



Review

Ionic Regulation of T-Cell Function and Anti-Tumour Immunity

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Abstract: The capacity of T cells to identify and kill cancer cells has become a central pillar of immune-based cancer therapies. However, T cells are characterized by a dysfunctional state in most tumours. A major obstacle for proper T-cell function is the metabolic constraints posed by the tumour microenvironment (TME). In the TME, T cells compete with cancer cells for macronutrients (sugar, proteins, and lipid) and micronutrients (vitamins and minerals/ions). While the role of macronutrients in T-cell activation and function is well characterized, the contribution of micronutrients and especially ions in anti-tumour T-cell activities is still under investigation. Notably, ions are important for most of the signalling pathways regulating T-cell anti-tumour function. In this review, we discuss the role of six biologically relevant ions in T-cell function and in anti-tumour immunity, elucidating potential strategies to adopt to improve immunotherapy via modulation of ion metabolism.

Keywords: T cell; ions; tumour microenvironment; immunomodulation; nutrient competition



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1. Introduction

T lymphocytes undergo a metabolic reprogramming upon TCR-stimulation, which sustains the biosynthetic requirements of clonal expansion and differentiation. Indeed, the engagement of specific metabolic pathways requires the presence of particular metabolites that are not only necessary to promote the synthesis of ATP and macromolecules but also to mediate signalling regulation of T-cell function and fate [1–3]. The role of metabolism in modulating T-cell responses becomes evident in the context of anti-tumour immunity, where cancer cells acquire suppressive mechanisms to evade the immune system [4]. Nutrient competition between cancer and immune cells in the tumour microenvironment (TME) or the secretion of cancer-cell suppressive metabolic waste products (e.g., adenosine or kynurenine) have been deeply studied during the last decade [5,6], and a myriad of promising interventions has been developed to overcome these metabolic barriers and to boost anti-tumour T-cell responses [7,8].

The role of glucose, amino acids, and lipids in the regulation of T-cell responses against cancer has been studied and reviewed extensively elsewhere [9–14]. Here, we focus on the underrepresented function of ions. T cells require an appropriate balance of extracellular and intracellular ion levels to maintain cell and mitochondrial membrane potential ($\Delta\Psi_m$). Furthermore, ions operate as second messengers for TCR signalling, act as cofactors for a multitude of enzymes, and interact with DNA to stabilise its structure. Disturbances in ionic concentrations or in the expression of ionic channels are detrimental for T-cell performance and lead to the appearance of immune-related diseases. Although it is well-known that ionic homeostasis is essential for T-cell survival and activity, the functional relevance of ions within tumours remains poorly understood. Recent reports have shown that tumour necrotic cells release ions within the TME and that several cancer types modify ion-channel expression to adapt to the ionic conditions of the TME [15,16]. In this review, we will discuss how ions shape T-cell immunity and describe the latest

advances in the context of anti-tumour immunity. Specifically, we will focus on six ions with potential translational application: potassium, manganese, zinc, selenium, iron, and magnesium.

2. Potassium

Potassium (K^+) is the most abundant ion in mammalian cells, with intracellular K^+ levels ($[K^+]_i$) reaching ~ 130 mM, while extracellular levels $[K^+]_e$ are ~ 3 – 5 mM [17,18]. In T lymphocytes, K^+ gradient is balanced through the action of two ion channels mediating K^+ efflux: the voltage-gated $K_v1.3$ and the Ca^{2+} -activated $K_{Ca}3.1$ channels (Figure 1) [19]. Alterations in the expression of these channels and, subsequently, in $[K^+]_i$, lead to aberrant T-cell functionality.

