Dysregulation of Mg^{2+} homeostasis contributes to acquisition of cancer hallmarks

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Abstract

Derangement of magnesium homeostasis underlies the pathophysiology of many diseases, including cancer. Recent advances support the view that aberrant expression of Mg^{2+} channels and other Mg^{2+} homeostatic factors may affect many hallmarks of cancer. The seminal idea of magnesium as a key regulator of cell proliferation has been enriched by novel intriguing findings that link magnesium and Mg^{2+} transporters to distinctive and complementary capabilities that enable tumour growth and metastatic dissemination. In this review, we examine the evidence on the involvement of members from the TRPM, CNNM and SCL41 protein families in cancer progression, and discuss their potential as therapeutic targets.

Highlights

- Cancer progression associates with deranged magnesium homeostasis
- Magnesium channels are aberrantly expressed in human cancers
- Magnesium channels control cell proliferation, survival, invasion and metabolism
- Selective targeting of magnesium channels may have a therapeutic potential

Abbreviations

CNNM, cyclin M; CRC, colorectal cancer; EMT, epithelial-mesenchymal transition; Mg, magnesium, (indicating both the free and bound form); MHC, myosin heavy chain; MRS2, mitochondrial RNA splicing 2; mTOR, mammalian target of rapamycin; PRL, phosphatase of regenerating liver; SLC, solute carrier; SNP, single nucleotide polymorphism; TRPM, transient receptor potential melastatin type; TRPV, transient receptor potential vanilloid type.

Keywords: cyclin M, invasion, metabolism, proliferation, solute carrier, transient receptor potential melastatin type.

The last decades have witnessed a greater appreciation of the importance of magnesium (Mg) for human health, and disturbances of Mg homeostasis have been implicated in the pathophysiology of a variety of diseases [1]. Nevertheless, the relationship between Mg and cancer development remains controversial. In the face of a consistent and growing body of epidemiological evidence showing an inverse correlation between Mg intake and the incidence of many types of cancer [2], a more complex picture emerges at later stages in tumour progression [3]. Furthermore, the molecular mechanisms underlying the pleiotropic action of Mg have only begun to be elucidated, but a key role for Mg channels and transporters has emerged throughout the natural history of a tumour. In this review, we will explore in detail each stage of the multistep process of tumour progression, namely initiation, growth at the primary site and formation of distant metastases, as well as the response to therapy, with particular regard to the involvement of Mg^{2+} channels.

1. Magnesium and Multistep Carcinogenesis

The protective effect of Mg in the early stages of carcinogenesis has been ascribed to two main mechanisms: 1) modulation of oxidative stress and consequent oxidative DNA modifications that might lead to mutagenesis; 2) maintenance of genomic stability [4]. It is established that low Mg availability induces a pro-oxidant condition. If in vitro evidence is mostly indirect [5], in vivo investigations have consistently reported indexes of oxidative stress in Mg-deficient animals: enhanced lipoperoxidation, oxidative modifications of protein and nucleic acids, reduced antioxidant status, and increased plasma nitric oxide. The current view is that the major origin of the oxidative stress *in vivo* is the inflammatory response triggered by Mg deficiency [6]. In addition to the indirect inflammation-mediated effects on genome stability, Mg could also have a direct role in maintaining genome fidelity, by stabilizing nucleic acids structure and by serving as an essential co-factor in almost all enzymatic DNA processing and repairing systems [7, 8].

The relationship between Mg and cell proliferation is one of the best-known aspects of Mg cellular physiology, which can be recapitulated simply stating that no proliferation can occur without an adequate Mg supply [3]. This implies that highly proliferating tumour cells should be extremely avid for their Mg supply. Indeed, tumour cells have a higher intracellular Mg content; however, they are more refractory to the growth inhibition induced by low Mg availability in comparison with normal cells [4]. This apparent contradiction can be reconciled by increasing experimental evidence showing that overexpression of Mg^{2+} channels is a common feature shared by several types of cancer and has an involvement in tumour development and progression, as we will discuss in the next sections.

A growing tumour is not simply a mass of proliferating tumour cells, but a tissue whose complexity approaches and may even exceed that of normal healthy tissues. It is therefore worth noting that Mg availability can modulate the functions of a variety of normal cells present in the tumour microenvironment, first and foremost microvascular endothelial cells, the real players of tumour neo-angiogenesis: low Mg availability retards their proliferation, migration and differentiation, without affecting MMP production and 3D organization [9]. Not surprisingly, overall Mg availability does inhibit tumour growth *in vivo* [10], which is accompanied by a decreased number of tumour vessels and an increased oxidative damage to DNA [11]. Unexpectedly, the same animal studies drew attention to an alarming twist in the story: in spite of the smaller size of primary tumours and the low degree of neovascularization therein, mice on a low Mg diet developed far more lung metastases than controls [10]. Therefore, the intense inflammatory response triggered by Mg deficiency [6] seems not only to play a role in initiation and growth of the primary tumour, but could also foster further cancer progression, due to the presence of inflammatory cells and mediators, forging the tumour microenvironment.

