

Magnesium and cancer: a dangerous liason

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Abstract. A complex relationship links magnesium and cancer. The aim of this review is to revisit current knowledge concerning the contribution of magnesium to tumorigenesis, from transformed cells to animal models, and ending with data from human studies. Cultured neoplastic cells tend to accumulate magnesium. High intracellular levels of the cation seem to confer a metabolic advantage to the cells, contribute to alterations of the genome, and promote the acquisition of an immortal phenotype. In magnesium-deficient mice, low magnesium both limits and fosters tumorigenesis, since inhibition of tumor growth at its primary site is observed in the face of increased metastatic colonization. Epidemiological studies identify magnesium deficiency as a risk factor for some types of human cancers. In addition, impaired magnesium homeostasis is reported in cancer patients, and frequently complicates therapy with some anti-cancer drugs. More studies should be undertaken in order to disclose whether a simple and inexpensive intervention to optimize magnesium intake might be helpful in the prevention and treatment of cancer.

Key words: magnesium, cancer, metastasis, cetuximab, cisplatin

Even though cancer-associated death rates are falling steadily, the global burden of cancer continues to increase primarily as a result of an aging population, but also because of the adoption of cancer-causing behaviors, including smoking and a western-type diet [1]. In particular, statistical and epidemiological data point to diet as responsible for about 35% of human cancer mortality [2]. There is general agreement about the inverse correlation between the risk of cancer and the regular consumption of fruit, cereals and vegetables, rich sources of many beneficial micronutrients, vitamins and minerals. Magnesium, which is predominantly obtained by eating unprocessed grains and green leafy vegetables, is an essential micronutrient implicated in a wide variety of regulatory, metabolic and structural activities [3]. The occidental diet is relatively deficient in magnesium

because of the processing of many food items and the preference for calorie-rich, micronutrient-poor foods [4]. Magnesium deficiency complicates chronic gastrointestinal and renal diseases, diabetes mellitus, alcoholism, and therapies with some classes of diuretics and anticancer drugs [4].

A review of the literature reveals the relationship between magnesium and cancer, from the cellular level through to animal models and humans. Although controversy exists about the role of magnesium in tumors, most of the results available point to low magnesium as a factor contributing to tumorigenesis.

Magnesium and cancer: a focus on cultured cells

Magnesium acts as a secondary messenger, and activates a vast array of enzymes [3, 5]. Since magnesium participates in all major metabolic

Presented in part at the European Magnesium Meeting - EUROMAG Bologna 2011, San Giovanni in Monte, Bologna, Italy, June 8-10, 2011.

processes, as well as redox reactions, it is no surprise that it has a direct role in controlling cell survival and growth.

In normal diploid cells, the total concentration of magnesium increases throughout the G1 and S phases of the cell cycle. Accordingly, low extracellular magnesium markedly inhibits their proliferation [3]. Conversely, neoplastic cells are refractory to the proliferative inhibition by low extracellular magnesium but, being extremely avid for the cation, it accumulates in these cells even when cultured in low magnesium levels [6]. This avidity is due, at least in part, to an impairment of Na-dependent magnesium extrusion [7], and to the overexpression of one of the magnesium transporters, namely transient receptor potential melastatin (TRPM)7 [8]. High intracellular magnesium seems to provide a selective advantage for the transformed cells since magnesium contributes to regulating enzymes of various metabolic pathways and of the systems involved in DNA repair. Indeed, magnesium forms complexes with ATP, ADP and GTP, necessary for the activity of enzymes implicated in the transfer of phosphate groups such as glucokinase, phosphofructokinase, phosphoglycerate kinase and pyruvate kinase [9], enzymes of glycolysis known to be the pathway used preferentially by neoplastic cells to produce energy [10]. Magnesium also forms complexes with DNA polymerase, ribonucleases, adenylylase, phosphodiesterases, guanylate-cyclase, ATPases and GTPases, being therefore implicated in the metabolism of nucleic acids and proteins, and in signal transduction [9]. Since mutation is a driving force in the development of cancer, it is worth noting that magnesium is involved in the inhibition of N-methylpurine DNA-glycosidase, which initiates base excision repair in DNA by removing a wide variety of alkylated, deaminated, and lipid peroxidation-induced purine adducts [11]. In addition, the nuclear Ser/Thr phosphatase PPM1D (also known as WIP1), which is overexpressed in various human primary tumors, requires magnesium for its activity. PPM1D is involved in the regulation of several essential signaling pathways implicated in tumorigenesis [12, 13]. In particular, PPM1D dephosphorylates and, therefore, inactivates the p53 tumor suppressor gene, a canonical suppressor of proliferation. It also complements several oncogenes, such as Ras, Myc, and HER-2/neu, for cellular transformation both *in vitro* and *in vivo* [12].