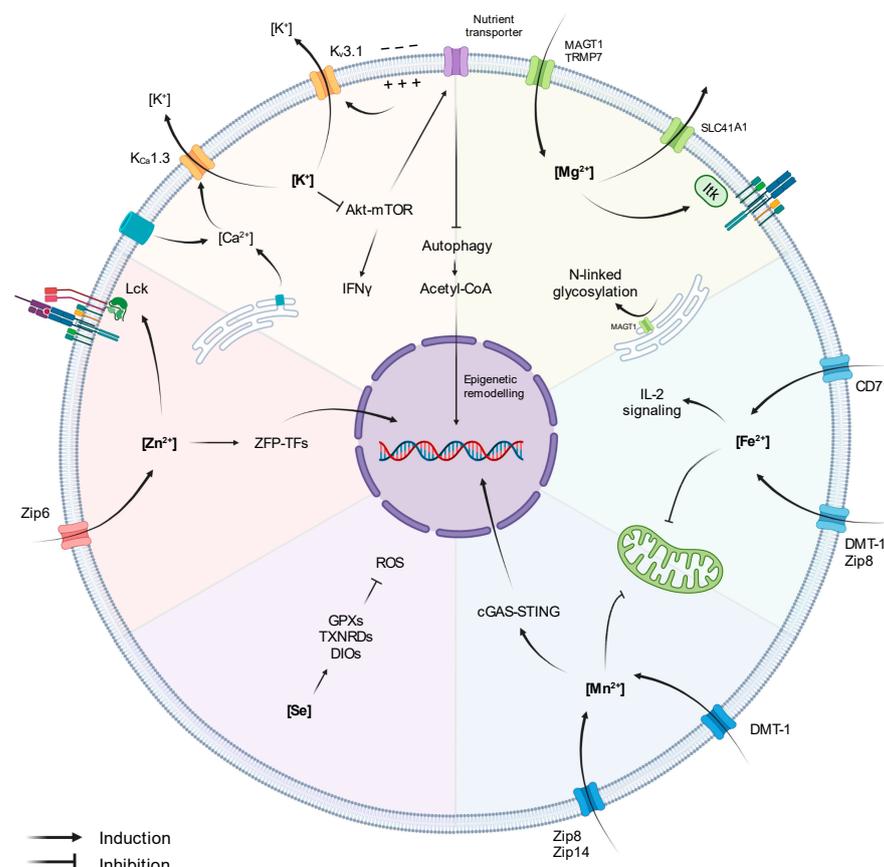


Figure 1. Influence of Ions on T-cell activity.

The role of K^+ in T cells is tightly linked to Ca^{2+} signalling. Upon antigen recognition, the activation of TCR signalling triggers the opening of Ca^{2+} channels (Orai1 in the ER and CRAC channels in the cell membrane), leading to increased intracellular Ca^{2+} levels. Importantly, Ca^{2+} induces NFAT expression and subsequent IL-2 production and T-cell activation [20]. However, the first wave of Ca^{2+} release generates an electrochemical imbalance that depolarises the membrane and hampers further Ca^{2+} influx. Membrane depolarisation and the elevated Ca^{2+} levels activate $K_v1.3$ and $K_{Ca}3.1$, respectively, promoting K^+ efflux, thus restoring membrane potential and enabling continuous Ca^{2+} entry and signalling amplification (Figure 1) [19,21]. Indeed, a blockade of $K_v1.3$ and $K_{Ca}3.1$ reduces Ca^{2+} signalling, demonstrating the key role of K^+ gradient in preserving the equilibrium of the membrane potential upon TCR stimulation and ensuring efficient T-cell activation [22]. In accordance, $K_v1.3$ and $K_{Ca}3.1$ are highly expressed upon T-cell activation, and they co-localize at the immunological synapse, together with CRAC channels [15,21,23]. Moreover, $K_v1.3$ and $K_{Ca}3.1$ have also been shown to influence T-cell migratory capacity [24,25].

Importantly, $K_v1.3$ and $K_{Ca}3.1$ expression vary between T-cell subsets. It has been described that T_h1 and T_h2 cells predominantly express $K_{Ca}3.1$, whilst T_h17 and T_{regs} express $K_v1.3$. In fact, $K_{Ca}3.1^{-/-}$ mice are resistant to the induction of autoimmune colitis, characterised by the presence of autoreactive T_h1 cells. In this model, depletion of $K_{Ca}3.1$ disrupted T_h1 activity without affecting the functionality of T_{regs} and T_h17 cells [26]. Similarly in humans, effector-memory T cells ($CD45RA^- CCR7^+$; T_{em}) are highly dependent on $K_v1.3$ for Ca^{2+} signalling, whereas central-memory T cells ($CD45RA^- CCR7^-$; T_{cm}) are mostly dependent on $K_{Ca}3.1$, and $K_v1.3$ inhibition only mildly affects their functionality [27,28]. The differences in expression levels are interesting from an immunotherapeutic perspective, as the application of K^+ channel blockers could be used to target specific T-cell populations.