In conclusion, the current state of the art delineates a complex picture where the positive consequences of a low Mg availability (i.e. inhibition of primary tumour growth and neo-angiogenesis) seem to be counterbalanced by negative outcomes in the very early and late stages of tumourigenesis (i.e. tumour initiation and stimulation of invasion and metastasis formation) (Figure 1). The immune-inflammatory response that complicates Mg deficiency appears as a recurrent theme playing throughout the natural history of a tumour.

2. Mg channels and transporters in human cancer

In the last decades, more and more epidemiological, experimental and clinical data have accumulated and contributed to better define the involvement of Mg in the modulation of tumour development. However, in many cases underlying molecular mechanisms have remained elusive. Extracellular Mg availability is translated into intracellular Mg content (and eventual signaling) by specific molecules that regulate ion transport through the plasma membrane. Therefore, the absolute requirement of Mg for cell growth implies that in tumour cells the regulation of Mg^{2+} transport must be more efficient to guarantee sufficient Mg availability and to sustain cell proliferation. Recently this concept has been corroborated and expanded by an ever-increasing number of studies showing that Mg^{2+} channels can be involved in the regulation of numerous hallmarks of cancer cells, including sustained proliferation, enhanced survival, angiogenesis, invasion and metastasis, deregulated energetics (Table 1).

2.1 TRPM7

TRPM7 is permeable to Mg^{2+}as well as Ca^{2+} and other divalent cations, and is most unusual in having a carboxy-terminal atypical alpha-kinase domain coupled to the transmembrane channel pore; functional channels are most likely organized as either homo- or heterotetramers with its close homologue TRPM6, which have distinct electrophysical properties and functions [12]. These unique features caught the attention of researchers worldwide, as they offer fascinating avenues to explore that could combine protein expression, ion entry and signal transduction events. A plethora of functions have been ascribed to TRPM7 in normal cell physiology, but discussion of this issue is beyond the scope of the present work; for recent reviews see for example [12]. More relevant to our context, a role for TRPM7 has been invoked in each phase of multistep tumour development.

As to carcinogenesis, a single nucleotide polymorphism (SNP) that substitutes TRPM7 threonine 1482 (T1482) to isoleucine (T1482I) has been linked to the development of adenomatous and hyperplastic polyps, which might eventually progress to carcinoma [13]. The same SNP was found to be associated with breast cancer risk in a Chinese population [14]. TRPM7 T1482 is a potential site of autophosphorylation or phosphorylation by TRPM6. *In vitro* studies found that heterologously expressed T1482I leads to an elevated sensitivity to inhibition by intracellular Mg^{2+} [15], which suggests that (re)absorption of Mg is more subject to inhibition among subjects bearing this substitution. A genomic analysis of 210 diverse human cancers found somatic mutations of TRPM7 in breast, gastric and ovarian carcinoma; out of the 518 protein kinase genes that were screened, TRPM7 figured among the approximately 130 genes showing evidence for bearing “driver” mutations contributing to the development of the cancers studied [16]. Unfortunately, the functional consequences of the newly identified mutations have not been investigated yet.

The role of TRPM7 in cancer development has been further supported by comparative transcriptomic analyses of TRPM7 expression in healthy *vs.* cancerous human tissues, which found altered expression of TRPM7 in several carcinomas [17]. Overexpression of TRPM7 in human tumours has been validated by other approaches (*e.g.* Western blot or immunohistochemistry) in prostatic [18,19], nasopharyngeal [20,21], pancreatic [22,23], breast [24,25] and ovarian [26] cancers as well as in glioblastoma [27]. Moreover, in most of these studies TRPM7 expression levels were correlated to clinical parameters such as Ki67 staining, tumour size, grade, or stage, and, most importantly, patient survival. In view of such findings, TRPM7 expression was proposed as a potential prognostic factor [28]. Not surprisingly, TRPM7 expression was also found to be in correlation with metastatic potential in nasopharyngeal [20], pancreatic [22,29] and breast [30,31] carcinomas.

