

1. Oncointegrazione e Chemioprevenzione

La patologia oncologica e l'acidosi (*acidemia*)

Science. 1956 Aug 10;124(3215):269-70.

On respiratory impairment in cancer cells.

WARBURG O.

PMID: 13351639 [PubMed - indexed for MEDLINE]

La cellula tumorale presenta un
metabolismo anaerobico-lattacido

La cellula tumorale è caratterizzata da un metabolismo prevalentemente anaerobico-lattacido determinando contestualmente un microambiente caratterizzato da ipossia e basso pH (2009)

The Genomic Analysis of Lactic Acidosis and Acidosis Response in Human Cancers

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Il processo di acidificazione delle matrici extratumorali aumentano significativamente il tasso di aggressività e metastatizzazione.

Cancer Res. 2006 Jul 1;66(13):6699-707.

Acidic extracellular pH promotes experimental metastasis of human melanoma cells in athymic nude mice.

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Abstract

Extracellular pH (pH(e)) is lower in many tumors than in the corresponding normal tissue. The significance of acidic pH(e) in the development of metastatic disease was investigated in the present work. Human melanoma cells (A-07, D-12, and T-22) were cultured in vitro at pH(e) 6.8 or 7.4 (control) before being inoculated into the tail vein of BALB/c nu/nu mice for formation of experimental pulmonary metastases. Cell invasiveness was studied in vitro by using Matrigel invasion chambers and angiogenesis was studied in vivo by using an intradermal assay. Protein secretion was measured by ELISA and immunocapture assays. Cells cultured at acidic pH(e) showed increased secretion of proteinases and proangiogenic factors, enhanced invasive and angiogenic potential, and enhanced potential to develop experimental metastases. Acidity-induced metastasis was inhibited by treatment with the general matrix metalloproteinase (MMP) inhibitor GM6001, the general cysteine proteinase inhibitor E-64, or blocking antibody against vascular endothelial growth factor-A (VEGF-A) or interleukin-8 (IL-8). Our study indicates that acidic pH(e) promotes experimental pulmonary metastasis in A-07, D-12, and T-22 human melanoma cells by a common mechanism involving acidity-induced up-regulation of the proteolytic enzymes MMP-2, MMP-9, cathepsin B, and cathepsin L and acidity-induced up-regulation of the proangiogenic factors VEGF-A and IL-8. One

Le condizioni di ipossia e di gradiente acido (basso pHe ed alto pHi) conferiscono alla massa tumorale radio-resistenza e chemio-resistenza.

Cancer Res. 1989 Aug 15;49(16):4373-84.

Acid pH in tumors and its potential for therapeutic exploitation.

Tannock IF, Rotin D.

Department of Medicine, Ontario Cancer Institute, Toronto, Canada.

Abstract

Measurement of pH in tissue has shown that the microenvironment in tumors is generally more acidic than in normal tissues. Major mechanisms which lead to tumor acidity probably include the production of lactic acid and hydrolysis of ATP in hypoxic regions of tumors. Further reduction in pH may be achieved in some tumors by administration of glucose (+/- insulin) and by drugs such as hydralazine which modify the relative blood flow to tumors and normal tissues. Cells have evolved mechanisms for regulating their intracellular pH. The amiloride-sensitive Na⁺/H⁺ antiport and the DIDS-sensitive Na⁺-dependent HCO₃⁻/Cl⁻ exchanger appear to be the major mechanisms for regulating pHi under conditions of acid loading, although additional mechanisms may contribute to acid extrusion. Mitogen-induced initiation of proliferation in some cells is preceded by cytoplasmic alkalinization, usually triggered by stimulation of Na⁺/H⁺ exchange; proliferation of other cells can be induced without prior alkalinization. Mutant cells which lack Na⁺/H⁺ exchange activity have reduced or absent ability to generate solid tumors; a plausible explanation is the failure of such mutant cells to withstand acidic conditions that are generated during tumor growth. Studies in tissue culture have demonstrated that the combination of hypoxia and acid pHe is toxic to mammalian cells, whereas short exposures to either factor alone are not very toxic. This interaction may contribute to cell death and necrosis in solid tumors. Acidic pH may influence the outcome of tumor therapy. There are rather small effects of pHe on the

L'Alcalinizzazione riduce il tasso di metastatizzazione.