In the context of anti-tumour T-cell responses, it has been shown that necrotic cancer cells within hypoxic areas release large amounts of K^+ , which directly inhibit effector functions of murine and human $CD8^+$ T cells [15,18]. Mechanistically, T-cell suppression derived from exposure to high extracellular $[K^+]_e$ is not directly caused by membrane-potential variations or Ca^{2+} signalling alterations but is rather due to an increase in intracellular $[K^+]_i$, which affects the Akt-mTOR pathway (Figure 1) [15,18]. In addition, it has been described that hypoxia downregulates $K_v1.3$ and $K_{Ca}3.1$ [29], suggesting that intracellular $[K^+]_i$ could be further augmented in the TME through other synergistic mechanisms. Importantly, overexpression of $K_{Ca}3.1$ decreases intracellular $[K^+]_i$ and restores T-cell Akt-mTOR signalling and $IFN\gamma$ secretion, resulting in improved tumour growth control and survival [15]. These reports indicate that levels of $[K^+]_i$ and K^+ channels in T cells might be used as markers of T-cell fitness within tumours. Accordingly, $K_v1.3$ and $K_{Ca}3.1$ activity in $CD8^+$ T cells derived from head- and neck-cancer patients correlate with increased T-cell infiltration and functionality [25,30,31]. Moreover, K^+ is also an important cofactor for the glycolytic enzyme hexokinase-II (HK-II), suggesting that K^+ might not only be involved in the regulation of anti-tumour immunity but also in the adaptation of cancer-cell metabolism in the TME. Altogether, these studies support the concept that K^+ acts as a suppressive element of anti-tumour immunity. However, a more recent report by Vodnala et al. (2019) showed that despite dampening T-cell effector functions, mTOR inactivation derived from high $[K^+]_e$ is accompanied by a decreased nutrient uptake, which initiates a starvation response. The authors define this state as 'functional caloric restriction', characterised by autophagy induction and acetyl-CoA-dependent epigenetic remodelling (Figure 1). Specifically, exposure to $[K^+]_e$ reduced the acetylation of effector/exhaustion-associated loci of genes such as *Pdcd1* (PD1), *Cd244* (2B4), and *Havcr2* (Tim-3) while preserving T-cell stemness through the induction of TCF1 expression. Consequently, T cells exposed to high $[K^+]_e$ during in vitro expansion enhanced T-cell persistence and anti-tumour response upon adoptive cell transfer in a B16 melanoma mouse model [32]. On the contrary, CD19-directed human CAR-T cells cultured for 48 h in cerebrospinal fluid (CSF), which contains low concentrations of glucose and K^+ , expressed elevated levels of genes encoding for survival and memory markers (e.g., BCL2, IL7R) and lower levels of effector genes (e.g., $IFN\gamma$, GrB, Tbet) [33]. Although plenty of evidence points at K^+ as an interesting target for immunotherapy, the dual roles of K^+ in anti-tumour T cells, the discrepancies observed in murine and human settings, and the direct effect of K^+ on cancer cells indicate that further investigations are required to unveil the best strategy to exploit K^+ in cancer therapy.

3. Manganese

Manganese (Mn^{2+}) is one of the most abundant metals found in the tissues of mammals, and it is crucial for intracellular processes regulating energy production, development, antioxidant defence and immune response [34]. Indeed, uptake, retention, and excretion of Mn^{2+} are tightly regulated due to its key role as cofactor of a variety of enzymes, such as Mn^{2+} superoxide dismutase (SOD), glutamine synthetase (GS), arginase, and pyruvate carboxylase. Intracellular Mn^{2+} homeostasis is regulated through non-exclusive metal-ion

transporters, including divalent metal transporter A (DMT1), calcium channel-dependent protein, and metal-transporter-family proteins like Zip8 and Zip14 (Figure 1) [35–37].

