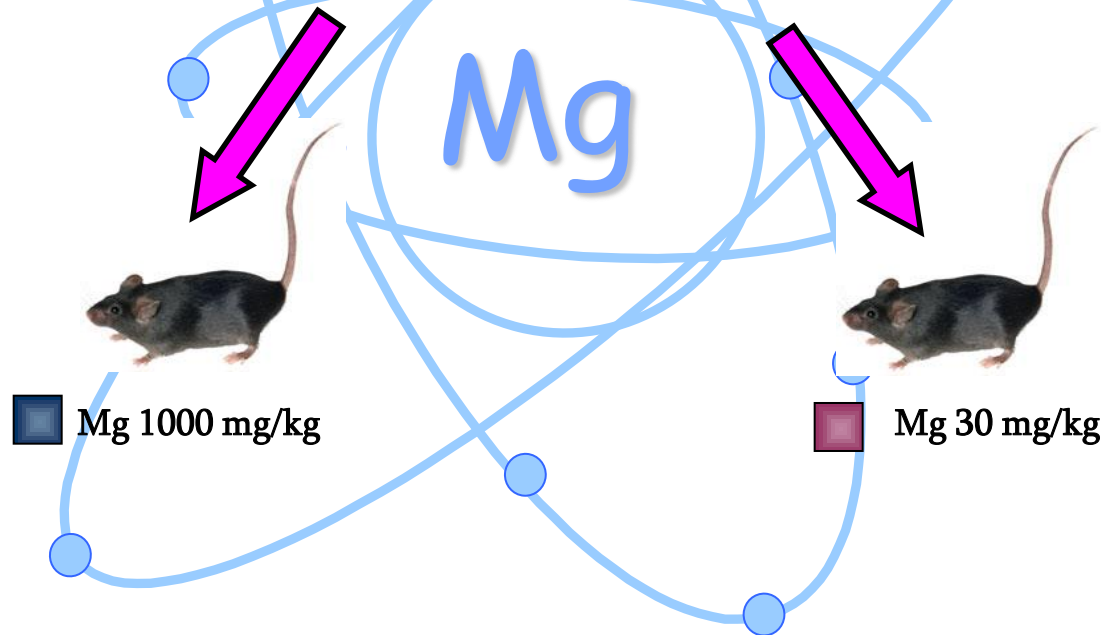
Influence of extracellular magnesium on capillary endothelial cell proliferation and migration.

S Banai, L Haggroth, S E Epstein and W Casscells

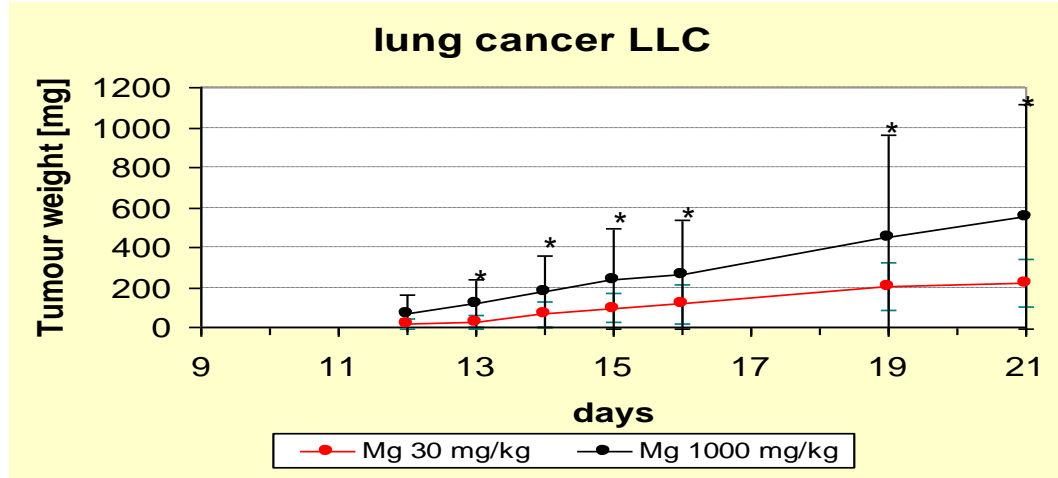
J. Maier, J. Maier, J. Maier, J. Maier

Magnesium and Tumour growth: *in vivo data*

TRANSPLANTED TUMOR CELLS



NATO collaborative linkage grant, 2004-2006



IN CONDITIONS OF HYPOMAGNESEMIA:

- TUMOR GROWTH (LUNG, COLON, MAMMARY) WAS SIGNIFICANTLY INHIBITED
- TUMORS WERE LESS VASCULARIZED
- TUMOR OXIDATIVE DNA DAMAGE WAS HIGHER
- CLEAR-CUT SIGNS OF IMMUNO-INFLAMMATORY RESPONSE

Nasulewicz A, et al. *Biochim Biophys Acta* 2004.

Maier JAM et al. *Nutr & Cancer*, 2007

Wolf FI et al., *Nutr & Cancer*, 2008


Inflammation and cancer

- **EXSTRINSIC**

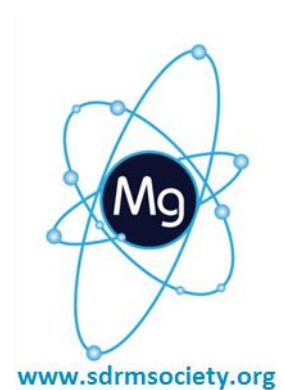
- INFECTIOUS,
INFLAMMATORY CONDITIONS

- **INTRINSIC**

- ONCOGENETIC EVENTS

- 
- The diagram illustrates the pathways from extrinsic and intrinsic factors to cancer-related inflammation. Two large purple arrows point from the 'EXSTRINSIC' and 'INTRINSIC' categories towards a central list of factors. A third large purple arrow points from this central list down to the final outcome, 'CANCER-RELATED INFLAMMATION'.
- Transcription factors (*NF-kB; STAT3; HIFs*)
 - Inflammatory cells (**PMN, Eo, Macro**)
 - CHEMOKINES, CYTOKINES PROSTAGLANDINS :
 - **IL-1, TNF, VEGF, CXCL8, CCL2, COX2**

CANCER-RELATED INFLAMMATION



CANCER-RELATED INFLAMMATION



Tumour microenvironment



Proliferation, survival, EMT;

angiogenesis and lymphangiogenesis;

migration, invasion, metastasis;

inhibition of adaptive immunity;