The dual nature of the TRPM7 molecule opens up intriguing scenarios with regard to the mechanisms that underlie its involvement in cancer growth and progression. It is still unclear whether the manifold roles of

TRPM7 are to be attributed to channel activity or to kinase function, or rather to a combined action of cation transductance and substrate phosphorylation. TRPM7 was shown to be essential for the proliferation of different cancer cells, including retinoblastoma, glioblastoma, leukemia, head and neck, lung, pancreas, stomach and breast cancer cells, and TRPM7-like currents were convincingly associated to proliferation (for a review, see [32]). However, the transported cation species was not always identified. In many cases, Ca^{2+} fluxes received most of the scrutiny, as Ca^{2+} signaling is central in normal as well as cancer cells [33]. Nonetheless, in some studies, Mg supplementation rescued the growth arrest induced by TRPM7 disruption, which strongly argues for an involvement of an Mg^{2+} influx [34]. It should be noted that recent research developments suggest that the extracellular Ca^{2+}/Mg^{2+} ratio could be more important than Ca^{2+} and Mg^{2+} concentrations on their own [35]; intriguingly the T1482I SNP is associated to greater risk of adenomas and hyperplastic polyps especially in subjects consuming a diet with high Ca^{2+}/Mg^{2+} intake [13], and an increase in the extracellular Ca^{2+}/Mg^{2+} ratio activates TRPM7 channel in prostate cancer cells [18]. Inhibition of TRPM7 channel expression and/or activity by RNA interference and/or channel blockers disrupts cell cycle and proliferative signals through various signaling cascades, including PI3K/AKT, MEK/MAPK, JAK2/STAT3 and/or Notch pathways, depending on the cell type [32]. Of note, TRPM7-mediated Mg^{2+} influx is required for sustained PI3K/Akt/mTOR-dependent growth signaling, leading to rapid quiescent/proliferative metabolic transitions [36,37].

TRPM7-mediated fluxes were also found to modulate cell migration, in particular a Ca^{2+} influx in prostate [19] and nasopharyngeal [20] cancer cells, and an Mg^{2+} influx in pancreatic adenocarcinoma [23], but the latest findings indicate that modulation of cell plasticity/motility by TRPM7 might be more dependent on its α-kinase activity. The relationship between the kinase activity and the channel function is still a matter of debate. The consensus in the field is that the kinase activity is not essential for opening of TRPM7 channels, but opening of TRPM7 channels could affect kinase function by causing a local increase in Ca^{2+} and/or Mg^{2+} concentration, which could possibly regulate kinase activity and/or the recruitment/targeting of TRPM7 kinase substrates [38]. Interestingly, TRPM7 kinase substrates include the three mammalian myosin II heavy chain isoforms, MHC-A, B, and C [39]. Consequently, TRPM7 kinase activity can affect actomyosin contractility that plays a key role in cell migration and invasion. Indeed, in a mouse xenograft model of human breast cancer, TRPM7-knockdown interfered with the metastatic potential of triple negative cells; mechanistic investigation revealed that TRPM7 regulated myosin II-based cellular tension, thereby modifying the number of focal adhesions, cell-cell adhesion and polarized cell movement [30]. These results were confirmed by an independent study, which provided further evidence for the involvement of TRPM7 kinase domain and MHC-A phosphorylation [40]. In addition, in breast cancer cells TRPM7 seems to play a role in the epithelial-mesenchymal transition (EMT), which represents a crucial switch towards an invasive phenotype [41]. TRPM7 also contributes to the invasive properties of neuroblastoma cells by affecting invadosome formation [42]. Intriguingly, in the last two cited papers, although the role of TRPM7 kinase domain and/or activity was not directly investigated, the Authors ruled out an involvement of Ca^{2+} fluxes. Thus, we are presented with two possibilities: 1) cation influx is dissociated from phosphotransferase activity, and the two different domains of the TRPM7 molecule simply coexist for an accidental evolutional step, but they in fact regulate different functions independently; or, more excitingly, 2) the fusion of a channel pore with a kinase domain represents an optimized and integrated unit, being able to couple extracellular sensing to intracellular signaling. In this regard, it is worth recalling that Mg is essential for transphosphorylation reactions, which are an integral part of signal transduction. To summarize, TRPM7 involvement seems to change during cancer progression: in early-stage tumours, TRPM7 is involved in the regulation of cell proliferation mainly through cation homeostasis control, while cell migration and invasion in advanced-stage and aggressive tumours require TRPM7 kinase activity and interaction with cytoskeletal proteins, which could nonetheless depend on local ion concentrations. Furthermore, it is worth noting that TRPM7 can be activated by hypoxia or acidic pH [43], acts as a sensor of oxidative stress [44] and modulates immune [45] and endothelial [46] cell functions; thus, it is the perfect candidate to carry out the remodeling of tumour microenvironment that is fundamental for cancer progression.