Mn²⁺ is present in all compartments. However, most intracellular Mn²⁺ is stored in the Golgi apparatus and in the mitochondria [38]. When supplemented at high concentrations in culture media, Mn²⁺ accumulates in the mitochondria and in the nucleus, impairing mitochondrial activity and inducing DNA damage (Figure 1) [39]. In HeLa and in THP1 cells, Mn²⁺ release from the mitochondria and Golgi to the cytosol increases the sensitivity of the DNA sensor cGAS and the downstream adaptor protein STING, which, in turn, induces type I IFNs and cytokine production [40]. However, its function in both adaptive and innate immunity has been poorly investigated. A recent study has shown that Mn²⁺ supplementation improved tumour-specific antigen presentation acting on macrophages and dendritic cell maturation [41]. As a consequence, both dendritic cells and macrophage maturation contribute to CD8⁺ T-cell activation and better tumour control in a B16 melanoma model. Congruently, as first reported in the 1980s, Mn²⁺ supplementation leads to a significant increase in the number of TILs [41–43]. In addition, Mn²⁺ treatment increases cytokine production capacity in both CD8⁺ T and NK infiltrating tumours, while depletion of Mn²⁺ from the diet results in a reduced T cells differentiation and increased tumour size. Mn²⁺ anti-tumoural activities, such as increased TIL number, function, or shifting macrophage polarization to a more anti-tumoural phenotype, has been exploited in combination with conventional chemotherapy and immune checkpoint blockade therapy to boost anti-tumour response [44,45]. Indeed, Mn²⁺ can induce type I IFN production and dendritic cell maturation, similarly to STING agonist, making Mn²⁺ a potential novel adjuvant for cancer vaccines (Figure 1) [41,46]. Taken together, due to its promiscuous effect in stimulating both myeloid (dendritic cells) and lymphoid (CD8⁺ T cells and NK) compartments, Mn²⁺ metabolism emerges as a potential novel target for anti-tumour therapies.

4. Zinc

Zinc (Zn²⁺) is the second most abundant trace metal in the human body after iron. It is an essential component of several proteins [47] and participates in a variety of cellular processes, including cell proliferation, differentiation, redox regulation, and apoptosis. [48–50]. Zn²⁺ is mostly intracellular and conjugated to zinc-binding proteins [51]. Zn²⁺ homeostasis is tightly controlled by a variety of transporters and chaperone proteins called metallothioneins [52]. Importantly, Zn²⁺ regulates both innate and adaptive immunity [53,54]. Chronic Zn²⁺ deficiency impairs proper T-cell development, differentiation, and function [55]. Indeed, Zn²⁺ deficiency reduces expression of the cytotoxic T lymphocyte marker CD73 in patients with sickle cell anaemia [56] and leads to a significant reduction of thymus-derived hormone thymulin, regulating T-cell differentiation and maturation [57]. Zn²⁺ is also involved in T-cell activation and differentiation, being involved in the interaction between the short cytoplasmatic domain of CD4 or CD8 α with p56^{lck} (Figure 1) [58]. Upon TCR signalling, cytoplasmatic Zn²⁺ concentration increases within 1 min due to the rapid upregulation of the zinc transporter Zip6 (Figure 1) [59], leading to Zap70 phosphorylation and sustained calcium influx, which supports T-cell proliferation in suboptimal conditions [59]. Moreover, inhibition of Zn²⁺ influx through Zip6 silencing impairs T-cell activation, resulting in reduced expression of activation markers, such as CD25 and CD69, and reduced production of cytokines, such as IL-2 [60]. Similarly, Zn²⁺ depletion blocks the ERK1/2 and PI3K/Akt pathways, inhibiting T-cell activation [61,62]. While the direct effect of Zn²⁺ on tumour growth has not been elucidated yet, few studies have indicated a potential immunosuppressive role of Zn²⁺ both *in vitro* [63] and in the tumour microenvironment [64]. Notably, it has been shown that a Zn²⁺-rich diet can promote prostate carcinogenesis and increase the risk of prostate cancer progression [65].

Finally, in the B16F10 murine melanoma model, it has been observed that TILs up-regulate metallothioneins and zinc-finger transcription factors, such as GATA-3 and IKZF2 (Figure 1) [66], indicating a possible role of Zn²⁺ homeostasis in T-cell differentiation and

exhaustion within the TME. The evidence gathered so far places Zn^{2+} metabolism as a potential target to dampen the immunosuppressive mechanism adopted by cancer cells. However, how Zn^{2+} acts as an immunosuppressive factor and which zinc-dependent proteins are involved in the process has yet to be defined.