Response to hormones and chemotherapeutic agents

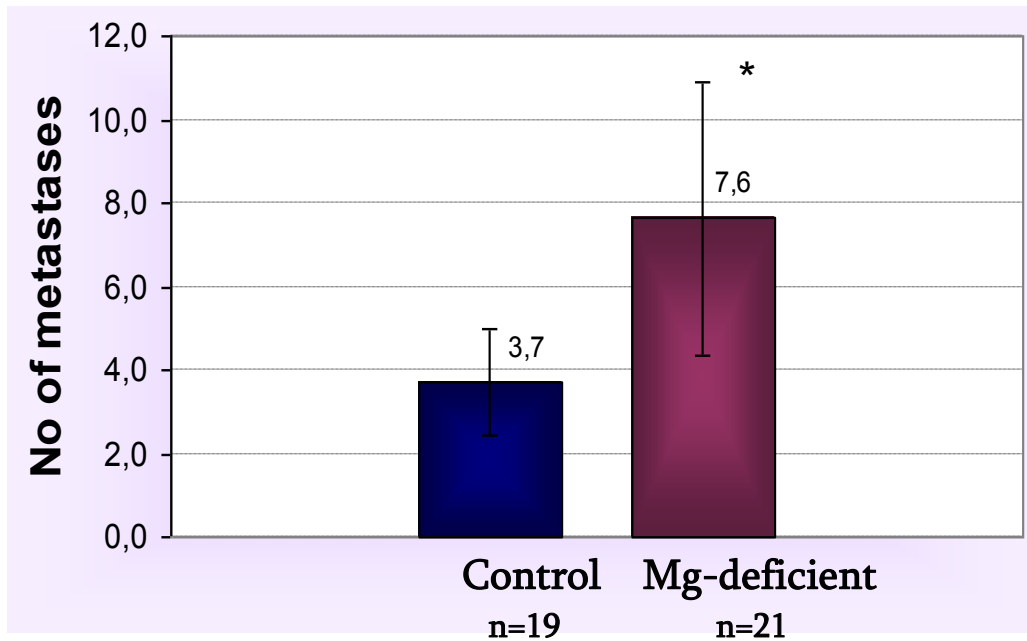


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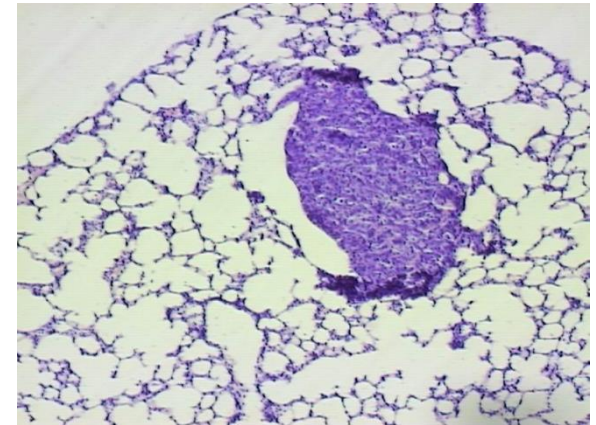
www.sdrmsociety.org

Mg deficiency enhanced metastatic potential of LLC cells in C57Bl/6 mice



* $p < 0.05$

Lung metastatic focus in
Mg-deficient mice



*Magnesium Deficiency Inhibits Primary Tumor Growth
But Favors Metastasis in mice.*

Nasulewicz A., et al., BBA, 2004

Magnesium and Tumour treatment

Cisplatin

EGFR mAb: cetuximab



Hypomagnesemia



- Normomagnesaemia: 1.9-2.5 mg/dL (0.78-1.03 mmol/L);
- Hypomagnesaemia : < 1.8 mg/dL (0.74 mmol/L);
- **NCI-CTCAE grading of symptomatic hypoMg:**
- **grade 1** [1.2 mg/dL (0.5 mmol/L)],
- **grade 2** [1.2-0.9 mg/dL (0.5-0.4 mmol/L)],
- **grade 3** [0.9-0.7 mg/dL (0.37-0.29 mmol/L)],
- **grade 4** [<0.7 mg/dL (< 0.29 mmol/L)];

.....does it affect treatment outcome ??

Magnesium and Tumour treatment:



Clinical Cancer Research

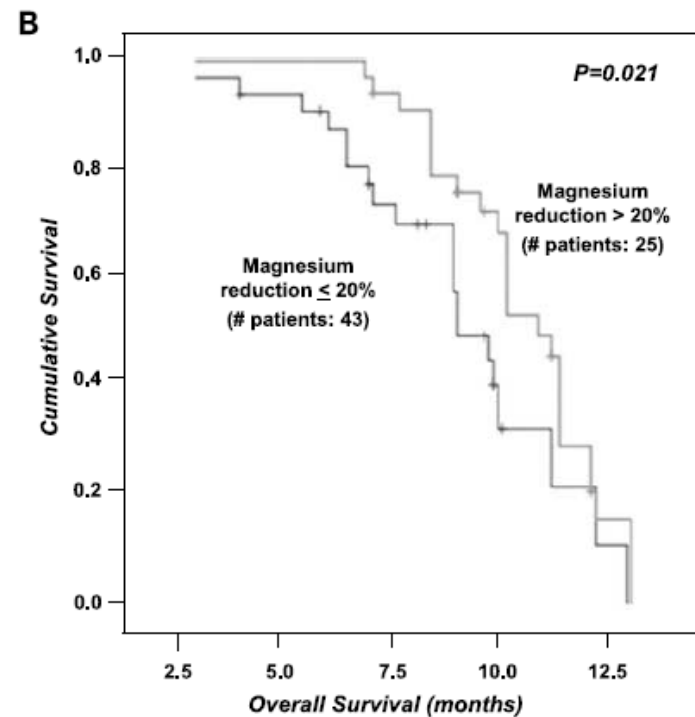
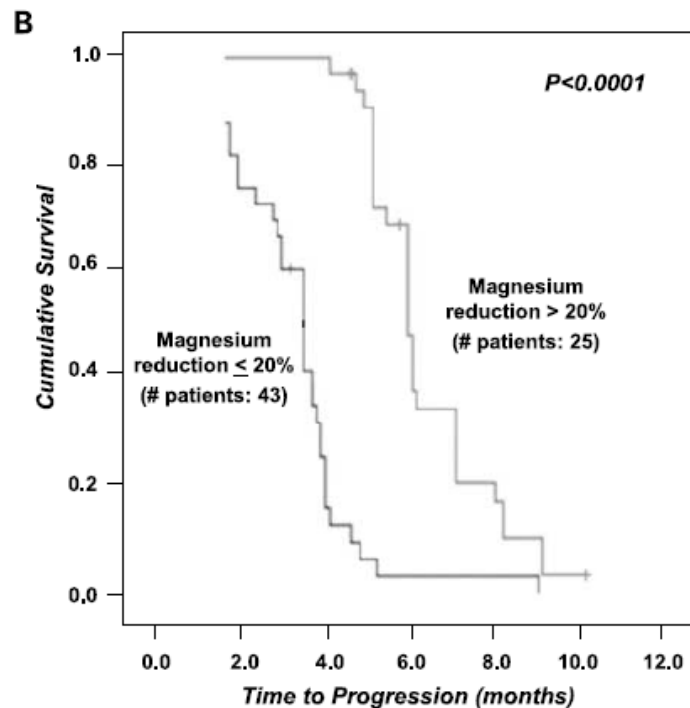
ACR

Early Magnesium Reduction in Advanced Colorectal Cancer Patients Treated with Cetuximab Plus Irinotecan as Predictive Factor of Efficacy and Outcome

Bruno Vincenzi, Daniele Santini, Sara Galluzzo, et al.