Cancer Res. 2009 March 15; 69(6): 2260–2268. doi:10.1158/0008-5472.CAN-07-5575.

Bicarbonate Increases Tumor pH and Inhibits Spontaneous Metastases

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Cosa sono gli ACIDI e le BASI?

Acidi e basi secondo la teoria di Arrhenius:

- acidi sono sostanze che in soluzione acquosa liberano ioni H^+ (ioni idrogeno);

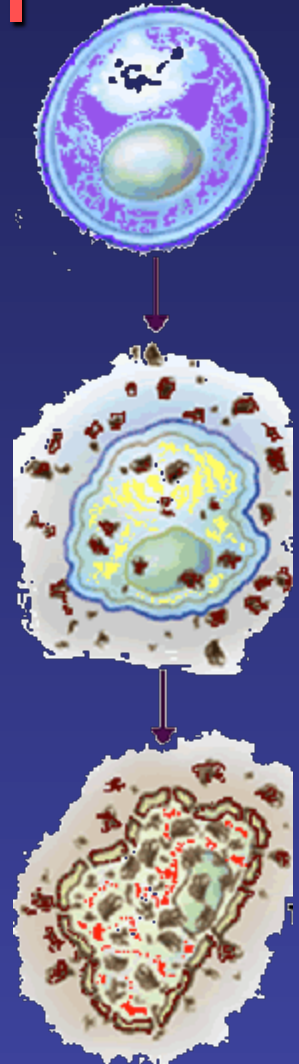
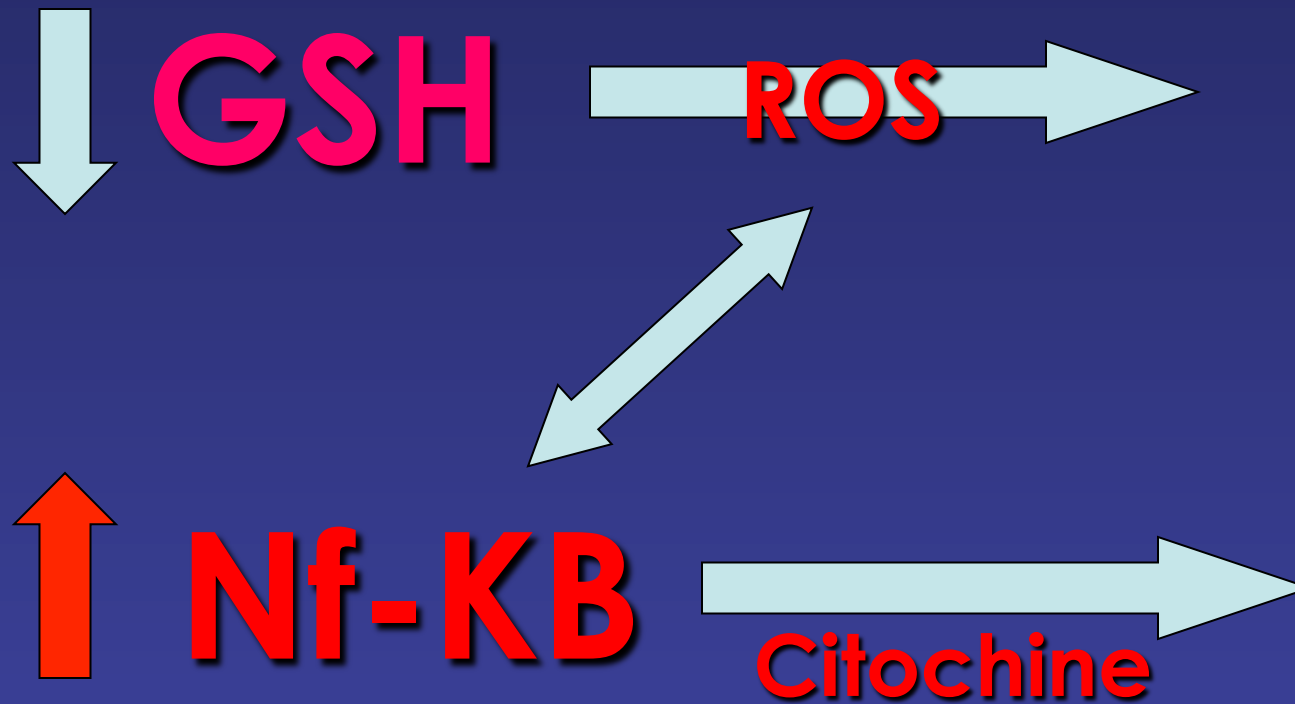
- basi sono sostanze che in soluzione acquosa liberano ioni OH^- (ioni idrossido o ioni ossidrile)

