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REVIEW

Why Nature Chose Potassium

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Abstract
The presence of most of the atoms involved in the building up of living cells can be explained by their intrinsic physico-chemical properties. Yet, the involvement of the alkali metal potassium cation (K^+) is somewhat of a mystery for most scenarios of origins of life, as this element is less abundant than its sodium counterpart in sea water, the original medium bathing the majority of proposed sites as the cradle of life. Potassium is involved in key processes that could as well have been fulfilled by sodium (such as maintenance of an electrochemical potential or homeostatic osmolarity). However, K^+ is also required for the setup of a functional translation machinery, as well as for a fairly enigmatic metabolic pathway involving the usually toxic metabolite methylglyoxal. Here we discuss the possibility that potassium has been selected because of some of its idiosyncratic properties or whether it is just the outcome of the accidental place where life was born. Specific physico-chemical properties of the K^+ ion would argue in favour of positive selection in the course of life's evolution. By contrast, the latter explanation would require that life originated on potassium-rich environments, possibly continental but yet of unknown location, making K^+ presence just a frozen accident of evolution.

Keywords Ribosome · Splicing · Water structure · nanoRNases · Abiogenesis · Landauer's principle

Introduction

The atoms of life are not a random sampling from Mendeleiev's table (Fig. 1, for a crude illustration of the elements abundance on Earth). A major constraint for the building up of cells comes from the fact that life as we know it rests on the construction of polymers. Polymer synthesis entails that, besides ions involved in electric charge and redox processes management, life's emergence has restricted its choice of atoms to those that easily form stable covalent bonds at the temperature of Earth (approximately 300 K). This chemical limitation has put aside unreactive atoms such as those making « rare gases », and restricted the atoms' choice essentially to hydrogen and to the second row of the periodic table, involving 2 *s* and 2*p* electron orbitals. This view points out that the quasi-absence of boron in biomolecules makes it a notable exception. Such dearth of boron is likely due to the fact that this atom is relatively rare for cosmological reasons. Together with lithium and beryllium, the nucleosynthesis of boron is known to have been defective during the early periods of the development of our Universe (Prochaska et al. 2003). Phosphorus, placed in the same column as nitrogen (but with a further shell of electrons), is an exception that has been discussed in a reference article where the remarkable role of phosphate for life is accurately highlighted (Westheimer 1987): phosphate-containing molecules are critical for life because life develops in water under conditions where phosphate bond hydrolysis is both energetically favoured and difficult (it must surpass a high activation energy barrier). Sulphur, finally, is widespread on the Earth's crust, and it is a remarkable carrier of electron transfers, displaying oxidation states that range from −2 to +6 in the biological context (Sekowska et al. 2000). This certainly accounts for its ubiquitous presence in living cells.

Formation and disruption of covalent bonds require a variety of electron-sharing and electron-transfer activities. These processes are performed in living cells via a very

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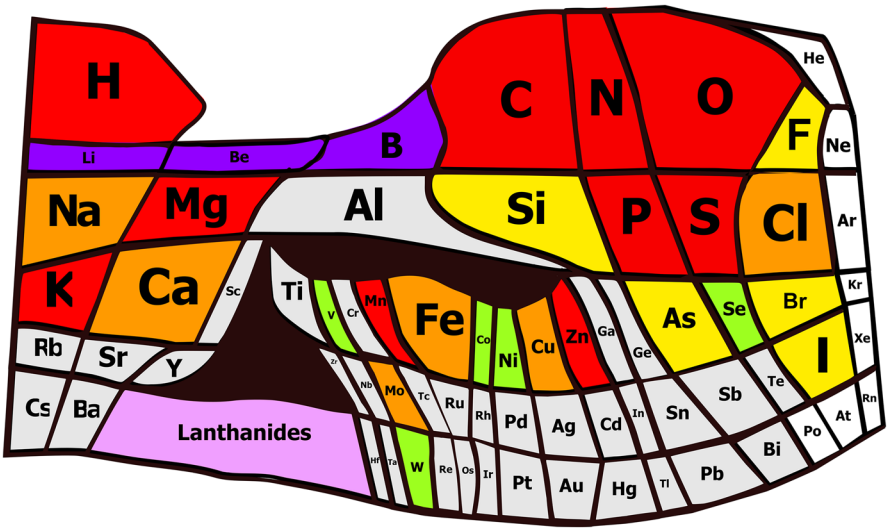