Clin. Cancer Res. 2008;14:4219-4224

http://googleads.g.doubleclick.net/aclick?sa=L&ai=CzmtIE5xxU9-XBqS_JAL42oDJCqigxNcEAA...



Magnesium and Tumour treatment:

Incidence and risk of hypomagnesemia in advanced cancer patients treated with cetuximab: A meta-analysis.

Chen P, Wang L, Li H, Liu B, Zou Z.
Oncol Lett. 2013 Jun;5(6):1915-1920.

The study concluded that cetuximab is associated with a significant risk of hypomagnesemia in patients with advanced cancer receiving concurrent chemotherapy.

Clinical relevance and utility of cetuximab-related changes in magnesium and calcium serum levels.

Stintzing S, Fischhaber D, Mook C, Modest DP, Giessen C, Schulz C, Haas M, Boeck S, Michl M, Stemmler J, Laubender RP, Heinemann V.
Anticancer Drugs. 2013 Oct;24(9):969-74.

“As hypomagnesemia was more prominent in patients receiving platinum agents, magnesium measurements may be advised in these patients.

In mCRC patients treated with cetuximab, day-14 magnesium serum levels correlated with treatment efficacy.”



Magnesium and Tumour treatment:



Annals of Oncology 24: 953–960, 2013

doi:10.1093/annonc/mds577

Published online 8 November 2012

Association of hypomagnesemia with inferior survival in a phase III, randomized study of cetuximab plus best supportive care versus best supportive care alone: NCIC CTG/AGITG CO.17

M. M. Vickers¹, C. S. Karapetis², D. Tu³, C. J. O'Callaghan³, T. J. Price⁴, N. C. Tebbutt⁵, G. Van Hazel⁶, J. D. Shapiro⁷, N. Pavlakis⁸, P. Gibbs⁹, J. Blondal¹⁰, U. Lee¹¹, J. M. Meharchand¹², R. L. Burkes¹³, S. H. Rubin¹⁴, J. Simes¹⁵, J. R. Zalcberg¹⁶, M. J. Moore¹⁷, L. Zhu³ & D. J. Jonker¹⁸

Conclusions: In contrast to prior reports, cetuximab-induced hypomagnesemia was associated with poor OS, even after adjustment for grade of rash.



Conclusions



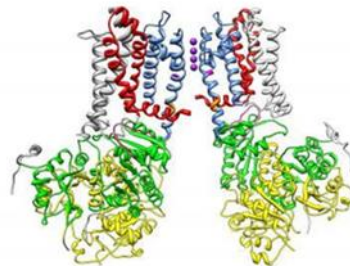
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- ❖ Magnesium affects all steps of carcinogenesis and tumour growth
 - ❖ Low magnesium enhances neoplastic transformation
- ❖ Low magnesium inhibits tumour growth but favors metastasis
- ❖ Hypomagnesemia is a consequence of nephrotoxic therapeutic drugs
- ❖ Its role as predictor factor of therapeutic efficacy or as chemotherapy enhancer is debated

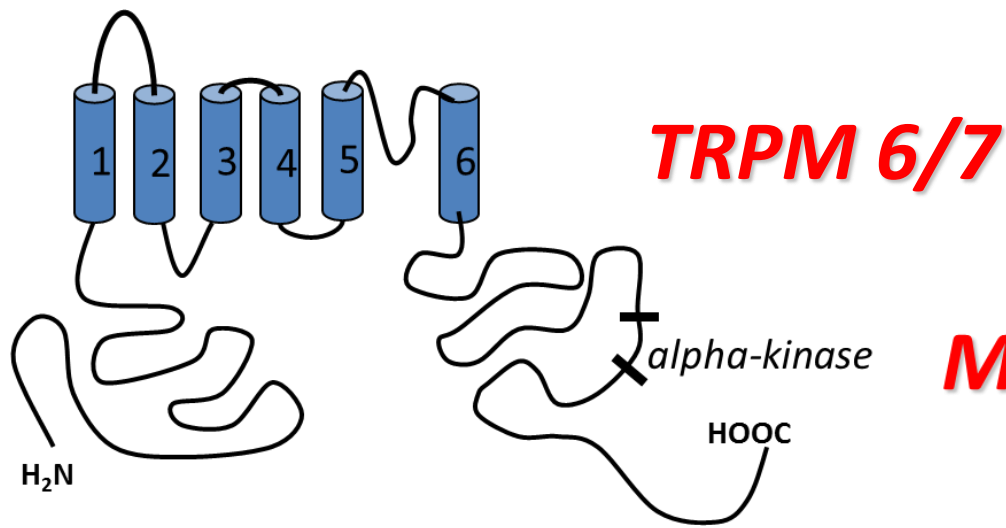
Magnesium and Tumour :

From bedside back to
Bench

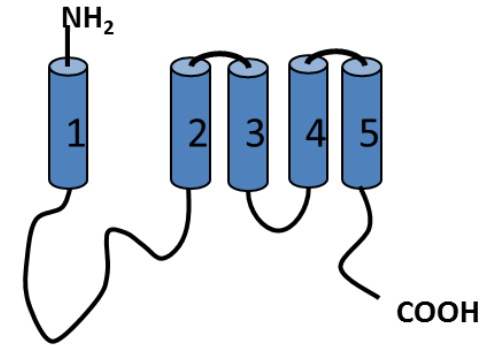
ION CHANNELS AND MAGNESIUM HOMEOSTASIS



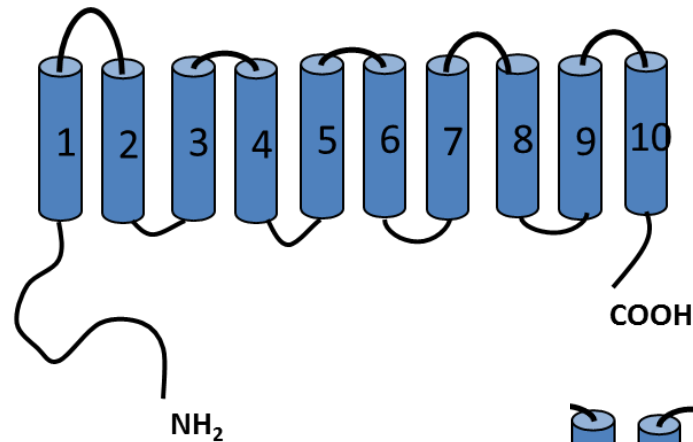
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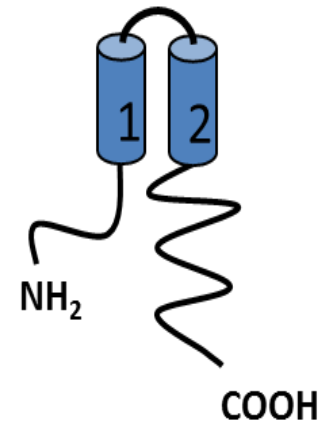
MagT1