Secondo la teoria di Lewis

un acido è una sostanza capace di accettare un doppietto elettronico da un'altra specie chimica.

una base è una sostanza capace di donare un doppietto elettronico ad un'altra specie chimica.

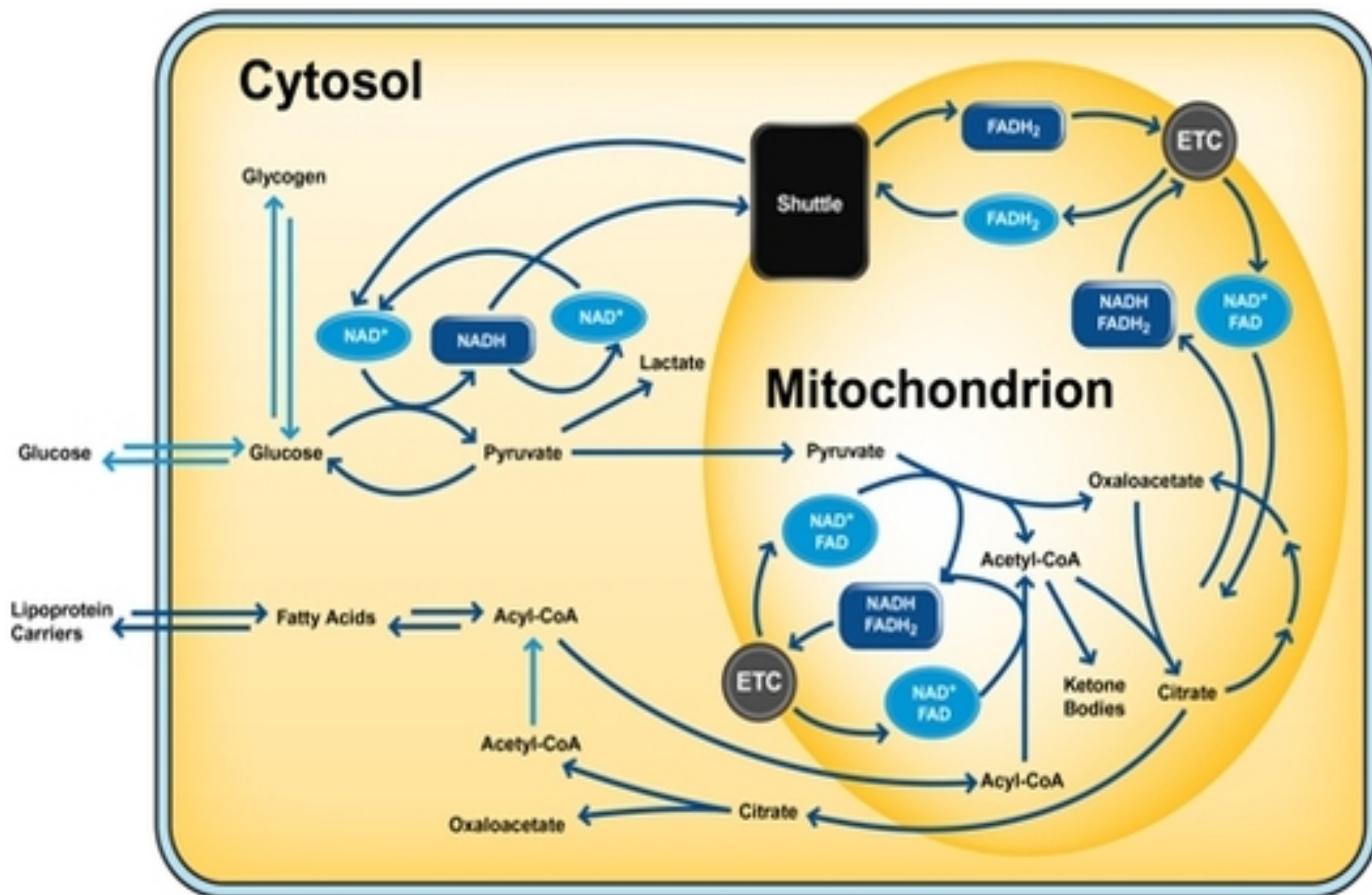
SOSTANZE OSSIDANTI / RIDUCENTI



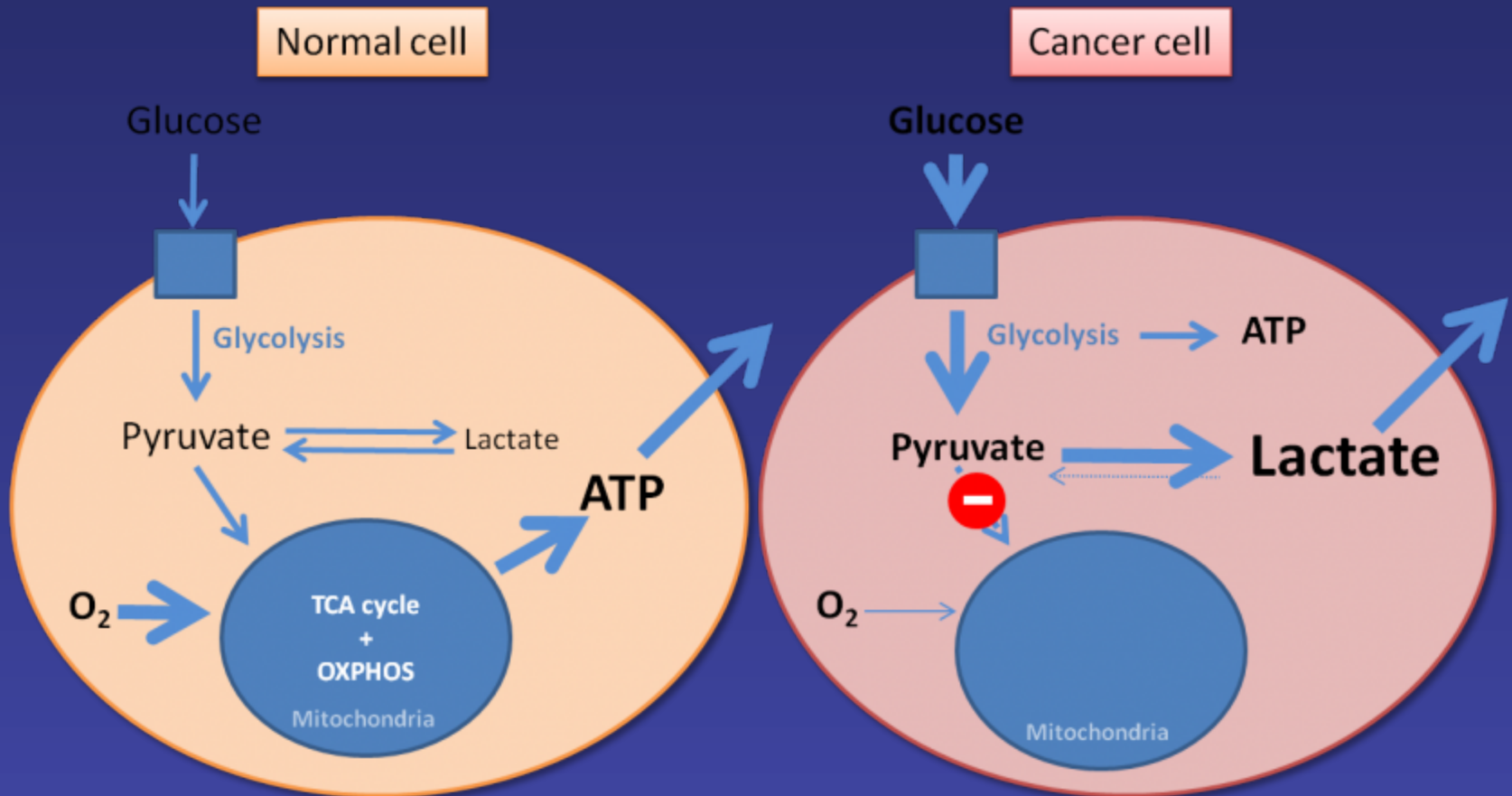