Fig. 1 Mendeleiev's table roughly conjuring up element abundance. This table, redrawn and adapted from (Sheehan 1976), presents a crude view of the table of element with a highly schematic view of their abundance. A more accurate view can be seen at http://research.google.com/bigpicture/elements/, a picture inspired by Sheehan's table (http://wnycradiolab.tumblr.com/post/36883321435/feminerds-totally-in-love-with-this-image-oh). We focus on the relative abundance of alkali metals for the discussion relevant to this review

rich catalogue of chemical reactions, in particular reactions involving generalized acid catalysis, often mediated by metal ions. The ubiquitous presence of negatively charged groups (mainly carboxylates and phosphates) both in small metabolites and macromolecules also asks for the presence of positively charged counterparts to ensure electroneutrality of the cytoplasm. The key role of multipurpose positive ions to counteract the large negative charge of nucleic acids and membrane lipids is essentially ensured in extant living cells by the monovalent potassium cations (K^+), while divalent cations have a more chemically specific role. The selection of K^+ as a critical component of cells despite the dominant presence of sodium (Na^+) in most aquatic environments is puzzling (Hunt 1891). Here, we explore the many functions of potassium engaged in life's processes and we attempt to understand whether potassium was chosen by chance and remained present as a ubiquitous component of cells as a frozen accident, or whether potassium has highly specific features that made it overcome competition with the widely available sodium ion, being submitted to positive selection in the course of evolution.

The Alkali Metal Ions

The first column of Mendeleiev's table is composed of metallic atoms that possess a single electron in their outermost *s*-orbital. At 300 K in water, they never exist as free elements as they immediately lose their only electron, which is easily captured by atoms or molecules of their surroundings, resulting in a soluble, monovalent positively charged ion. Sodium and potassium are omnipresent in living organisms, with lithium confined to specific biochemical environments. Interestingly, potassium- and sodium-specific binding to nucleic acids is much more pervasive than previously anticipated, making an analysis of their specific role particularly relevant (Leonarski et al. 2019). On this background, we start off with a short discussion of the role of lithium in cells, and then we discuss general physico-chemical properties of potassium as compared to those of sodium, with emphasis on properties that are potassium-specific. We subsequently examine the role of rubidium and caesium. Since water is the omnipresent bathing fluid of life, we restrict our discussion to chemical properties of the ions that are linked to water. A water molecule has a diameter of 2.78 Å. Ions have a hydration sphere (Ball 2017) that considerably depends on other compounds in their surroundings. The number of water molecules present in the hydration sphere decreases once the hydrated ions are close to one another (Marcus 2014). In this context, each alkali metal ion has a specific behaviour that may be important for its biological role, as discussed below (Table 1). In further sections, trying to answer the riddle of potassium choice as the main monovalent counterion in biological cells, we go more in depth and explore what we think are the most important roles of potassium in living processes.

Lithium

The lithium ion (Li^+) has a very small ionic radius (0.76–0.90 Å), similar to that of divalent ions (in the range 0.7–0.9 Å). This feature creates a strong local electric potential that organizes its ligands in a fairly constrained way. As remarked above, lithium is a fairly rare element. Also, this metal is special in that it can be oxidized by dinitrogen and could thus have played a role in the early formation of ammonium. However, this would have asked for conditions where metallic lithium reacted with dinitrogen, forming lithium nitride—a fairly unlikely scenario. By contrast, the lithium ion is present in a variety of environments and a

Table 1 Comparative properties of lithium, sodium and potassium

Physico-chemical feature	Lithium	Sodium	Potassium
Ionic radius	0.76–0.90 Å	1.02–1.16 Å	1.38–1.52 Å
Water coordination	1.95 Å	2.42 Å	2.84 Å
First hydration shell	4 (6)	6 (8)	6–8
Clathrate hydrates	20, 49, 51, 53, 55	No preference	20 and 16, 18, 41
Water structuring	Kosmotropic	Neutral	Chaotropic
Preferred binding atoms	O, N	O	O
Water exchange rate	5.8 ns	1.3 ns	1 ns

limited number of biochemical reactions are dependent on, or modulated by lithium.