On these bases, it is possible to conclude that high intracellular magnesium has a role in promoting genetic instability.

Another peculiarity of tumor cells is their limitless proliferative potential [14, 15]. It is therefore relevant to point out that magnesium is required to activate telomerase [16-18], a specialized DNA polymerase that extends telomeric DNA and counters the progressive telomere erosion associated with cell duplication. The presence of telomerase activity correlates with a resistance to induction of both senescence and apoptosis which are considered to be crucial anticancer defenses [14, 15].

These points are summarized in *figure 1*, which also underlines the contribution of high intracellular magnesium to some of the hallmarks of cancer, as highlighted by Hanahan and Weinberg [14, 15].

Mentioning only studies performed on neoplastic cells would be simplistic, since tumors are more than just masses of proliferating cancer cells. Rather, they are complex, heterotypic tissues where normal cells in the stroma, far from being passive bystanders, actively collaborate to cancer development and progression [14, 15]. Many of the growth signals driving the proliferation of and invasion by carcinoma cells originate from the stromal cell components of the tumor mass. It is therefore worth noting that low magnesium modulates the functions of a variety of normal cells present in the tumor microenvironment. In particular, endothelial cells cultured in low magnesium release higher amounts of metalloproteases and growth factors [19]. Similar results were obtained in cultured human fibroblasts (unpublished results). In addition, low magnesium promotes endothelial and fibroblast senescence [20], and senescent cells can modify the tissue environment in a way that synergizes with oncogenic mutations to promote the progression of cancers [21].

Only the behaviour of microvascular endothelial cells cultured in low magnesium seems not to fit with the picture described above. It is well known that angiogenesis is crucial to nourish the tumor and facilitate its spreading, but low extracellular magnesium impairs acquisition of the angiogenic phenotype by microvascular endothelial cells. Exposure to low magnesium retards endothelial proliferation, migration and differentiation *in vitro* ([22] and manuscript submitted). Accordingly, magnesium-deficient mice develop tumors which are significantly less vascularized than the controls [23].