5. Selenium

Selenium (Se^{2-}) is taken up through the diet in either organic forms, seleno-L-methionine (SeMet) and seleno-L-cysteine (SeCys), or as inorganic forms, selenide and selenite, which are all ultimately metabolized within mammalian cells into SeCys. Indeed, SeCys, also known as the 21st amino acid, is an essential element of selenoprotein catalytic sites [67,68]. In humans, 25 genes encoding for selenoproteins have been identified, with most of them involved in the regulation of redox balance and protection against oxidative stress. Enzymatic glutathione peroxidases (GPXs), thioredoxin reductases (TXNRDs), or iodothyronine deiodinases (DIOs) (Figure 1), as well as the non-enzymatic selenoprotein P (SELENOP) and selenoprotein K (SELENOK), are amongst the most important selenoproteins [67,68]. SELENOP is known to be one of the most important Se^{2-} carriers in circulation. On the other hand, the molecular mechanisms involved in Se^{2-} cellular uptake have not yet been completely elucidated [67,68].

In an immunological context, Se^{2-} supplementation boosts immune function via regulation of selenoprotein levels. Shrimali et al. (2008) generated mice with T-cell-specific ablation of the SeCys tRNA^{[Ser]^{Sec}} and described that loss of selenoprotein synthesis in T cells leads to ROS hyperproduction and suppression of T-cell expansion after TCR stimulation [69]. Furthermore, another report by Verma et al. (2011) showed that T cells lacking SELENOK, an ER transmembrane protein that regulates Ca^{2+} flux, display reduced Ca^{2+} signalling during T-cell activation and, subsequently, defective immune responses during viral infection [70]. These investigations, together with epidemiological studies showing that Se-deficient diets are associated with a loss of immunocompetence [71], indicate that Se^{2-} levels and selenoproteins are essential for appropriate regulation of T-cell-mediated immunity.

Even though the role of Se^{2-} in T-cell anti-tumour responses has been poorly elucidated, a combination of preclinical and clinical studies indicate that increased Se^{2-} serum levels are associated with overall improved survival in patients [72]. In particular, sodium-selenite-enriched diets have shown to reduce tumour size in mice by enhancing the cytotoxicity of both $CD8^+$ T cells and NK cells, suggesting a direct effect on anti-tumour immunity [73]. Importantly, selenoprotein GPX4 has been described as a fate and functional determinant of TILs. Specifically, decreased GPX4 expression in TILs is associated with an accumulation of oxidized lipids that induces T-cell death via ferroptosis [74]. GPX4-mediated regulation of ferroptosis is also a survival mechanisms of cancer cells, which can increase GPX4 levels through the induction of selenophosphate synthetase 2 (SEPHS2), an enzyme involved in SeCys biosynthesis [75]. Altogether, these reports indicate that cancer progression is influenced by Se^{2-} levels, by both affecting cancer-cell survival and immune-cell function, opening the way to Se^{2-} modulation as a possible future strategy to boost cancer immunotherapy.

6. Magnesium

Magnesium (Mg^{2+}) is the most abundant divalent cation in eukaryotic cells (~10–30 mM). While only ~5% of intracellular Mg^{2+} is found free ($[Mg^{2+}]_i$), most of it is complexed to ATP or bonded to other molecules functioning as a cofactor. In T cells, $[Mg^{2+}]_i$ levels are finely regulated by the ion channels MAGT1, TRPM7, mediating Mg^{2+} influx, and SLC41A1, mediating Mg^{2+} efflux through Na^+ exchange (Figure 1) [76].

T-cell antigen recognition is followed by a rapid transient Mg^{2+} influx, which acts as second messenger in TCR signalling [77,78]. Specifically, Mg^{2+} directly interacts with IL-2-inducible T-cell kinase (ITK) promoting its activation (Figure 1) [79]. On the contrary, lymphocyte activation in low $[Mg^{2+}]$ conditions limits CD69 and CD25 upregulation, Ca^{2+}

influx, and cell proliferation [79]. Indeed, mice fed Mg^{2+} -restricted diets and infected with influenza A virus have reduced numbers of virus-specific T cells [79]. Furthermore, patients carrying loss-of-function mutations in *MAGT1* gene develop a rare primary immunodeficiency known as XMEN disease ('X-linked immunodeficiency with Mg^{2+} defect, Epstein-Barr virus (EBV) infection, and neoplasia'). T cells from patients with XMEN disease exhibit limited Mg^{2+} influx and recapitulate most of the features observed in low $[Mg^{2+}]$ conditions (i.e., deficient TCR signalling, Ca^{2+} influx, T-cell activation and proliferation) [77,78,80]. Interestingly, *MAGT1* localizes in the ER, where it mediates N-linked glycosylation, a post-translational modification influencing protein half-life (Figure 1) [81,82]. In XMEN patients, $CD8^+$ T cells lose *CD70* and *NKG2D* expression due to its diminished glycosylation, which has been linked to an increased susceptibility to EBV infection [81–83].