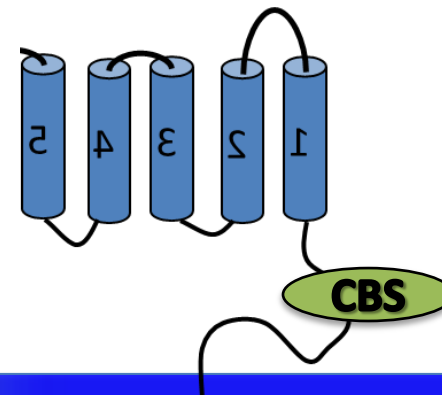
SLC41A2



Mrs2



CNNM1-4

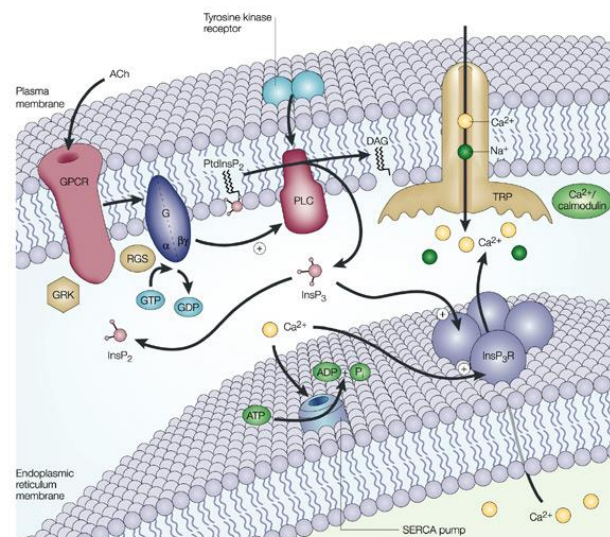


Ion channels in tumours

Regulate:
Proliferation
Invasion
Chemoresistance

Hence.....

*Inhibition of Ion channels can be exploited as
New Therapeutic strategy*



Nature Reviews | Drug Discovery

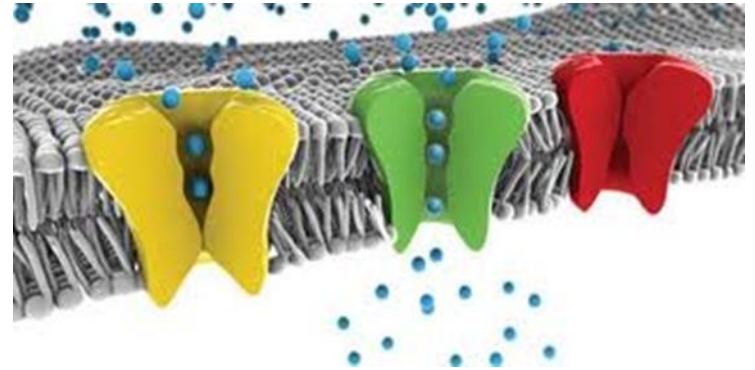
TRPM7 in cancer

Functions:

Regulates cell proliferation

Metabolic reprogramming

Migration



TRPM7 and metabolic reprogramming

Cancer cells: Warburg Effect (Aerobic glycolysis)

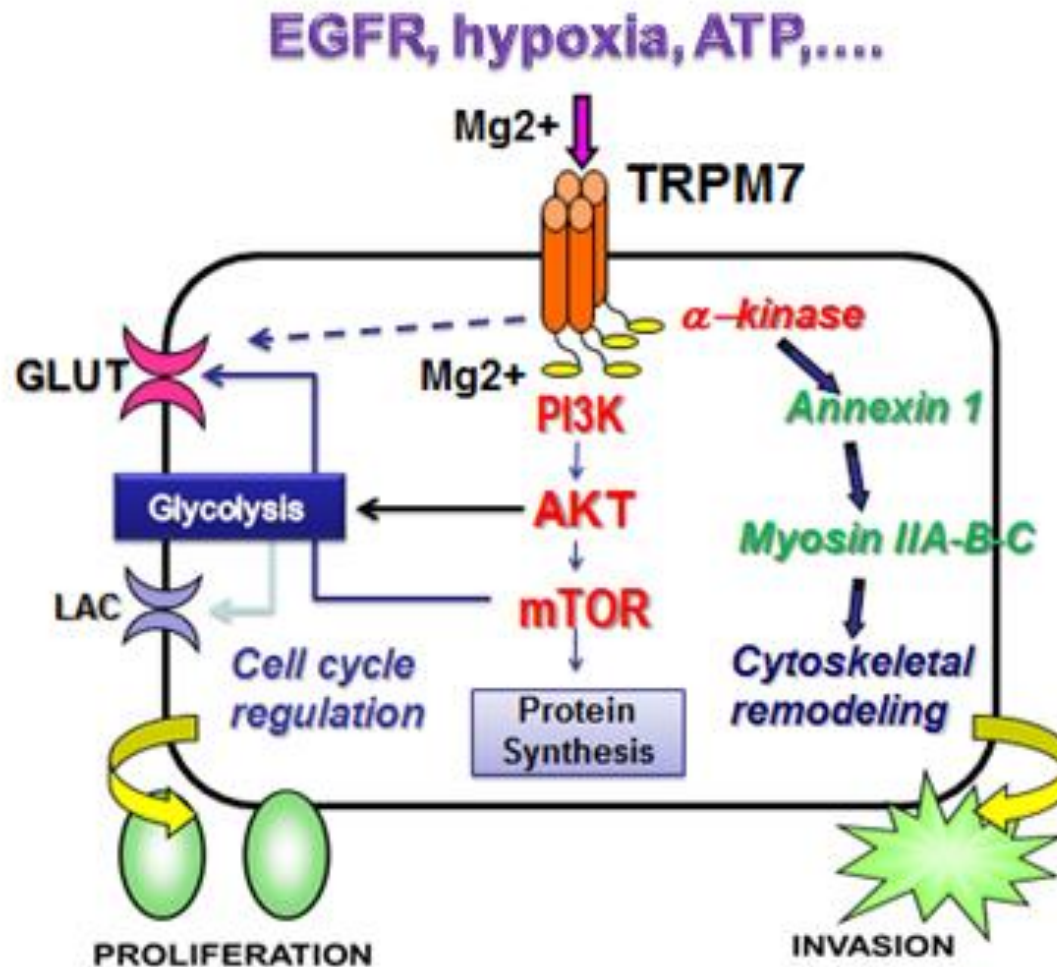
Proliferating cells : Metabolic reprogramming

*High glucose consumption,
Macromolecules biosynthesis,
DNA synthesis
Cytoskeletal remodelling*



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TRPM7 metabolism and proliferation



Wolf & Trapani, Clin Sci, 2012

TRPM7 in proliferation and cancer

Am J Physiol Cell Physiol 297: C493–C502, 2009.
First published June 10, 2009; doi:10.1152/ajpcell.00624.2008.