One last remark concerns a possible involvement of the TRPM7 channel and/or kinase also in the response to the chemotherapeutic doxorubicin. Both protein expression and Mg^{2+} fluxes were correlated to cell sensitivity to doxorubicin in two different cellular models [47,48]. At present, the underlying molecular mechanisms are unknown, though two hypotheses have been put forward: TRPM7 kinase could affect intracellular drug trafficking [47], or Mg availability modulated by TRPM7 could influence activity of drug efflux pumps [48].

2.2 TRPM6

The TRPM6 channel has received much less attention than its closest homologue TRPM7. The reason partly lies in its selective tissue expression, which focused the attention on its physiological role in mediating Mg^{2+} absorption and reabsorption at the colon and kidney level, respectively. However, seminal work by Chubanov and coworkers made clear that the functional channel at the plasma membrane is a multimeric complex consisting of either TRPM7 homotetramers or TRPM6/7 heterotetramers, each possessing different biophysical properties [12]. Recent work highlighted that TRPM6 and TRPM7 differentially contribute to regulatory characteristics of the heteromeric TRPM6/7 channel, so that the activity of the complex is hardly affected by physiological intracellular concentrations of Mg^{2+} and Mg-ATP [49] or by osmotic changes [50]. This mechanism appears to be an indispensable prerequisite for efficient transcellular Mg^{2+} transport in intestinal cells, where a high and constant Mg^{2+} uptake should be uncoupled from cellular metabolism, and should remain unaffected by frequent osmotic changes. Such a functional fingerprint is probably not required in other cell types, which indeed only express TRPM7.

Despite the essential role of TRPM6 in adult survival and Mg homeostasis, its involvement in cancer is still unclear. An in silico systems biology approach identified TRPM6 as a candidate gene associated with colorectal cancer (CRC) and a potential drug candidate to prevent tumour growth [51]. TRPM6 mutations were identified in melanoma [52] and breast cancer [53], but no further characterization is available. More recently, a pathway enrichment analysis based on microarray expression profiling data identified TRPM6 as one of the genes predicted to play an important role in the development of CRC [54]. TRPM6 was confirmed to be downregulated in colon cancer tissues by qPCR; furthermore, high expression of TRPM6 was indicative of a prolonged overall survival in CRC patients from the same database [54]. Similarly, analysis of an RNAseq database yielded a significant downregulation of TRPM6 in CRC vs normal tissues, in particular in proximal tumours [55], which generally have a poorer prognosis [56].

In the absence of more mechanicistic studies on the role of TRPM6 in cancer tissues, it is difficult to interpret these findings. However, it is tempting to speculate that decreased expression of TRPM6 might be indicative of a less differentiated state. As mentioned above, TRPM6 is present in specialized epithelia to carry out the key physiological role of mediating Mg^{2+} absorption and regulating systemic Mg status. Vice versa, TRPM6 expression is blunted by inflammation [57] and inversely correlates with stemness features, including CD133 and P-gp expression [58]. In tissues co-expressing both TRPM6 and TRPM7, any alteration in the expression ratio between the two proteins may result in different functional properties of the functional channel at the plasma membrane [59]. The emerging picture in tumours is an increased TRPM7 expression in the face of reduced TRPM6 expression, as if acquisition of a more malignant phenotype implied lesser dependence from Mg^{2+} uptake (i.e. merely proliferation), while strongly hinging on other functions, conferred more specifically by TRPM7 (i.e. tumour microenvironment reshaping, possibly mediated also by other ion fluxes and/or kinase activity).

2.3 CNNM Proteins

Under the premise that differential gene expression is involved in the maintenance of cellular Mg homeostasis, microarray analyses in epithelial cells exposed to low extracellular Mg^{2+} concentrations have been classically used to designate proteins involved in Mg^{2+} transport [60]. One of the protein families identified with this approach was the CNNM family. CNNM proteins have been proposed to facilitate epithelial Mg^{2+} extrusion since at least two members of this family, CNNM2 and CNNM4, localize in the basolateral membrane of epithelial cells where apical-to-basolateral Mg^{2+} transport occurs [61,62]. However, evidence supporting this hypothesis is controversial [63,64]: it still remains uncertain whether they are genuine exchangers by themselves or cooperatively function with one or several further proteins, including the well-characterized Na^{+}/ Mg^{2+} exchangers of the SLC41 family [65,66].