For yet unexplained reasons, the ubiquitous phosphatases that control a reaction essential for life (degradation of very short oligonucleotides) interact with Li^+. This latter lytic function is performed by nanoRNases, such as those present in *Escherichia coli* (Orn) or in *Homo sapiens* (REXO2). These enzymes are inhibited by accumulation of the widespread metabolite 3′,5′-adenosine bisphosphate (pAp), mainly produced as a by-product of sulphur and lipid metabolic pathways (Mechold et al. 2007, 2006). As a consequence, overexpression of genes encoding pAp-phosphatases can rescue lithium toxicity both in yeast and bacteria (Mechold et al. 2006; Spiegelberg et al. 2005). This feature is a general property of this family of enzymes: human pAp-phosphatase (Yenush et al. 2000) is also highly sensitive to lithium. The number of pAp-regulated (hence indirectly lithium-sensitive) enzymes may expand as we discover more targets, such as poly(ADP-ribose) polymerase-1 [PARP-1 (Toledano et al. 2012)]. The activity of pAp-phosphatases appears to be promiscuous. Many of its members have dual function, behaving also as inositol phosphate monophosphatases (Faisal Tarique et al. 2014; Lopez-Coronado et al. 1999; Parthasarathy et al. 1994; Patel et al. 2002). This lithium-dependent activity is evidenced in a variety of organisms, such as lithium-sensitive phosphatases in chickpea (Saxena et al. 2013) or in *Caenorhabditis elegans* (Meisel and Kim 2016). Yet, the number of identified enzymes that recognize lithium specifically remains extremely limited. Another lithium-sensitive enzyme appears to be regulatory glycogen synthase kinase (Abousaab and Lang 2016).

This narrow range of activity asks for understanding the underlying reason of this lithium specificity. Three-dimensional analyses of proteins of interest show that this specificity originates in the very compact structure of the monovalent ion-binding site in the cognate enzymes (Erickson et al. 2015). This property, obviously picked up by natural selection, makes Li^+ an important component of a large number of living organisms despite its rarity. Another physico-chemical feature of ions explains the uniqueness of Li^+: the ionic radius of the other alkali metal ions increases with their mass in the order sodium (1.02–1.16 Å) < potassium (1.38–1.52 Å) < rubidium (1.52–1.66 Å) < caesium (1.67–1.81 Å) (Shannon 1976). This occurrence results in fewer restrictions on their hydration sphere, accounting for the lack of overlap with the properties of the lithium ion.

Sodium

A great many proteins are metalloproteins, and enzyme function is often strictly dependent on the presence of a metal ion. The role in catalysis of omnipresent divalent metals, such as Mg^{2+} (frequently found as a co-factor of nucleotides), Zn^{2+} (in many enzymes and regulators) or transition metal ions (in particular, Fe^{2+}, Mn^{2+} or Ni^{2+}, involved in redox reactions), is widely recognized. Transport, electroneutrality and maintenance of osmolarity aside, less frequently appreciated is the key contribution that monovalent cations such as Na^+ and essentially K^+ often play (Gohara and Di Cera 2016; Vasak and Schnabl 2016).

Analysis of various salt crystal structures revealed specific water coordination distances for Na^+ and K^+ of 2.42 Å and 2.84 Å, respectively (Auffinger et al. 2016). Sodium makes ionic bonds with water via dipolar interactions and, under dilute conditions, its first hydration sphere is organized as an octahedron (http://www1.lsbu.ac.uk/water/ion_hydration.html). In general, the presence of Na^+ weakens hydrogen bonds in water. Analysis of the ligands involved in monovalent ion binding to nucleic acids and proteins shows that besides charged residues (Schulz et al. 2013), they are often neutral [asparagine and glutamine in proteins, or the 2′-OH group of RNA (Francis 2013)]. However, because of the smaller ionic radius of this alkali metal, more energy is required to displace water from Na^+ than K^+ [see Table 2 in Tansel (2012)]. For historical reasons—because sodium is a major component of sea water and present as a main component of bathing fluids of multicellular organisms—most biochemical studies were developed in the presence of Na^+ and not K^+ (Auffinger et al. 2016; Chen et al. 2006; Gebala et al. 2019). This unfortunate tradition accounts for the difficulty we have today to identify structures or processes that strictly depend on either one of these ions. For example, it has only been clearly recognized recently that the widely studied β-galactosidase enzyme of *E. coli* indeed

prefers sodium over potassium—binding Na^+ about 10 times tighter than K^+. This preference means that under conditions that prevail in the actively metabolizing cell's cytoplasm, the ratio of Na^+ to K^+ bound to β-galactosidase would be close to 1:1 (Wheatley et al. 2015). This property has been completely overlooked. Yet, it should be known when biochemical or physiological studies involving the LacZ protein (extensively adopted as a reporter) are undertaken in minimal growth media. This limitation will be especially relevant in culture media formulations that omit sodium, such as the widely used M63 minimal medium (Klumpp et al. 2009; Miller 1972). Such occurrence is likely to be biologically significant. It fits with the idea that the enzyme is of recent descent and suggests that, for some reason, natural selection retained (or perhaps even favoured) this sodium specificity of the enzyme.