Evidence that TRPM7 is required for breast cancer cell proliferation

Arnaud Guilbert,^{1*} Mathieu Gautier,^{1*} Isabelle Dhennin-Duthille,¹ Nathalie Haren,¹ Henri Sevestre,^{1,2} and Halima Ouadid-Ahidouch¹

¹Laboratoire de Physiologie Cellulaire et Moléculaire, JE 2530: Canaux Ioniques dans le Cancer du Sein, Faculté des Sciences, and ²Service d'Anatomie Pathologique, Centre Hospitalier Universitaire Nord, Amiens, France

Table 1. Correlation between TRPM7 expression and tumor grade

Tumor Grade	TRPM7 Overexpression	<i>n</i>	χ^2
Grade I	45.4%	11	0.5051
Grade III	60%	10	

Correlation between melastatin transient receptor potential (TRPM)7 expression and tumor grade in 21 patients by χ^2 analysis is shown. A significant statistical correlation is identified when the returned *P* was <0.05.

RESEARCH ARTICLE

Disease Models & Mechanisms 4, 240–254 (2011) doi:10.1242/dmm.004564

Transient receptor potential ion channel Trpm7 regulates exocrine pancreatic epithelial proliferation by Mg²⁺-sensitive Socs3a signaling in development and cancer

Nelson S. Yee^{1,2,*}, Weiqiang Zhou^{1,2,5} and I-Chau Liang^{1,2,5,†}

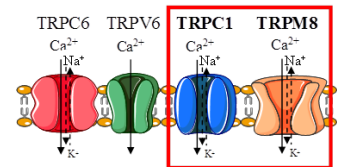


High Expression of Transient Receptor Potential Channels in Human Breast Cancer Epithelial Cells and Tissues: Correlation with Pathological Parameters

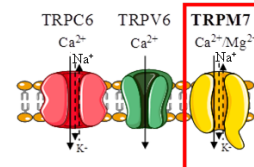
Isabelle Dhennin-Duthille¹, Mathieu Gautier¹, Malika Faouzi¹, Arnaud Guilbert¹, Marie Brevet^{1,2}, David Vaudry³, Ahmed Ahidouch^{1,4}, Henri Sevestre^{1,2} and Halima Ouadid-Ahidouch¹

A Proliferative status

Grade I
size < 2cm
Ki67 < 10%

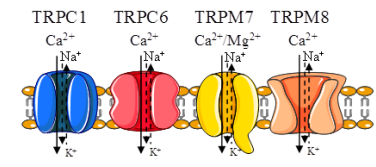


Grade III
size > 2cm
Ki67 > 10%

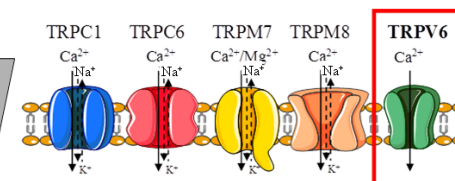


B Invasive status

Non-invasive



Invasive



aggressiveness

TRPM and migration

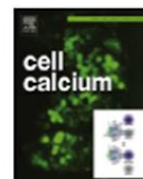
Cell Calcium 50 (2011) 559–568



Contents lists available at SciVerse ScienceDirect

Cell Calcium

journal homepage: www.elsevier.com/locate/ceca



EGF enhances the migration of cancer cells by up-regulation of TRPM7

Haixia Gao^{a,b}, Xingjuan Chen^{a,b}, Xiaona Du^{a,b}, Bingcai Guan^{a,b}, Yani Liu^{a,b}, Hailin Zhang^{a,b,*}

^a The Key Laboratory of Neural and Vascular Biology, Ministry of Education, Hebei Medical University, Shijiazhuang, PR China

^b The Key Laboratory of Pharmacology and Toxicology for New Drugs, Department of Pharmacology, Hebei Medical University, Shijiazhuang, PR China

BJ www.biochemj.org

Biochem. J. (2011) 434, 513–521 (Printed in Great Britain) doi:10.1042/BJ20101678



TRPM7 regulates polarized cell movements

Li-Ting SU^{*1,2}, Wei LIU^{†1}, Hsiang-Chin CHEN^{*}, Omayra GONZÁLEZ-PAGÁN^{*}, Raymond HABAS^{†3} and Loren W. RUNNELS^{*3}

^{*}Department of Pharmacology, Robert Wood Johnson Medical School, 675 Hoes Lane, Piscataway, NJ 08854, U.S.A., and [†]Department of Biology, College of Science and Technology, Temple University, 1900 North 12th Street, Philadelphia, PA 19122, U.S.A.

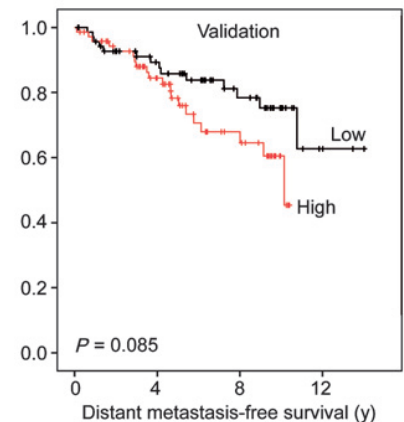
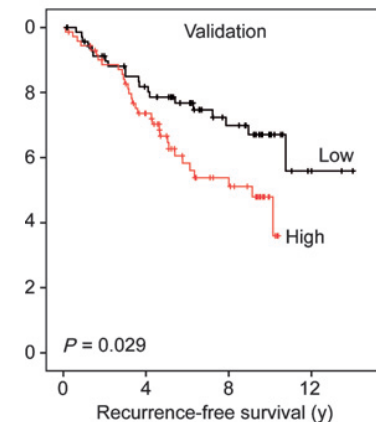
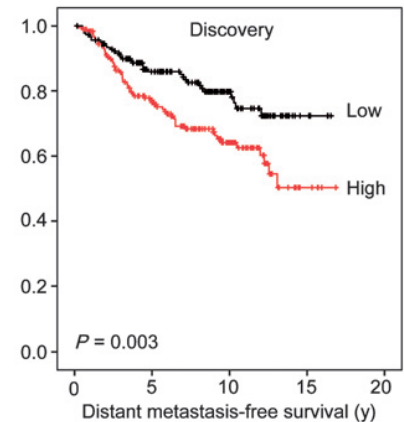
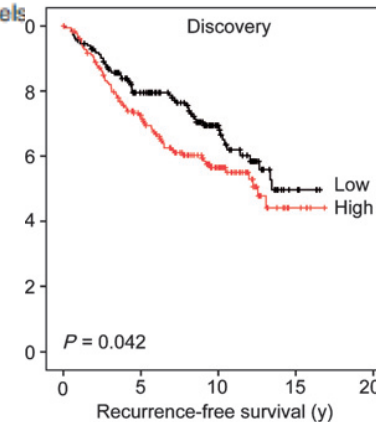
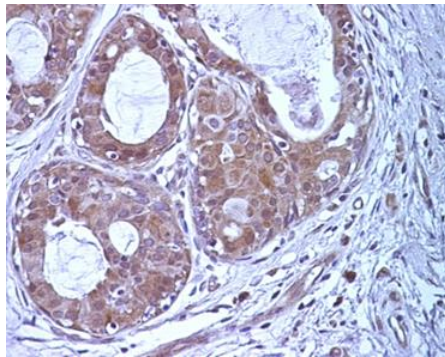
TRPM7 expression in breast cancer