All CNNM proteins (CNNM1–4) can bind to members of phosphatase of regenerating liver PRL family (PRL1–3), that are overexpressed in malignant cancers and have been proposed to have a role in malignant progression [67]. The first link between Mg homeostasis, PRL-CNNM complex and cancer was seen in the context of breast cancer. Mg depletion was shown to upregulate both PRL-1 and -2 protein levels, as well as their association with CNNM3; this interaction induces an increase in intracellular Mg through a proposed influx mechanism [68]. Disruption of PRL2-CNNM3 interaction decreased the ability of cells to proliferate under Mg-deprived situations and under anchorage-independent growth conditions, demonstrating a PRL-2-CNNM3 complex-dependent oncogenic advantage in a more stringent environment [69]. Funato et al. identified an analogous interaction between PRL-3 and CNNM4 in colorectal cancer: they proposed that CNNM4 acts as a Mg^{2+}/Na^{+} exchanger that promotes Mg^{2+} extrusion from cells, which is inhibited by binding with PRL-3 [70]. Thus, we are presented with two opposing mechanisms of action for the PRL/CNNM complexes regarding Mg^{2+} transport: 1) a PRL/CNNM complex at the membrane promotes directly Mg^{2+} influx, or stimulates the activity of a Mg^{2+} transporter [68,69]; 2) CNNMs promote the extrusion of Mg^{2+} from the cell, and the binding with PRLs inhibits this mechanism [70]. It remains unclear whether the CNNMs can exert dual transport roles depending on their localization and other binding partners, or act as Mg^{2+} sensors. In any case, in both models, PRL-CNNM complex formation results in accumulation of intracellular Mg that promotes cancer progression. Interestingly, in both models, higher intracellular Mg levels have been linked to energy metabolism and circadian rhythms [70,71].

Recently, it has been shown that CNNM4 deficiency might affect not only Mg homeostasis, but also calcium signaling. In fact, the increase in intracellular Mg^{2+} levels found in CNNM4-deficient colon cells seems to be associated to defective Ca^{2+} influx due to severe defects in activation of TRPV1 [72]. A similar inhibition of channel function by intracellular Mg^{2+} has also been reported for TRPV3, and a pore-blocking model was proposed to account for the effect [73]. The antagonism between calcium and Mg in the physiology of muscle and nervous system is well known, but these results establish a functional interplay between Mg^{2+} and Ca^{2+} also in the colon epithelium, which seems crucial for maintaining the dynamic homeostasis of this tissue.

2.4 SLC41A1

The solute carrier family 41 (SLC41) encompasses three members: A1, A2, and A3. Based on their distant homology to the bacterial Mg^{2+} channel MgtE, all have been linked to Mg^{2+} transport [74]. There is only very limited knowledge on the molecular biology and exact functions of SLC41A2. On the contrary, SLC41A1 was established as a Na^{+}/ Mg^{2+} exchanger that facilitates Mg^{2+} extrusion dependent on Na^{+} influx [65]. Similarly, SLC41A3 was shown to facilitate Mg^{2+} efflux, but at the inner mitochondrial membrane, rather than at the plasma membrane [75]. In recent years, there has been increasing interest in the diagnostic and therapeutic potential of SLC proteins in several human diseases [76], in particular cancer, because their aberrant expression may be responsible for nutrient and ion transport to meet the needs of proliferating tumour cells, as well as for drug elimination and chemoresistance [77]. In this context, a recent transcriptomic analysis found downregulation of SLC41A1 in pancreatic ductal adenocarcinoma vs. normal tissues; moreover, SLC41A1 expression correlated with overall survival in patients and gradually decreased with tumour stage [78]. Vice versa, overexpression of SLC41A1 suppressed tumour growth and invasiveness in both in vitro and in vivo models. Mechanicistically, this was associated to increased susceptibility to apoptosis mediated by AKT/mTOR activity [78]. The anti-tumour mechanism of SLC41A1 was proposed to be Mg^{2+}-dependent, in that Mg^{2+} efflux via SLC41A1 may result in intracellular Mg depletion and, consequently, AKT/mTOR inhibition and Bax induction. In this study, the involvement of Mg^{2+} fluxes in the proposed mode of action was only inferred from the rescuing effect of Mg supplementation. However, another in vitro study convincingly proved that overexpression of SLC41A1 significantly lowers intracellular Mg^{2+}, which correlates with attenuation of pro-survival AKT signaling [79].