Commonly, the activity of enzymes secreted into the cell bathing fluids of multicellular organisms tends to prefer sodium over potassium. However, these enzymes make only a limited sample of those encoded in the genomes of living cells. Such Na^+-dependency implies that their physico-chemical properties are associated to functions that have been selected during evolution of the corresponding enzymes and are not primitive (Page and Di Cera 2006). A case in point is thrombin, a mammalian enzyme triggering blood clotting and localized in Na^+-rich extracellular environments. Fittingly, thrombin is activated by Na^+. By contrast, besides enzymes that are active outside the cell's cytoplasm, the number of enzymes that respond specifically to sodium appears to be as limited as in the case of lithium—a marked difference with those that are K^+-dependent, as we shall see. Nevertheless, for obvious reasons pertaining to the pressure of natural selection for keeping potassium as the critical counterion of the cytoplasm, sodium exporters have a considerable selectivity for sodium, allowing cells to maintain a high internal K^+ concentration coupled to a limited amount of Na^+ (Dibrova et al. 2015). Sodium-specific enzymes are usually inhibited in the presence of K^+, Rb^+ or NH_4^+.

Finally, the most important specific role of the sodium ion is perhaps in driving transport in a variety of systems, belonging to all three domains of life (Lu 2019; Markovich 2012; Patching 2018). As a case in point, Na^+ is essential for some C4 plant species, where it participates in the carbon cycle, chlorophyll synthesis and photosystem II activity, mainly via controlling pyruvate transport (Ohnishi et al. 1990). In these sodium-dependent symporters, the Na^+ gradient across the cell membranes is used as the driving force. The cation is later exported in an energy-dependent fashion. Similar features are observed in bacterial and in animal cells (Lu 2019). In particular, it appears that Na^+ is essential to substitute for the missing protons in driving membrane-associated cation-dependent functions (transport and ATP synthesis, for example) for bacteria that live in alkaline environments (Hicks et al. 2010). Many reviews dealt with these systems and we do not document them further here. Suffices it to note that where Na^+ is a key component of the cell's life, evolution has selected highly specific systems to interact with the ion, exactly as observed with the lithium ion.

Potassium

In general, when K^+ is used just as a negative charge-neutralizing counterion, its relevant properties are quite similar to those of other alkali metal ions, except for Li^+ (Auffinger et al. 2016; Shiman and Draper 2000; Tansel 2012). The details of these electrostatic interactions are still open to discussion because, perhaps surprisingly, the organization of water molecules around ions is a matter of much speculation. With its fairly large ionic radius, K^+ binds water extremely weakly, with a water exchange rate in its hydration shell of the order of 1 ns at 300 K (Table 1). For this reason, in contrast to kosmotropic (water-structuring) Li^+ and water-structuring neutral Na^+, K^+ is a chaotropic agent, favouring a fairly random organization of water molecules (Ball and Hallsworth 2015). The potassium and rubidium inner shell is made of six to eight water molecules and water is bound to the ion less strongly than in water–water interactions. Yet, there is evidence of some further water organization outside this shell, with water molecules organized in the form of clathrate hydrates, comprising 20 water molecules. Interestingly, in contrast to potassium, sodium stabilizes a continuum of clathrate hydrates with no privileged structure, suggesting that it plays a minimal role in the long-range structuring of water (Cooper et al. 2013). This may explain why it was selected to play the role of H^+ in alkaline environments. Furthermore, when it comes to displacing solvation water, the differences between Na^+ and K^+ are sometimes biologically significant. The activity of the K^+ transporter KcsA is a case in point. The increased energy required to desolvate water has been proposed to be the reason that the transporter shows high specificity for K^+ over Na^+ (Biggin et al. 2001). Another property that may favour K^+ over Na^+ is the greater ability of K^+ to maintain solubility of cell components in which carboxylate and phosphate are the principal anions (Collins 1997). Preferential involvement of potassium in biochemical processes may have evolved as the earliest simple biochemical system became more complex with the appearance of nucleic acid and ribosomal protein syntheses and phospholipid-containing membranes (Francis 2015). This may account for retaining K^+ in many water-driven biological processes. A further remarkable property of the K^+-water clathrates is that NH_4^+ stabilizes the same clathrate hydrate structure as does potassium (Chang et al. 2013). This observation is not trivial, as ammonium is a multiatomic compound able to

build up hydrogen bonds with water. This property would be expected to favour a privileged shape of its inner sphere of water interaction (Singh et al. 2017). Together with a number of almost identical physical properties, this common type of interaction with water molecules might be at the origin of the frequently recognized similarity in the behaviour of K^+ and NH_4^+ in biological reactions [references in Weiner and Verlander (2010)], a feature that has important consequences for the metabolism of nitrogen. Biological processes in which potassium is specifically involved are detailed in further sections of this article.