Tumor and Stem Cell Biology

Cancer
Research

TRPM7 Is Required for Breast Tumor Cell Metastasis

Jeroen Middelbeek¹, Arthur J. Kuipers¹, Linda Henneman⁶, Daan Visser⁶, Ilse Eidhof¹, Remco van Hoesen², Bé Wieringa², Sander V. Carisius⁷, Wilbert Zwart⁹, Lodewyk F. Wessels¹, Paul N. Span⁵, Frank N. van Leeuwen¹, and Kees Jalink⁶



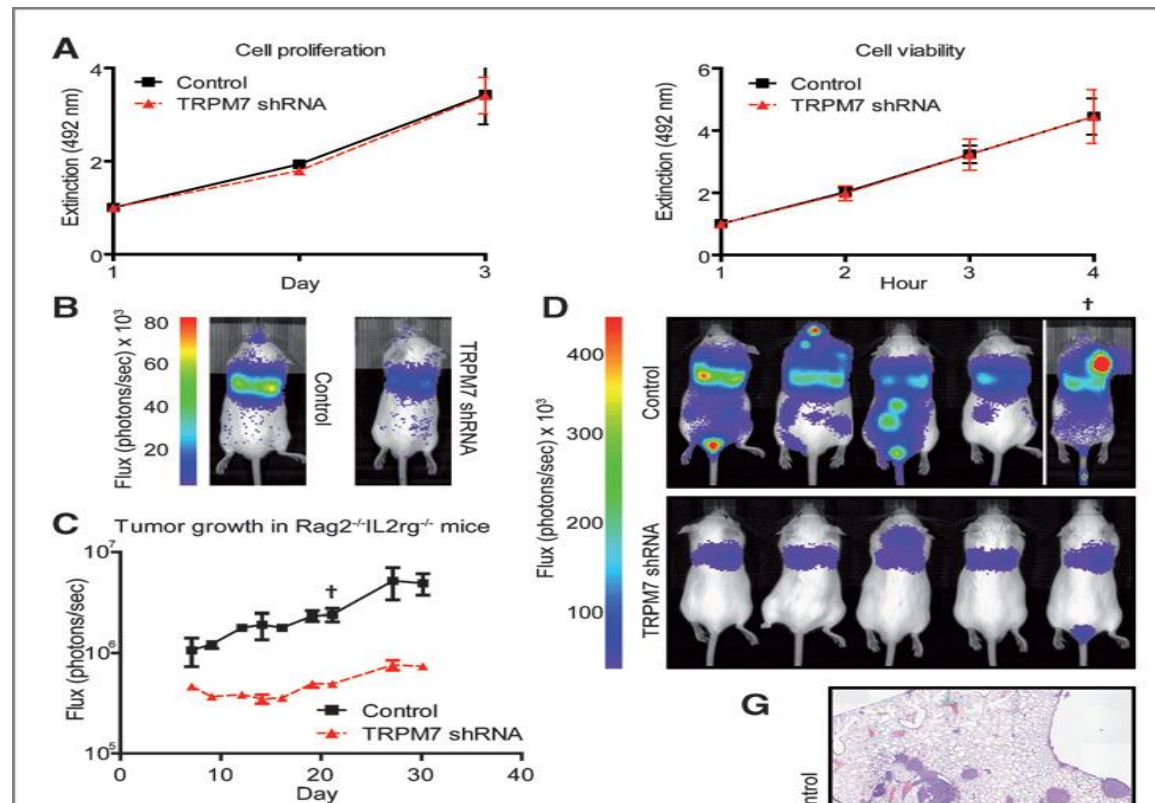
TRPM7 expression in cancer

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Contents lists available at SciVerse ScienceDirect

Cancer Letters

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TRPM7 mediates breast cancer cell migration and invasion through the MAPK pathway

Xiaojing Meng^{a,1}, Chunqing Cai^{a,1}, Jiguo Wu^a, Shaoxi Cai^b, Changsheng Ye^c, Haiyang Chen^a, Zhengduo Yang^d, Hongqiang Zeng^a, Qiang Shen^{d,*}, Fei Zou^{a,*}

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^c Breast Center, Nanfang Hospital, Southern Medical University, Guangzhou, China

^d Department of Clinical Cancer Prevention, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

European Journal of Cancer (2013) 49, 3694–3707



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journal homepage: www.ejancer.com



Transient receptor potential melastatin 7 is involved in oestrogen receptor-negative metastatic breast cancer cells migration through its kinase domain

A. Guilbert^{a,d}, M. Gautier^{a,d}, I. Dhennin-Duthille^{a,d}, P. Rybarczyk^a, J. Sahni^b, H. Sevestre^{a,c}, A.M. Scharenberg^b, H. Ouadid-Ahidouch^{a,*}

TRPM7 over-expression in ductal pancreatic carcinoma



IJC
International Journal of Cancer

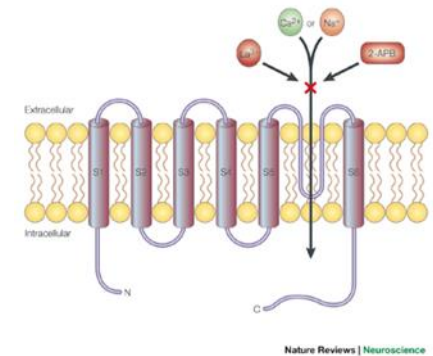
Transient receptor potential melastatin-related 7 channel is overexpressed in human pancreatic ductal adenocarcinomas and regulates human pancreatic cancer cell migration

Pierre Rybarczyk¹, Mathieu Gautier¹, Frédéric Hague¹, Isabelle Dhennin-Duthille¹, Denis Chatelain², Julie Kerr-Conte³, François Pattou³, Jean-Marc Regimbeau⁴, Henri Sevestre^{1,2} and Halima Ouadid-Ahidouch¹

TRPM7 regulates cell migration by a Mg^{2+} -dependent mechanism.

TRPM7 is a promising biomarker of PDAC progression and prognosis.

TRPM7 as a therapeutic target



SiRNA o KO inhibits cell proliferation /migration

KO cells can survive only in 30 mM Mg^{2+}

Chemical inhibition

Co-examine, APB

Imipramine / Quinidine

Waixenicin (*Zierler, JBC, 2011*)

NS8593 -SCCa-Ki (*Chubanov, BJP, 2012*)

TRPM7 inhibition

BJP British Journal of
Pharmacology

RESEARCH PAPER

Natural and synthetic modulators of SK (K_{Ca2}) potassium channels inhibit magnesium-dependent activity of the kinase-coupled cation channel TRPM7

V Chubanov^{1*}, M Mederos y Schnitzler^{1*}, M Meißner¹, S Schäfer¹,
K Abstiens¹, T Hofmann² and T Gudermann¹

¹Walther-Straub-Institute of Pharmacology and Toxicology, University of Munich, Munich,
Germany, and ²Institute of Pharmacology, University of Marburg, Marburg, Germany

DOI:10.1111/j.1476-5381.2012.01855.x
www.bjppharmacol.org

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*These authors contributed
equally.