Mg^{2+} is important for the stabilisation of DNA structure and operates as a cofactor for enzymes involved in DNA repair, suggesting that Mg^{2+} deprivation might lead to accumulation of DNA damage and carcinogenesis. Accordingly, low Mg^{2+} intake is associated with higher risk of pancreatic, lung, and breast cancer [84–86], while alterations in *MAGT1* and *SLC41A1* expression have been associated with aggressive colorectal cancers and pancreatic ductal adenocarcinomas (PDAC) [87,88]. Interestingly, Diao et al. (2017) described that chronically activated $CD8^+$ T cells in hepatitis B virus (HBV)-infected patients show a decline in $[Mg^{2+}]_i$ and *MAGT1* expression associated with PD-1 upregulation and loss of *NKG2D* [89]. To date, this phenotype has not been identified in the exhausted TILs. However, the necrosis-derived release of ions [15] added to the alterations in the expression of Mg^{2+} transporters in cancer cells suggests that Mg^{2+} levels might vary in the TME and thus have an immunomodulatory role within the TME.

7. Iron

Iron (Fe^{2+}) is an essential element involved in several enzymatic reactions and cellular processes, such as proliferation, DNA synthesis, metabolism [90], and immune function [91,92]. For this reason, Fe^{2+} levels are tightly regulated. Most of the Fe^{2+} delivered to the cells is bound to transferrin protein (Tf). The Tf-iron complex is taken up by the cells through transferrin receptor (*CD71*) endocytosis. Notably, T cells can also take up Fe^{2+} via non-specific metal-ion transporters, like *DMT-1* and *ZIP-8* (Figure 1) [93,94]. During activation, T cells increase expression of *CD71* (Figure 1) [95]. On the contrary, anergic T cells have reduced expression of *CD71* [96]. Reduced Fe^{2+} uptake due to defective Tf-receptor endocytosis impairs T-cell function and results in severe immunodeficiency [97]. Furthermore, reduced intracellular Fe^{2+} levels impaired *CD25* expression and *IL-2R* signalling and compromised mitochondrial function in T cells (Figure 1). Notably, Fe^{2+} supplementation in an iron-deficiency culture system restore proper mitochondrial potential and biogenesis [98].

A recent report revealed a role of Fe^{2+} in an inflammatory context. In autoimmune diseases, iron deposition is frequently observed. According to Wang et al., Fe^{2+} promotes proinflammatory cytokine production in immune cells, including T cells [99]. On the other hand, it has been reported that Fe^{2+} is released by tumour-associated macrophages (TAMs) and tumour-associated neutrophils (TANs) in the TME. In this scenario, Fe^{2+} might sustain TAMs and TANs in supporting cancer progression and impairing T and B cell activity by inducing cell death. Fe^{2+} has been involved in the induction of ferroptosis by mechanisms that are still poorly understood [100]. Although the impact of Fe^{2+} secretion by TAMs and TANs is not directly proven, it is likely that high Fe^{2+} levels may contribute to the induction of ferroptosis in T cells and cancer cells. Furthermore, TAMs and TANs can also impair proper APC maturation and antigen presentation [101,102]. In light of the cited reports, altering Fe^{2+} concentration in the tumour microenvironment could be a promising approach to improve current therapies [102,103].