Rubidium and Caesium

Heavier alkali metal ions seldom participate in cellular processes, except as contaminants of K^+-related functions. The water structure making the inner and outer hydration shell of rubidium and caesium is similar to that of potassium. As counterions, these ions have a neutralizing activity quite similar to that of potassium and they are chaotropic as well. They display a biologically related role in transport systems. As a case in point, caesium inhibits plant growth by clogging the potassium transport system (Adams et al. 2019a). This effect is due, as we shall see below, to the fact that the main K^+ transport systems comprise an exquisite three-dimensional channel with remarkably tight structural requirements (Renart et al. 2017).

Finally, it is worth mentioning here that thallium, under the Tl^+ form, is a dangerous toxic mimic of K^+ (Gehring and Hammond 1967; Kashket 1979; Kemnic and Coleman 2019)—despite the fact that it is a heavy metal belonging to the boron and aluminium column of Mendeleiev's table, not the alkali metal column. This is yet another feature that shows that potassium might have original physico-chemical properties that favoured its selection by early cell metabolism (Douglas et al. 1990). Note that the potassium ionic radius reported in this paper (1.33 Å) is far too small when compared to the ionic radius of Tl^+ (1.44 Å); however, as discussed previously, the range of values now proposed for potassium is 1.38–1.52 Å. These figures imply that the argument for similarity between Tl^+ and K^+ is even more significant than assumed at the time.

Specific Biological Processes Involving Potassium

Most cells maintain a concentration of the potassium cation higher than 100 mM. This happens in environments where, frequently, the concentration of sodium is approximately of the same order or significantly higher (480 mM in sea water on average, as compared to 10 mM potassium). As a consequence, K^+ transport is a critical biological function, discussed here first. Subsequently, we explore a function which is tightly coupled to K^+ transport, detoxification of methylglyoxal and other dicarbonyls. Then we focus on the role of potassium in the translation machinery and turn to enzyme activities that are K^+-dependent. Finally, we explore other miscellaneous functions that appear to frequently require potassium.

Potassium Transport

As other metabolites, K^+ must be transported and then concentrated into cells, with specific transporters allowing the ion to climb up a concentration gradient while discriminating against Na^+. Emanuel Epstein proposed in 1973 that K^+ entered cells via two different, sequentially acting processes. A first process involves pumps promoting active transport, while the second process (which became evident only at K^+ concentrations higher than those giving essentially the maximal rate of absorption via active transport) uses channels that would close in an orderly fashion to prevent potassium leakage (Epstein 1973). This two-step process has been substantiated over the years, and it is still the dominant view of the way K^+ is imported and maintained at a high concentration within cells.

Without entering the arcanes of the biochemical processes involved, we briefly summarize the situation here. Potassium transporters have been studied in the three domains of life, with a particular emphasis in Eukarya on the plant family (Wang and Wu 2013), because of its importance in agriculture and also because management of osmolarity is critical for organisms that may reach a considerable size. Three major families of K^+ importers have been discovered: Trk/Ktr/HKT (Szollosi et al. 2016), Kup/HAK/KT (Sato et al. 2014) and Kdp (Greie and Altendorf 2007; Stock et al. 2018). Note, however, that the nomenclature has evolved over time (and is still evolving), making a thorough analysis of the literature somewhat awkward. Among those, two families, HKT (Zhang et al. 2017) and Kup (Adams et al. 2019b), are widely present in plants, which have developed sophisticated mechanisms for potassium acquisition. These transporters are energized by co-transport of protons or sodium ions (the latter are subsequently exported from the cell's cytoplasm, protons are dealt with in metabolic pathways).

Studies investigating the regulation of K^+ transporters have been much developed in Bacteria. For example, it has been established that the genes encoding the Trk/Ktr and Kup transporters are constitutively expressed in *E. coli*, with the uptake rate of Ktr system being 10 times higher than that afforded by the Kup transporter (Rhoads et al. 1976). By contrast, the KdpFABC ATPase is an inducible system, exhibiting high affinity and selectivity for K^+ uptake. This Kdp transporter system is a model of a most widespread

family of highly selective K^+ transporters. Kdp couples ATP hydrolysis to transport in a way that is reminiscent of information-manipulating agents that can use energy to discriminate efficiently between highly similar substrates (such as K^+ ions in a Na^+-rich context). In this process, the energy of one ATP molecule is used to allow the ion to climb up the concentration gradient, while a second, apparently expletive one, uses Landauer's principle (Landauer 1961) to guarantee the selectivity of the information linked to the nature of the substrate (Boel et al. 2019). This system becomes operational under low K^+ concentrations [approximately 2 µM, as estimated from the K_m value of the ion binding to the transporter (Epstein 2016)] when other K^+ uptake systems such as Trk and Kup are inactive (Altendorf et al. 1992). This system is specific to prokaryotes (Diskowski et al. 2015) and may be of relatively recent origin.