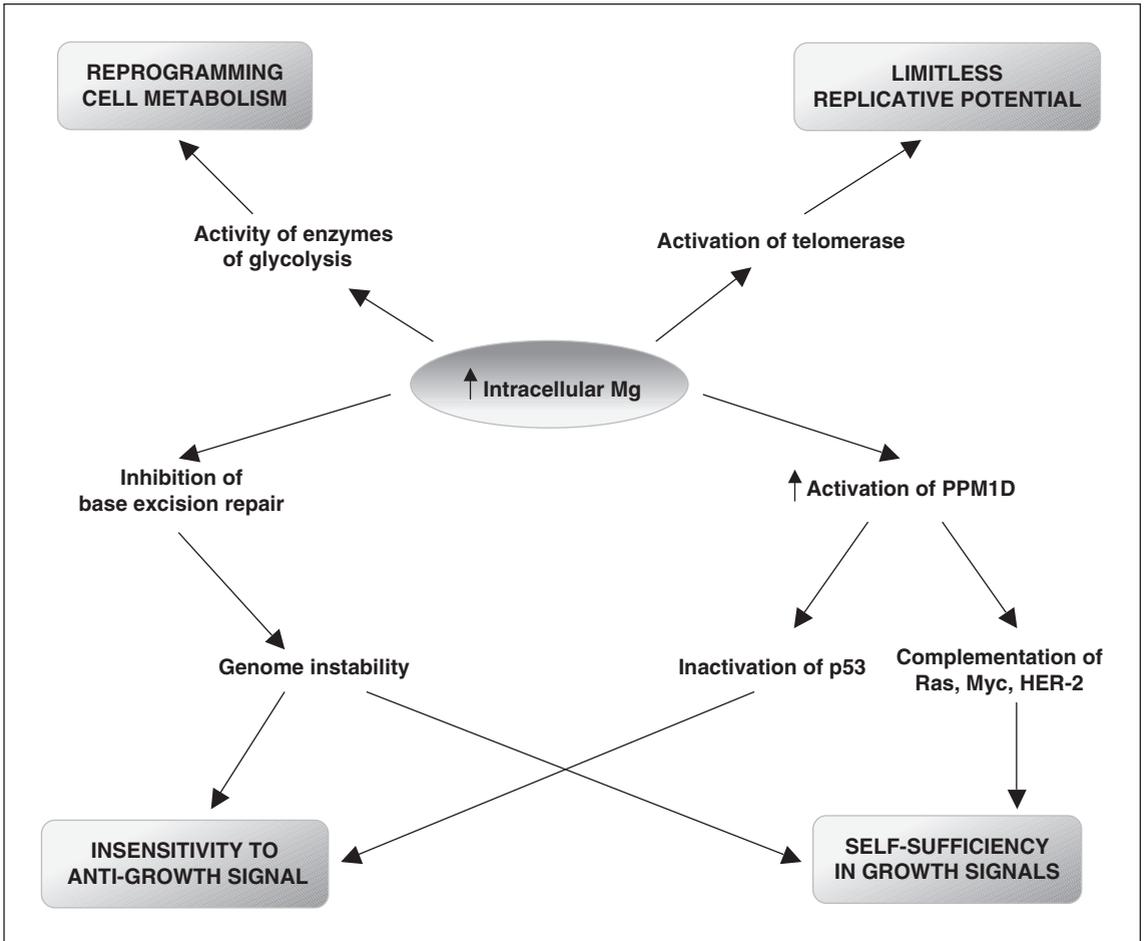


Figure 1. Neoplastic cells tend to have high intracellular concentrations of magnesium, which contribute to the regulation of various metabolic pathways and of systems involved in DNA repair, thus providing a selective advantage for the transformed cells. The figure also links the effects of high intracellular concentrations of magnesium on cell functions to some hallmarks of cancer as highlighted by Hanahan and Weinberg [14, 15].

**Magnesium and cancer:
a focus on animal models**

Several animal model studies have indicated that magnesium exerts a protective effect in the early phases of chemical carcinogenesis. Magnesium prevents lead and nickel-induced lung tumors in mice [24], inhibits nickel-induced carcinogenesis in the rat kidney [25], and protects against 3-methyl-cholantrene-induced fibrosarcomas in rats

[26]. Magnesium acts as a protective agent in colorectal cancer by inhibiting c-myc expression and ornithine decarboxylase activity in the mucosal epithelium of the intestine [27]. Thus, it is feasible to propose that magnesium acts as a chemopreventive agent.

We now discuss the impact of nutritionally-induced magnesium deficiency on tumor growth in rodents. In young male rats with Walker 256/M1 carcinosarcomas, dietary magnesium deprivation

inhibited tumor growth by limiting the synthesis of glutathione (GSH) [28] for which magnesium is an obligatory cofactor. More recently, in mice subcutaneously injected with Lewis lung carcinoma, mammary adenocarcinoma and colon carcinoma cells, a low magnesium-containing diet was shown to inhibit primary tumor growth, an effect which was promptly reversed by re-introducing magnesium into the diet [29]. Two different mechanisms might contribute to the inhibition of tumor growth: *i*) low magnesium-induced oxidative stress, which might exert toxic, lethal effects on the cells, and *ii*) impaired angiogenic switch since, as mentioned earlier, magnesium-deficient mice develop tumors which are significantly less vascularized than the controls [23]. The angiostatic effect of low magnesium can be ascribed to the direct inhibition of endothelial growth, migration and differentiation, pivotal steps in the formation of new vessels (manuscript submitted), and to the suppression of hypoxia-inducible factor (HIF)-1 α activity [30], with consequent impaired release of angiogenic factors.

Unexpectedly, magnesium-deficient mice developed far more lung metastases than controls [29]. This event is mainly related to the intense inflammatory response which occurs in magnesium-deficient rodents [31]. Inflammation is involved not only in the early stages of tumorigenesis by inducing genetic instability, but also in the late events, since inflammatory mediators promote invasion and metastasis [32]. Tumor necrosis factor (TNF) α , interleukins (IL) 1 and 6, all induced under magnesium deprivation [31], augment the capacity of cancer cells to metastasize [33]. TNF α and IL1 also upregulate endothelial adhesion molecules in lung capillaries, thus facilitating the tethering of metastatic cells to the vessel wall, their subsequent transmigration to and colonization of the adjacent tissues.

In addition, magnesium is an absolute requirement for the function of the metastasis-suppressor gene product NM23-H1 [34]. Hypomagnesemia might therefore mimic what happens in NM23-H1 knock-out mice, which show accelerated and massive metastasis [35].

Experimental evidence therefore leads to the conclusion that in rodents, magnesium deficiency participates both in early (initiation) and late (progression) phases of tumorigenesis (figure 2).

Low magnesium and cancer: a focus on human studies

Several epidemiological studies have provided evidence that a correlation exists between dietary magnesium and various types of cancer. High levels of magnesium in drinking water protect against oesophageal and liver cancer [36, 37]. In addition, magnesium concentration in drinking water is inversely correlated with death from breast, prostate, and ovarian cancers, whereas no correlation existed for other tumors [36, 38, 39].