2.5 MRS2

Recent evidence suggests that not only the presence of Mg per se, but also its redistribution among subcellular compartments may modulate a broad variety of processes, and that indeed Mg^{2+} may act as a second messenger [80]. Extensive work by Oka and collaborators demonstrated that mitochondria are intracellular Mg stores [81], and that Mg^{2+} mobilization from mitochondria can occur following several pathophysiological stimuli [82-86]. Mg can be accumulated inside the mitochondria via the Mg^{2+}-selective channel MRS2 [87], that takes advantage of the driving force produced by the mitochondrial membrane potential and is feedback regulated by increasing Mg^{2+} concentration in the matrix. MRS2 is essential for the survival of eukaryotic cells: knockdown of MRS2 caused cell death by inducing loss of respiratory complex I and by triggering mitochondrial membrane depolarization [88]. Rats bearing a functionally inactivating mutation of MRS2 have major mitochondrial deficits with a markedly elevated lactic acid concentration in the cerebrospinal fluid, a 60% reduction in ATP, and increased numbers of mitochondria in oligodendrocytes [89]. Bearing in mind that mitochondria are central effectors in energy metabolism and programmed cell death, a link between mitochondrial Mg and cancer progression, in particular resistance to apoptosis, should not come as a surprise. MRS2 is overexpressed in gastric cancer cells exhibiting the multi-drug resistance (MDR) phenotype and most likely acts as an enhancer of MDR by influencing the activity of cell cycle proteins and the release of pro-apoptotic factors from mitochondria [90,91]. These findings are consistent with data showing that metabolic impairment, resulting from MRS2 knock-down and consequent reduction in intracellular Mg, induces cellular vulnerability to several stress conditions, including oxidative stress [92] and chemotherapeutics such as staurosporine and doxorubicin [93]. Since MRS2 was one of the genes associated with pluripotency in a transcriptomic analysis [94], it is intriguing to speculate that stemness and MDR may share a magnesium-regulating mechanism such as the overexpression of the MRS2 channel [95].

3. Perspectives for Cancer Treatment

Despite identification of Mg^{2+} channels whose altered expression and/or function promote certain malignant phenotypes and frequent optimistic claims in the literature that they can serve as promising therapeutic targets, not many of pharmacological agents acting on these molecules can successfully complete the drug development process. An ideal target should display a very limited expression in normal tissues and a strong overexpression in tumours; moreover, it should have selective nontoxic ligands with minimum side effects [96]. Most of the Mg^{2+} transporters we have discussed are still insufficiently characterized to envisage any translational applications in the near future. At present, the TRPM7 channel seems to offer the best prognostic and therapeutic potential, in view of the extensive research efforts on this subject. Unfortunately, most known inhibitors of TRPM7 lack the required specificity; to date, the most selective and potent TRPM7 channel blockers are NS8593 and waixenicin A, which both act on the pore region and are Mg^{2+}-dependent [97]. However, TRPM7 is ubiquitously expressed in all tissues, and is essential for a myriad of physiological processes [12]; thus, its pharmacological targeting is likely to cause significant toxicity. Targeting the kinase function appears more appealing, because should result in less significant side effects. The kinase activity has been more specifically involved in the metastatic process. Studies on TRPM7-deficient mice have shown that, while deletion of the kinase domain dramatically disrupts Mg homeostasis and is lethal [98], kinase function inhibition by a point mutation does not impair channel activity, Mg homeostasis or development [99,100]. Research on pharmacological tools able to modulate the TRPM7 kinase is ongoing, but no suitable drug candidates are available yet [97]. In the long term, in addition to traditional pharmacological tools, novel siRNA and antisense oligonucleotide-based therapies in combination with effective, reliable, and nontoxic gene transfer technologies should be considered to enable selective ion channel targeting only in tumours. Antibody-based therapies may also be possible, due to cell-surface accessibility and overexpression; alternatively, antibodies could be used as carriers for radionuclides, toxic molecules, or nanoparticles.

4. Conclusions

Following the discovery of the TRPM6/7 channel kinase around the turn of the millennium, magnesium research has boomed for the last 20 years. A plethora of possible Mg homeostatic factors and/or putative Mg^{2+} transporters have added to the molecular entities that could be used to explore the molecular biology of Mg homeostasis and to translate such knowledge into the field of clinical medicine and pharmacology. An increasing body of evidence supports the view that derangement of Mg homeostasis, mediated by aberrant expression of Mg-regulating factors, may recapitulate most hallmarks of cancer [101]. Indeed, the seminal idea of Mg as a key regulator of cell proliferation has been enriched by novel intriguing findings that link Mg and Mg^{2+} transporters to distinctive and complementary capabilities that enable tumour growth and metastatic dissemination (Figure 2). Sustained proliferative signaling through upregulation of TRPM7 expression (see Section 2.1) or modulation of CNNM-PRL interaction (see Section 2.3), which favor intracellular Mg accumulation, is not unexpected. However, the emerging picture is much more exciting, because both TRPM7 and the CNNM-PRL complexes have been implicated in the control of cellular metabolism, thus their abnormal expression or activity may contribute to deregulate cellular energetics. TRPM7 also participates in activating invasion and metastasis, most likely through its kinase domain, and may play a role in moulding a permissive microenvironment by affecting redox and immune status. Last, but not the least, there is evidence that downregulation of SLC41A1 (section 2.4) or upregulation of MRS2 (section 2.5) may result in reduced susceptibility to apoptosis.