A variety of other systems exist in different bacterial clades and in Archaea. For example, *Bacillus subtilis* has two ATP-driven transporters (KtrAB and KtrCD) that differ from those of *E. coli* (Gundlach et al. 2017; Rocha et al. 2019). Potassium homoeostasis in these bacteria is maintained by a third system (KimA) that binds the regulatory molecule cyclic-di-AMP. This regulatory molecule interacts with both potassium transporters and riboswitch molecules in the mRNA leaders encoding the K^+ transporters that are functionally associated to glutamate transport. This complex transport control has been thoroughly discussed previously [see Stülke and coworkers for further insight (Gundlach et al. 2019)] and is not further discussed here as it is unlikely to reveal a highly specific physico-chemical feature of K^+ as compared to other alkali metal ions. Potassium transport against a concentration gradient requires energy dissipation in a variety of ways (in particular involving the electrochemical potential, as outlined below). When possible, a noteworthy energy supply is that provided by photons. This situation is witnessed in light-activated ion-pumping systems that collect light, for example using rhodopsin variants (Pinhassi et al. 2016). We simply emphasize here that the multiplicity of potassium transporters and regulators is consistent with an involvement of the ion since the origin of the first cells.

Subsequently, following active pumping, ion-specific channels also transport potassium (Capera et al. 2019)—but they are unable to permit the ion to climb up a steep concentration gradient. The situation is best illustrated in plants, because their roots face extremely variable environmental conditions in terms of water and, in particular, salt content. There, beside active transporters, a large number of channels maintain the concentration of the cation in the various compartments of the plant cell. As a case in point, the KcsA voltage-gated channel family is present in most—if not all—plants (Blasic et al. 2015; Posson et al. 2013; Renart et al. 2017), but also in animals (Delemotte 2018) and Bacteria [with an interesting role of polyphosphates as a modulator of activity (Negoda et al. 2009)]. We have discussed previously the physico-chemical role of metal solvation as a possible cause of its preference for the K^+ ion. The role of channels is contributing to transport against an opposite concentration gradient, acting as « passive » transporters and maintaining a steady concentration of the ion, working when the K^+ concentration is relatively high [in the mM range (Locascio et al. 2019)]. Specificity of the KcsA transporter aside, not much at this point can tell us whether K^+ has been retained because it was present at the early time when protocells evolved into living organisms, or whether it displays a function that can hardly be substituted for by other ions (in particular, by Na^+).

Potassium Sensing

Extant cells must scavenge potassium from a variety of environments, where the ion is often present in a fairly limited amount. Hence, besides requiring the acquisition of efficient K^+ importers and Na^+ exporters, the cells needed to be able to sense their environment while being able to distinguish between the two cations, based on small differences in their physico-chemical properties and especially in their ionic radii. In Bacteria, two-component signal transduction systems (TCSs) constitute the predominant strategy used to sense signals and adapt to fluctuating environments (Ali et al. 2017; Schramke et al. 2017). The KdpD/KdpE system, crucial for K^+ homoeostasis, is one of the most widespread TCS. In *E. coli*, the KdpD histidine kinase senses K^+ availability, and signals it to the response regulator KdpE that has several potassium-related targets. A low concentration of K^+ triggers the expression of the genes encoding the high-affinity K^+ uptake system KdpFABC. Kdp, one of three saturable K^+ uptake systems in *E. coli,* is the system with the highest affinity for K^+ and the only one whose expression is strongly controlled by the K^+ concentration in the medium. In addition, the KdpD sensor is versatile, and it responds to a great many signals such as low K^+ concentration, but also to the pH of the medium (Epstein 2016). Interestingly, this system is exquisitely sensitive to the ATP intracellular availability (Hamann et al. 2008).