DIETA ANTI STRESS ELETTROFILO

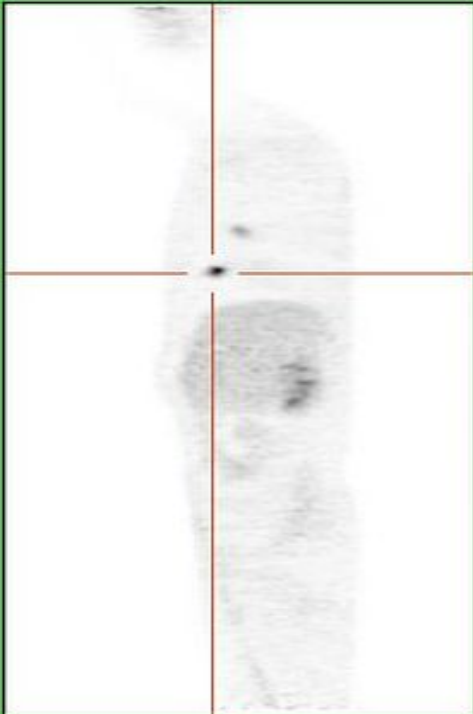
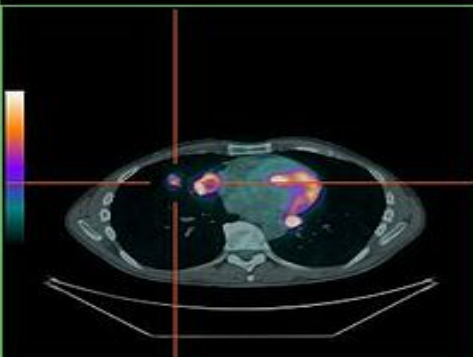
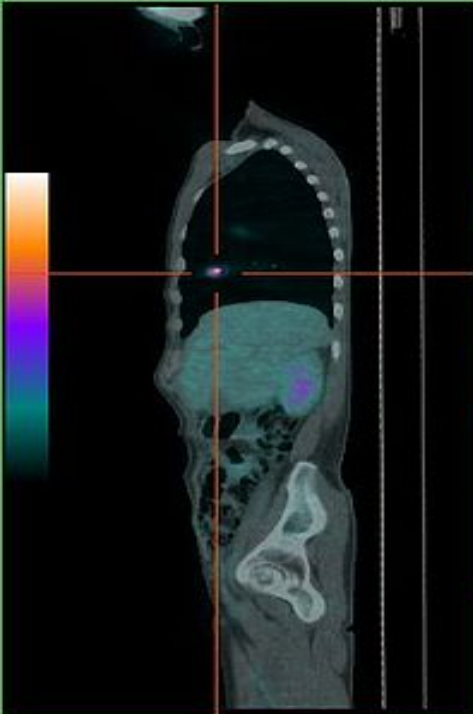
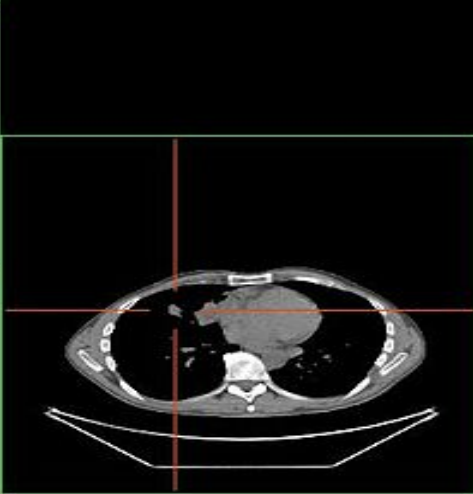
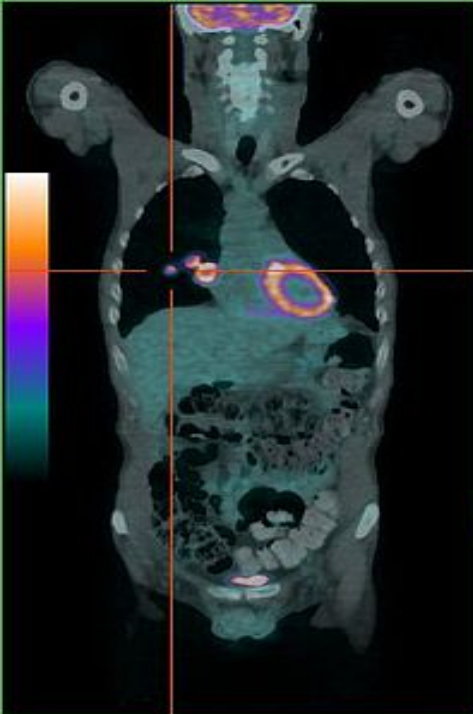
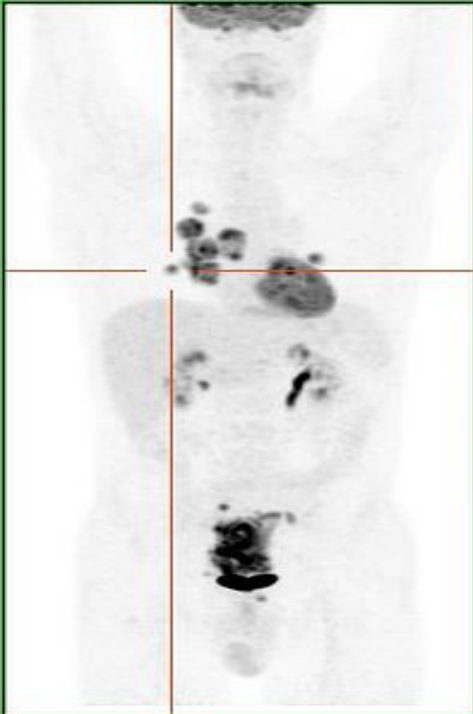
Nel Paziente Oncologico Chemioterapico

Metabolic Pathways



Effetto Warburg





I traccianti utilizzati negli alimenti sono
ma il più comune è il
essenziale
dal
met
per
meta
la gl
si ana



**L' effetto Warburg è valido sempre.
Ma le cellule neoplastiche cerebrali
mostrano una importante differenza.**

**Le cellule sane sono capaci di
nutrirsi in modo efficace di
corpi chetonici, quelle
neoplastiche NO.**

Fasting induces anti-Warburg effect that increases respiration but reduces ATP-synthesis to promote apoptosis in colon cancer models

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POSTPOSED AGING=POSTPOSED AGING-ASSOCIATED DISEASES. Open circles are tumours. Please, note that they are 50% less in 60% calorie restricted than in ALmice, and appear at a much later age