Epidemiological studies conducted in various countries demonstrate an association between low intake of magnesium and the risk of colon cancer [40-43]. In addition, a large population-based prospective study in Japan shows a significant inverse correlation between dietary intake of magnesium and colon cancer in men but not in women [44]. Intriguingly, the association between low intake of magnesium and colon cancer is linked to the increased formation of N-nitroso compounds, most of which are potent carcinogens [43]. A further link between magnesium and colon neoplasia is highlighted by the association of adenomatous and hyperplastic polyps, which might progress to carcinoma, with a genetic polymorphism of TRPM7 [45], an ubiquitous ion channel with a central role in magnesium uptake and homeostasis [46].

Results concerning the contribution of magnesium to lung cancer are controversial. A first case-control study correlates low dietary magnesium with increased lung cancer risk both in men and women [47]. This link is more evident in the elderly, current smokers, drinkers and in those with a late-stage disease. To explain the protective effect of magnesium against lung cancer, the authors recall that magnesium regulates cell multiplication, protects against the oxidative stress invariably associated with magnesium deficiency [48], and maintains genomic stability. A recent prospective analysis however, does not support the previous report [49]. These contrasting data could result from recall bias, the difficulty in evaluating diet composition and the fact that smoking is a very strong risk factor for lung cancer.

Apart from a contribution of altered magnesium homeostasis to tumorigenesis in humans, a second crucial topic should be considered, *i.e.* whether the actual presence of a tumor

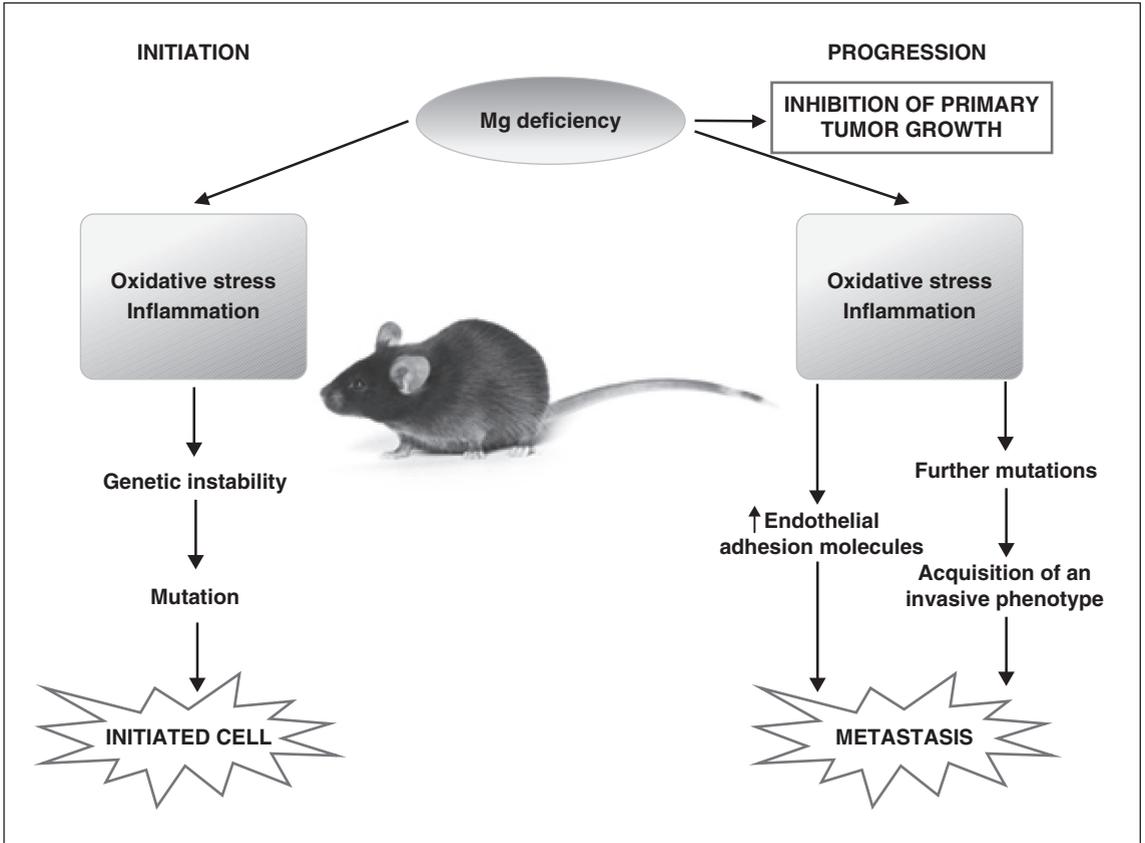


Figure 2. In mice, magnesium deficiency participates both in early and in late phases of tumorigenesis. Initiation: low magnesium promotes oxidative stress and inflammation, which generate genetic instability and increases the risk of mutations. Mutations might generate the so-called “initiated” cell, which is potentially capable of triggering a tumor. Progression: once the tumor has developed, the persistence of oxidative stress and inflammation might generate further mutations that facilitate metastatic spreading, in the face of an inhibition of primary tumor growth.