In line with this relationship between control and expression, the *kdpFABC* operon is often found adjacent to *kdpDE* in the bacterial chromosome. KdpD/KdpE is also critical for virulence of pathogenic species (Yang et al. 2018). KdpD senses at least two distinct signals inside the cell (Na^+ and NH_4^+) and probably detects other monovalent cations as well. KdpD has an autokinase activity and KdpE-directed phosphotransferase and phosphatase activities. Inhibition of KdpD phosphatase leads to an accumulation of phospho-KdpE and to the activation of *kdpFABC* transcription. KdpD phosphatase activity directed at KdpE was initially suggested to be inhibited by turgor pressure, but

this hypothesis has been since refuted (Epstein 2016). Since high K^+ concentration lowers the amount of phospho-KdpE, it also downregulates the KdpD autophosphorylation activity, resulting in less phosphotransfer to KdpE. Finally, a salt shock increases ATP concentrations and probably stimulates KdpD phosphatase activity since a deletion of the ATP-binding site of KdpD deregulates its phosphatase activity. This trait may be yet another way to implement the information-gathering, energy-dependent process that follows Landauer's principle (Boel et al. 2019; Landauer 1961)—here meant to discriminate K^+ against other competing ions, a feature that may be taken as an indication of sufficient K^+ specificity to have retained it instead of Na^+ via natural selection.

Because of the essentiality of potassium, the requirement of specific mechanisms for sensing its presence is not restricted to bacteria. It is an omnipresent function solved in a variety of ways by gathering relevant structures and processes in all domains of life. For example, animals have evolved sophisticated ways to control K^+ homoeostasis under conditions where the serum K^+ concentration does not vary, using a complex hormone cascade (Oh et al. 2013). In plants, which are extremely sensitive to nitrogen availability, K^+ sensing is also related to NH_4^+ sensing (Ho and Tsay 2010). This is yet another indication of an overlap between K^+ and NH_4^+ that must have had important consequences in the progresses mediated by the evolution of life. This also fits with yet another role of KdpD in bacteria, which interacts with PtsN in a nitrogen-sensing process (Mork-Morkenstein et al. 2017). To be sure, among the important—and puzzling—signals that affect KdpD, the dephosphorylated $EIIA^{Ntr}$ protein PtsN of the phosphoenolpyruvate-dependent phosphotransferase system (PTS) binds to (and stimulates) sensor kinase KdpD activity, increasing the levels of the cognate phospho-KdpE regulator (Deuschle et al. 2015). PtsN binds specifically to the catalytic DHp domain of KdpD, which is also contacted by KdpE, apparently competing for binding. However, PtsN and KdpE bind different protomers in the KdpD dimer. In particular, PtsN binds one protomer to stimulate phosphorylation of the second KdpD protomer, which then phosphorylates bound KdpE. Phosphorylation of PtsN prevents its incorporation in ternary complexes. Interaction with the conserved DHp domain enables PtsN to regulate additional kinases such as PhoR, thus coupling potassium, ammonium and phosphate metabolism (Luttmann et al. 2012).

Maintaining the Transmembrane Electrochemical Potential and Osmotic Pressure

Life is sustained in cells via the selective role of membranes that maintain a significant electrochemical potential to import essential metabolites, export waste and generate energy. Cells are negatively charged inside, with a potential generally in the order of −50 to −70 mV. Considering the average size of the lipid bilayer, this situation translates into a considerable electric field between the inside and the outside of the cell, in the order of 100,000 V/cm. This potential is maintained by a combination of cation diffusion across membranes mediated by differences in concentration inside and outside the cell, together with the presence of electrically charged molecules (such as nucleic acids) in different compartments of the cell. K^+ ions are mainly intracellular, while Na^+ ions generally dominate in extracellular environments. Here, the role of the potassium ion is ubiquitous and crucial, whereas outside ions, although being important, are variable in their chemical nature—depending on the organism and its environment (Roux 2017). While this physical feature is a key component of the cell's life, it seems obvious that maintaining a relevant electrochemical potential is a physical property that does not draw on the specific chemistry of the potassium cation, but on the relative concentration of the various ions within and outside cells, with a key role of protons in the generation of energy and transport (Papa et al. 2018). For this reason, we just outline some of the roles of K^+ in this process (and in maintaining osmolarity) without getting into fine details [see for example Roux (2017) for further insight].

A first constraint is the maintenance of a proper Na^+/K^+ balance, a phenomenon well illustrated in plants. Plants do not usually thrive in the presence of a high sodium concentration. By contrast, animal cells are usually in contact with a sodium-rich environment, either as a body fluid or as sea water. This explains the omnipresence of a potassium transport process performed by Na^+/K^+ ATPases, belonging to families that are generally missing in bacterial cells (Gumz et al. 2015). These transporters have a considerable role in maintaining the electric potential of the cell not only for general electrochemical processes, but more specifically for ruling the behaviour of nerve cells via generation of action potentials (Pivovarov et al. 2018).