8. Conclusions and Perspectives

Many clinical trials have demonstrated therapeutic efficacy of T-cell based immunotherapy, which exploits the capacity of T cells to recognize and kill a specific target, including cancer cells [104]. While it is well established that metal ions can regulate immune-system and T-cell function and metabolism, it is not clear how the manipulation of ion concentrations in the TME can improve T-cell activity and possibly T-cell-based immunotherapy. Recent studies cited in this review underline the role of ions in shaping T-cell capacity controlling tumour growth (Figure 2). Although there is an increased interest in understanding the role of ions in the context of the tumour microenvironment [15,105], the complex interplay between ion concentration, immune cells, and cancer cells has not been sufficiently investigated. Recently, cutting-edge gene-targeting technologies, like CRISPR, have been adopted to reveal processes involved in nutrient sensing and consumption in T cells in vivo [106]. Implementing these approaches to ion channels and ion-dependent enzymes would provide a deeper view on the molecular processes orchestrated by specific ions and on how these processes influence T-cell activity. Another challenging aspect is the development of strategies capable of locally altering ionic concentration in the TME. While adequate diet and nutrient supplementation can modulate ion blood levels, it is not known whether a systemic change in ion intake might lead to a local effect. Further studies are needed to elucidate whether a tailored supplementation of a given ion would be adequate to optimize immune function in the TME. Another possibility would be to design methods to locally deliver or deplete a specific ion. Canale et al. used engineered bacteria to locally deliver arginine in the TME, enabling metabolic modulation of the tumour microenvironment and improving adaptive immune responses against cancer cells [107]. A similar approach suited for ions would provide a tool to alter ion concentration only in the TME. Indeed, a large body of evidence has shown how metabolism and nutrient consumption are key factors for a proper and robust anti-tumour immune response [12,108]. In this context, elucidating the role of ions in both homeostatic and anti-tumour T-cell activity might help in the development of novel strategies aimed to improve T-cell-based therapies.

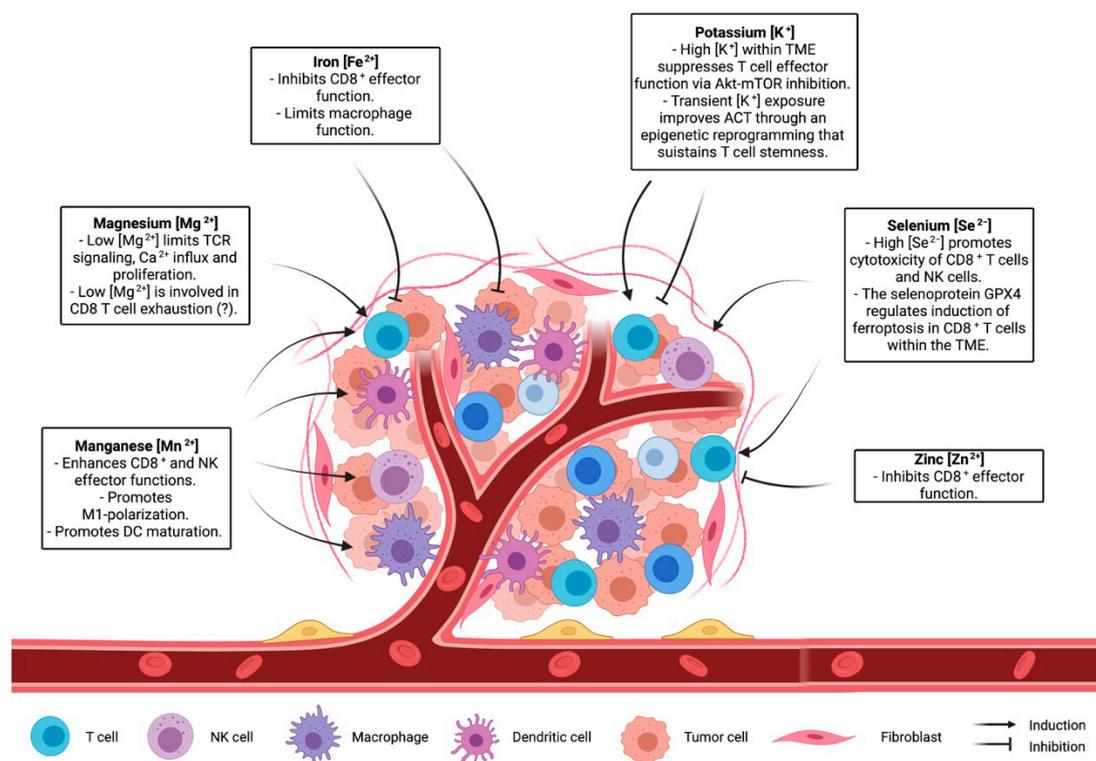


Figure 2. The role of ions in shaping the immune landscape of the microenvironment.

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