alters magnesium homeostasis. Serum magnesium concentrations are frequently decreased in patients with solid neoplasia, independent of therapies, and the decrease correlates to the stage of malignancy [50]. An explanation resides in the fact that tumors behave as magnesium traps. In addition, therapies influence magnesium homeostasis. Serum magnesium decreases by the end of the first week of radiotherapy [51], as well as after treatment with different chemotherapeutics that induce magnesium waste, such as cisplatin, which is nephrotoxic [52]. Recently, it became evident that cetuximab, a monoclonal antibody against the epidermal growth factor (EGF) recep-

tor, specifically and reversibly inhibits magnesium reabsorption in the renal distal convoluted tubule [53].

At the moment, it is not clear whether radiation- or drug-induced hypomagnesemia amplifies the effect of DNA-damaging cancer treatments by acting as a chemo- and radio-sensitizer. Decreased serum magnesium has been suggested to contribute to the therapeutic effects of cetuximab in patients with colon carcinoma [54], and the circulating level of magnesium is proposed as a simple and inexpensive biomarker of efficacy and outcome in terms of time-to-progression and overall survival in patients with advanced

colorectal adenocarcinoma treated with cetuximab [55]. However, it remains controversial whether to supplement or not severely hypomagnesemic cancer patients with magnesium [6].

A last intriguing issue to consider is the involvement of inflammation in the initiation and development of cancer in magnesium-deficient individuals. A low magnesium status has been clearly associated with increased inflammatory stress in humans [56], and the inflammation-cancer connection is a well established paradigm [32]. Indeed, inflammation is involved in the early and late stages of the most common solid tumors because inflammatory mediators induce genetic instability, promote metastatic colonization and impair response to therapies [32].

In spite of the wealth of information available, several important questions remain unanswered.

Firstly, is magnesium deficiency sufficient for the development of cancer? Even though low magnesium determines inflammation and increases the levels of free radicals, which both generate genetic instability, it is more likely that a low magnesium status only contributes to tumorigenesis by synergizing with other factors.

Secondly, what about the aberrant calcium:magnesium ratio that is inevitably associated with magnesium deficiency? Nutritional surveys performed by the United States Department of Agriculture from 1977 through 2007-8 have reported a rising calcium:magnesium ratio intake from foods for all USA adults [57]. Recently, a high calcium:magnesium ratio has been suggested as a novel risk factor that increases the development of postmenopausal breast cancer [58]. In western populations, and in particular, in postmenopausal women who are recommended to take calcium supplements in order to prevent osteoporosis, a high calcium:magnesium intake is rather common and this induces a negative magnesium balance since the two minerals compete for the same transporters in almost all tissues. An increased calcium:magnesium ratio is also associated with an increased incidence of colorectal cancer in young adults [45, 57]. While this is a "hot" issue, studies involving the calcium:magnesium balance and cancer are scarce.

Thirdly, can the results obtained in mice predict what happens in humans? Magnesium deficiency retards primary tumor growth, but enhances metastases in mice. It would be relevant to consider this issue also in human tumors.

The final and most important question is: can the knowledge about the connection between low magnesium and cancer be translated into useful approaches for the prevention and treatment of cancer? Hypomagnesemia has been proposed by some authors to be beneficial in fighting cancer by sensitizing neoplastic cells to radiation or chemotherapeutics, however, there is no consent among clinical oncologists about using this information in treating or not hypomagnesemia [6].

Conclusion

Although the evidence is still fragmentary, most of the data available point to magnesium as a chemopreventive agent, so that optimizing magnesium intake might represent an effective and low-cost preventive measure to reduce cancer risk. Doubts remain about supplementing cancer patients with magnesium.

The recently revived interest in the relationship between magnesium and tumors, both in experimental and clinical oncology, should encourage more studies that would advance our understanding of the role of magnesium in tumors, and could explore the possibility that optimizing magnesium homeostasis might prevent cancer or help in its treatment.

Disclosure

None of the authors has any conflict of interest or financial support to disclose.

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