Keywords

transient receptor potential;
TRPM7; SK channels; $K_{Ca2.1-2.3}$
channels; magnesium; cell
motility

Received

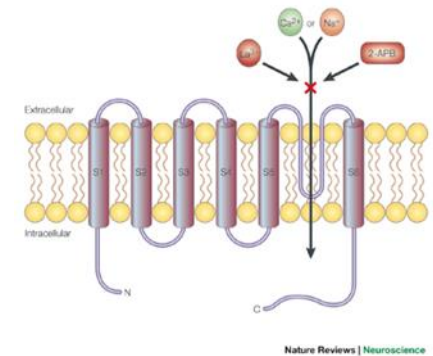
24 May 2011

Revised

15 December 2011

Accepted

4 January 2012



The Role of Waixenicin A as Transient Receptor Potential Melastatin 7 Blocker.

Kim BJ, Nam JH, Kwon YK, So I, Kim SJ.

Basic Clin Pharmacol Toxicol. 2012 Aug 18. [Epub ahead of print]

2007

Epidemiologic data: TRPM7 polymorphism and $\text{Ca}^{2+}/\text{Mg}^{2+}$ in colon carcinogenesis; (Dai, 2007)

TRPM7 and **proliferation** in human **head and neck carcinoma** cells (Jiang CR2007)

TRPM7 suppression induced **apoptosis** in **gastric cancer** (Kim, CS2008)

TRPM7 is required **for breast cancer** cell **proliferation**; overexpressed in grade III breast cancer samples (Guilbert, AJPCP 2009)

2010

TRPM7 regulates the **migration** of human **nasopharyngeal carcinoma** cell (Chen Cell Ca 2010)

Up-regulation of TRPM7 by EGF enhances the **migration** of cancer cells (Gao cell Ca 2011)

TRPM7 in human **breast ductal adenocarcinoma**: prognostic factor (Dhennin-Duthille CPB 2011)

TRPM7 has an important role in the **growth and survival** of **gastric cancer** cells (Kim CJPP 2012)

TRPM7 regulates cell **migration** in human **pancreatic ductal adenocarcinoma** (Rybarczyk IJC 2012)

2012

TRPM7 is required for **breast tumor** cell **metastasis**. (Middelbeek CR 2012)

TRPM7 activated by $\text{Ca}^{2+}/\text{Mg}^{2+}$ promotes **proliferation** of **prostate cancer** cells (Sun JBC 2013)

TRPM7 mediates **breast cancer** cell **migration and invasion** (Meng CL 2013)

2013

TRPM7 is involved in **EMT** in **breast cancer** cells (Davies O 2013)

TRPM7 is involved in ER-metastatic **breast cancer** cells **migration** (Guilbert EJC 2013)

Magnesium transporters in cancer: New raising star

Oncogene (2014), 1–10

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www.nature.com/onc



ORIGINAL ARTICLE

The protein tyrosine phosphatase PRL-2 interacts with the magnesium transporter CNNM3 to promote oncogenesis

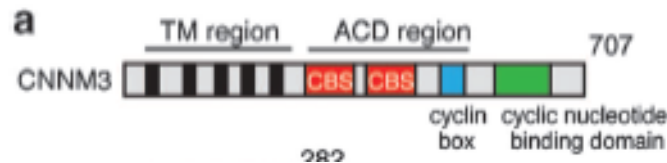
S Hardy¹, N Uetani¹, N Wong^{1,2}, E Kostantin^{1,2}, DP Labbé^{1,3}, LR Bégin⁴, A Mes-Masson⁵, D Miranda-Saavedra^{6,7} and ML Tremblay^{1,2,3}

- PRL-2 is key contributors to metastasis in several human cancers
- PRL-2 is overexpressed in breast cancer
- PRL-2 regulates intracellular magnesium levels by forming a functional heterodimer with the magnesium transporter CNNM3
- CNNM3 is not a phosphorylated substrate of PRL-2, the interaction occurs through a loop unique to the CBS pair domains

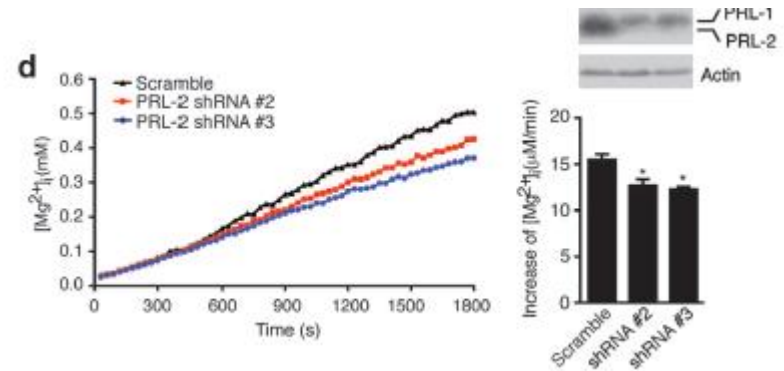
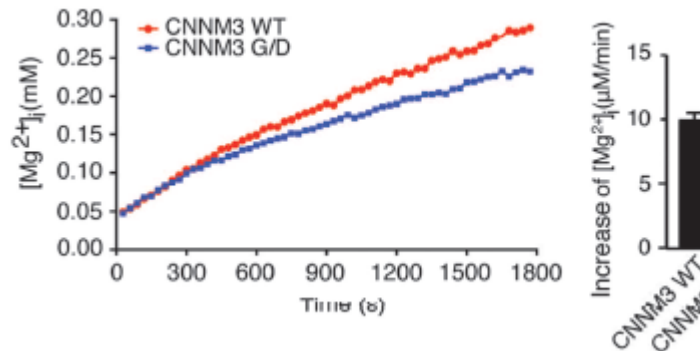


Magnesium transporters in cancer:

New rising star

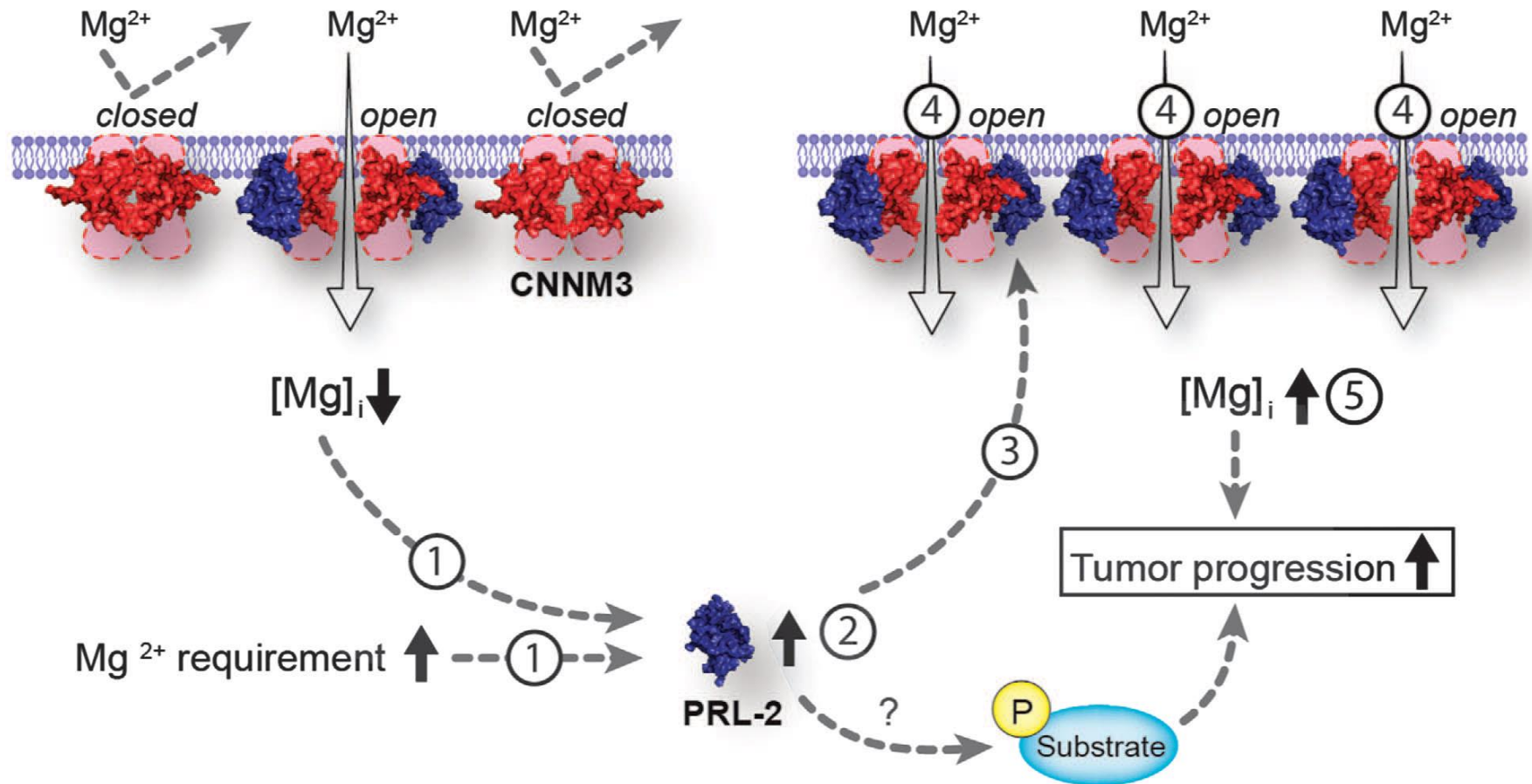


- PRL-2 knockdown results in a substantial decrease of cellular magnesium influx
- CNNM3 association is important for conferring transforming activities
- in human breast
- cancer tissues showing that CNNM3 levels correlate positively with both PRL-2 expression and the tumor proliferative index.

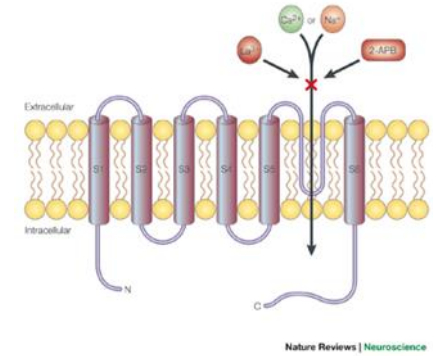


Magnesium in carcinogenesis

Biochemical, in vitro data



Conclusion



- ✓ Ion channels are able to affect tumour cell behaviours
 - ✓ TRPM7 is essential component of **metabolism, proliferation and invasion**
 - ✓ It is **overexpressed** in some tumours
 - ✓ It can be utilized as a prognostic factor
 - ✓ It can be exploited **as therapeutic target**

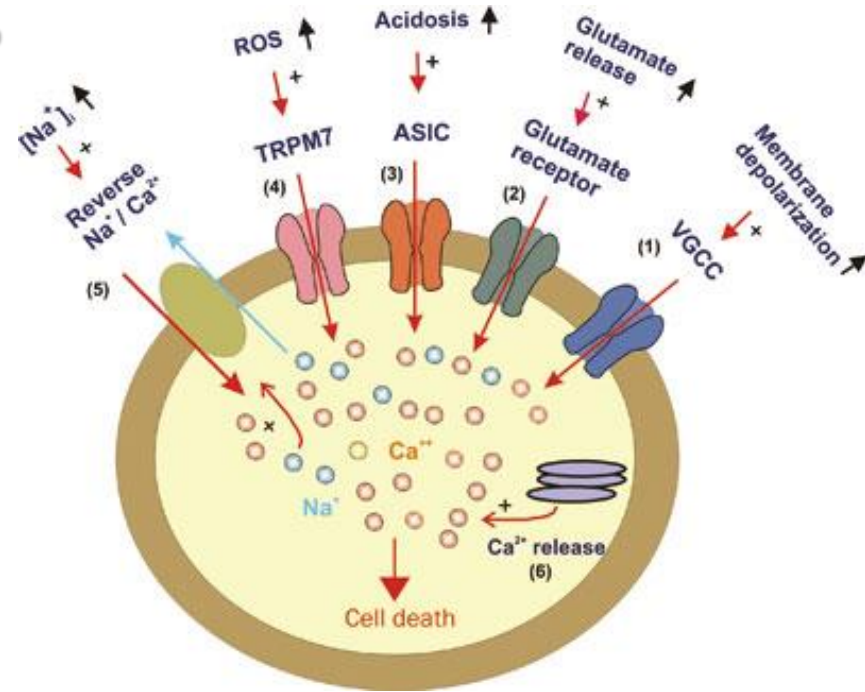
We propose....

To include the

«ion channel signature»

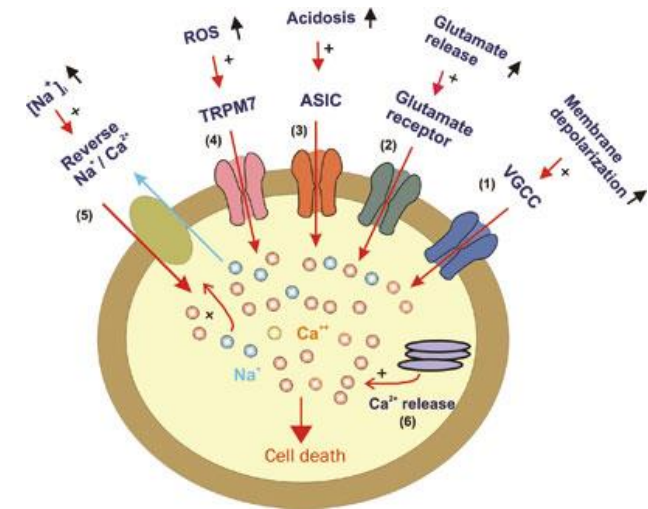
as a promising strategy for the treatment of
cancer

How far, How close.....



How close....

Other Magnesium transporters
or Mg transport-Related protein
are emerging



How far....

Further research from bench to bedside is required for
identifying the most efficient strategy to target
magnesium homeostasis as novel therapeutic
strategies.

Istituto di Patologia generale
Chairman Prof. Achille Cittadini

INRA Clermont-Ferrand,
France

Andrè Mazur

Valentina Trapani
Alessandro Sgambato
Alma Boninsegna
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