Not all aspects of Mg^{2+} channel functions are fully understood for different types of cancer, and not all results obtained in in vitro and even in vivo animal modeling can be easily transferred to human cancer, but the involvement of Mg and Mg^{2+} channels or putative transporters in cancer hallmarks appears indisputable. Although Mg^{2+} channels might not represent the optimal pharmacological targets, interaction of basic and clinical researchers can be an extremely powerful engine to push forward our knowledge of Mg homeostasis and Mg-homeostatic factors, which will enrich our molecular toolbox to develop better approaches to prevent cancer or help in its treatment.

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5. References

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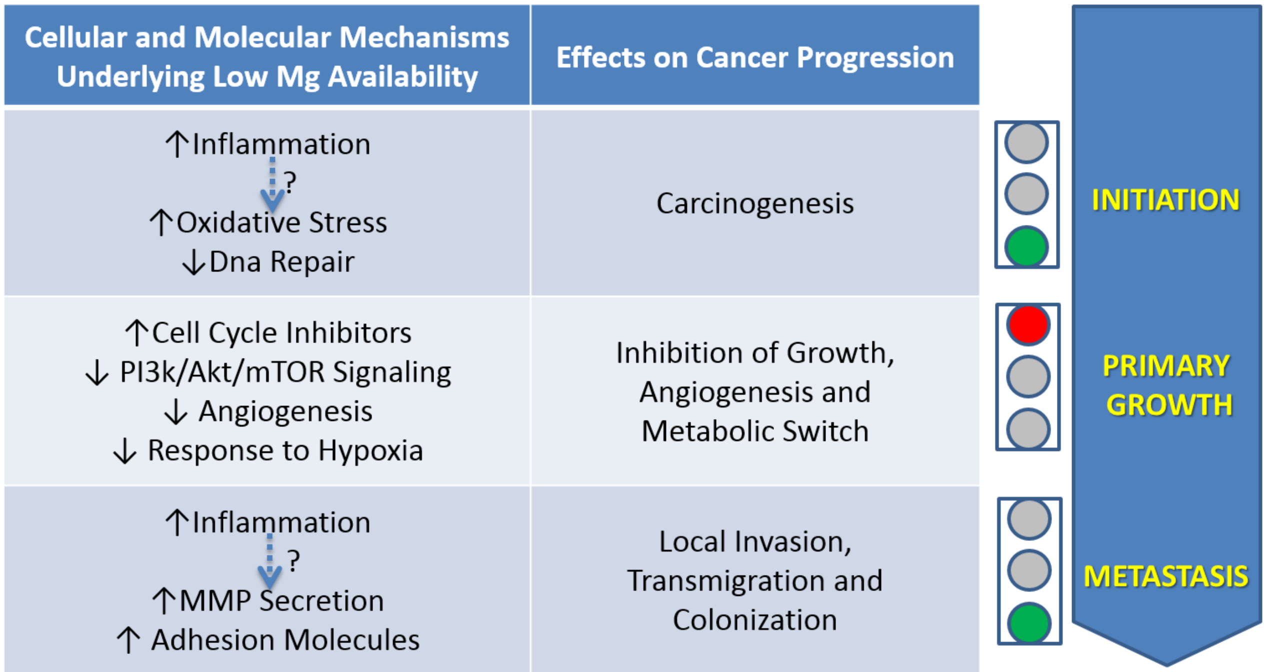
Figures



Cellular and Molecular Mechanisms Underlying Low Mg Availability	Effects on Cancer Progression
↑Inflammation ? ↑Oxidative Stress ↓Dna Repair	Carcinogenesis
↑Cell Cycle Inhibitors ↓ PI3k/Akt/mTOR Signaling ↓ Angiogenesis ↓ Response to Hypoxia	Inhibition of Growth, Angiogenesis and Metabolic Switch
↑Inflammation ? ↑MMP Secretion ↑ Adhesion Molecules	Local Invasion, Transmigration and Colonization

Figure 1. Effects of Mg availability on cancer progression. Low Mg availability can have both pro- and anti-cancer effects, depending on tumour stage. Mg deficiency is associated to increased cancer risk, due to direct or inflammation-mediated oxidative damage and impaired DNA repair capacity. Low Mg conditions hinder primary tumour growth mainly by inhibiting cell proliferation and angiogenesis, but can result in increased formation of metastases, likely via induction of inflammatory cytokines. For detailed discussion and references, see Section 1. ↑ and ↓ represent increased or decreased effect, respectively. Dashed arrows represent connections that have been hypothesized but not directly proven. Green and red traffic lights indicate promotion or inhibition, respectively.