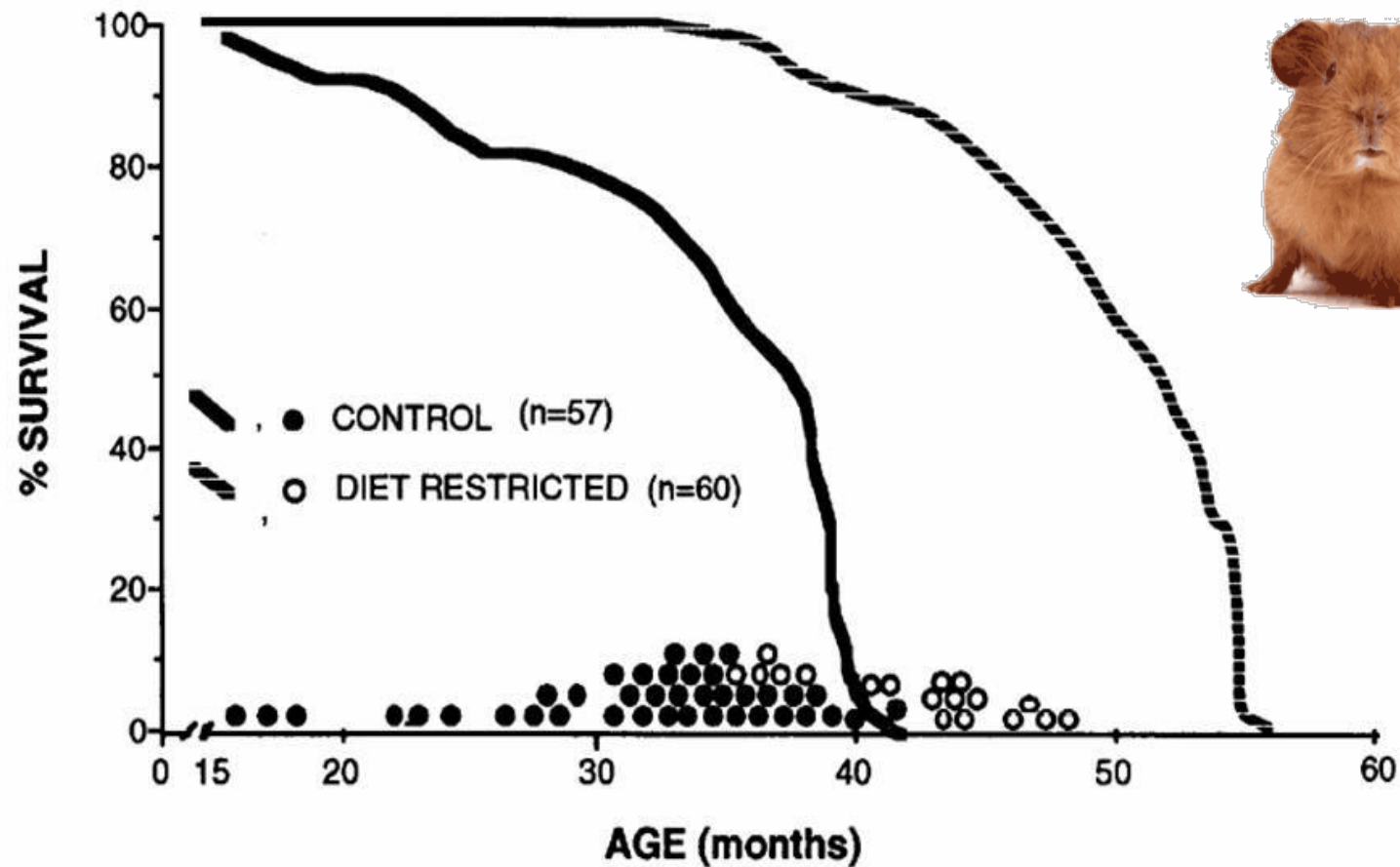


FIG. 3.3. Influence of dietary restriction started at 3 wk of age on life span and tumor incidence of female mice from the long-lived C3B10RF₁ hybrid strain. Survival curves are those for the 85 kcal/wk (control) and 40 kcal/wk (diet-restricted) cohorts shown in Figure 3.1. Circles show the age of death for tumor-bearing mice. [Adapted from (63) with permission.]