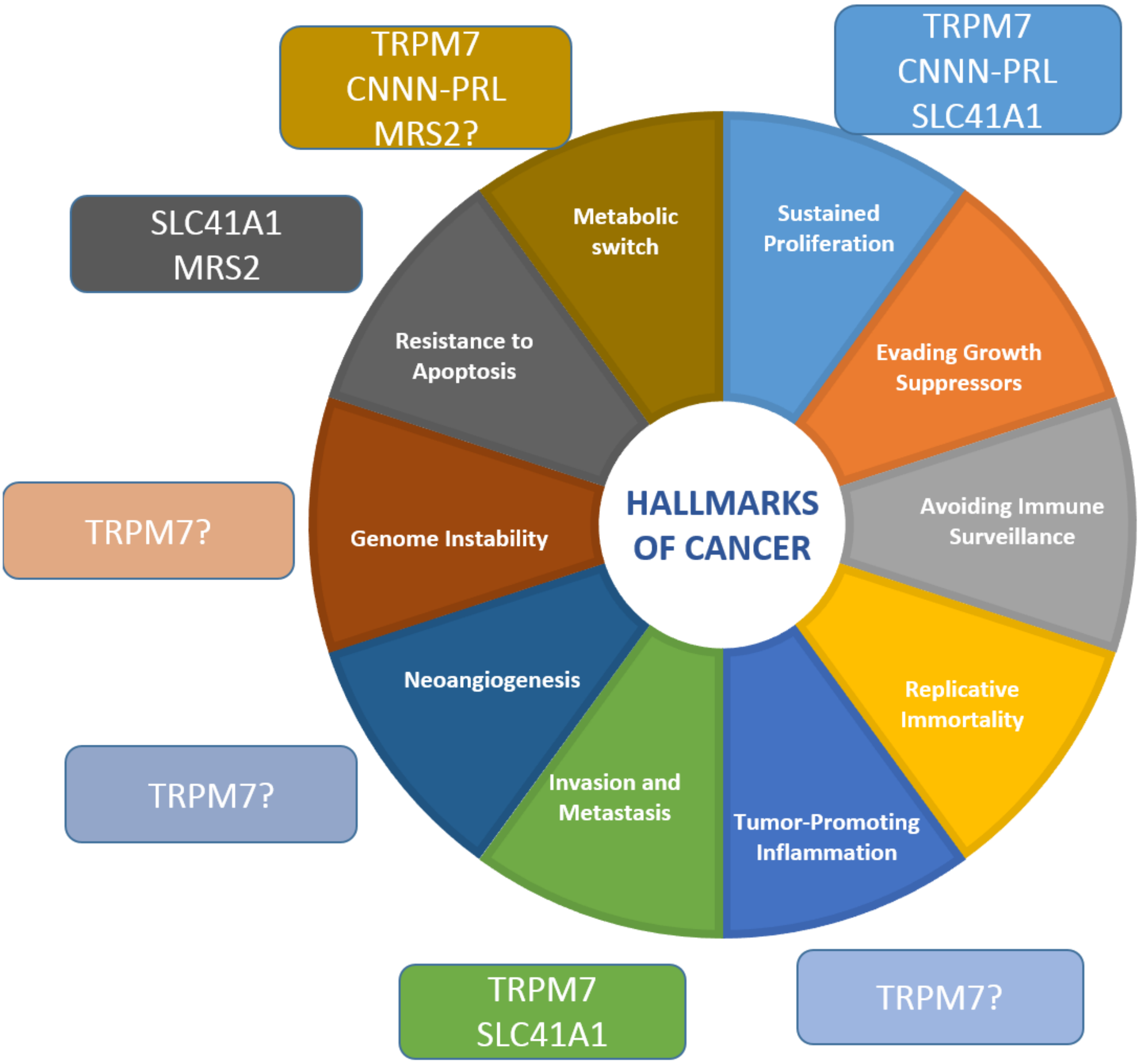


Figure 2. Mg^{2+} channels and transporters confer several cancer hallmarks. Many human tumours show aberrant expression of Mg^{2+} channels or putative transporters, which can facilitate acquisition of one or more hallmarks. Proliferation can be sustained by increased Mg accumulation, mediated by increased expression of influx-mediating molecules (TRPM7, CNNM3-PRL2) or efflux-mediating molecules (SLC41A1, CNNM4-PRL3). Increased intracellular (via reduced SLC41A1-mediated efflux) or mitochondrial (via increased MRS2-mediated influx) Mg accumulation may confer improved resistance to apoptotic stimuli. Increased influx via TRPM7 and CNNM-PRL complexes has also been linked to energy metabolism. Invasion and metastasis can be favoured by the kinase activity of TRPM7 or inhibited by a functional SLC41A1. To date, the involvement of TRPM7 in modulating enabling characteristics such as angiogenesis, genomic instability and tumour-promoting inflammation is merely speculative, as is the role of MRS2 in affecting energetics. See Section 2 for further details.