Besides active transport, gating, as a function of the physical and chemical status of the cell required to maintain a correct electrochemical potential, is essential. This homoeostatic process is achieved by channels, as discussed previously, but in an electric field-dependent manner. Hence, maintenance channels are often voltage-gated channels. They are found in Bacteria (Morgan et al. 2019), Archaea (Randich et al. 2014), mitochondria (Laskowski et al. 2016) and, naturally, neurons and muscle cells (Brown et al. 2019) among other cell types. Coupling with other important cell processes is achieved by a variety of regulatory processes such as allostery in heme-activated potassium channels (Negrerie 2019). Finally, the omnipresence of K^+ in cells has created an opportunity for predation or killing by organisms that could synthesize membrane permeable compounds—a situation that would allow for

potassium leakage. Streptomycetes, bacteria that thrive in complex microbiomes, have thus invented the non-ribosomal cyclododecadepsipeptide valinomycin, a highly specific K^+ ionophore (Varma et al. 2008). Non-ribosomal peptide synthesis is likely to have predated translation in prebiotic conditions (Caetano-Anolles et al. 2012; Danchin 1989, 2017b; Jakubowski 2017; Lipmann 1971) and the fact that such highly selective ionophores exist illustrates how potassium, very early on, might have been retained in cell processes.

In addition to maintaining its electrochemical potential, control of osmolarity is yet another key physical parameter essential to prevent the cell from bursting when the environment changes. The transmembrane movement of cations is a simple way to maintain homoeostasis. However, they are positively charged species, so that countertransport or transport of negative counterions is required in parallel. This constraint accounts for the observation that potassium and glutamate are the most abundant ions—remembering that for almost every feature of life there is an exception—in most if not all living cells (Muller et al. 2015). In bacteria, accumulation of this chemical duo has a widespread role in controlling osmolarity in parallel with the maintenance of the electrochemical potential (Gundlach et al. 2018). Note, again, that the ubiquitous osmolarity control function, while depending on K^+ in extant cells, could have easily been fulfilled by other ions as well. Furthermore, osmolarity is independent of the electric charge of the metabolites involved [it is indeed maintained by a variety of uncharged metabolites, such as the disaccharide trehalose (Hagemann 2011)] and therefore cannot be taken as a specific driving force for K^+ selection and maintenance. Interestingly, it has been observed that, while sodium glutamate would have had the same potential to control osmolarity, potassium glutamate has sometimes a general role that cannot be fulfilled by the sodium counterpart in extant cells, such as stabilization of the SecA ATPase required for protein secretion out of the cytoplasm (Roussel et al. 2019). Finally, as hinted in previous sections, this observation introduces an important caveat as most biochemical studies are still performed using sodium chloride and a surprising variety of biologically irrelevant salt conditions [see e.g. Lartigue et al. (2007) and Lin and Carey (2012)]—where potassium glutamate might have revealed unexpected properties.

The Methylglyoxal (MGO) Detoxification Cycle

The ubiquity of potassium in living cells is consistent with its presence very early on in the history of life. This makes of interest to explore whether K^+ is involved in highly specific pathways that, if not ubiquitous, are at least extremely widespread. Metabolic routes involving α,β–dicarbonyls are cases in point. These omnipresent metabolites are highly reactive and thus result in a variety of metabolic accidents (Danchin 2017a; Linster et al. 2013; Sun et al. 2017). Methylglyoxal (MGO) is one such α,β–dicarbonyl compound that appears to be a ubiquitous product of cellular metabolism despite its apparent toxicity. MGO is present in all cells, from Bacteria to higher eukaryotes, either under normal or pathological conditions. Both enzymatic and non-enzymatic routes are known to result in MGO formation. A considerable fraction of MGO is produced as a by-product of protein and fatty acid metabolism, but a major source of endogenous MGO formation is glycolysis (or the Calvin–Benson cycle in plants) via C3 metabolic intermediates. In particular, MGO is mostly formed through the fragmentation of glyceraldehyde-3-*P* (GA3P) and dihydroxyacetone-*P* (DHAP). Triose phosphates are unstable metabolites and show a high tendency to release an α-carbonyl proton, producing an enediolate-*P* intermediate that has a relatively low energy barrier for the elimination of phosphate groups. MGO may also be formed by Amadori rearrangement during production of a Schiff base, which involves the reaction of the aldehyde groups of sugars with free amino acids or the amino acids of proteins (Vistoli et al. 2013). The rate of MGO formation and accumulation depends on the organism, tissue, cell metabolism and physiological condition, and can vary widely across species. One way or the other, it is now clear that MGO is far more widely spread in cell metabolism than previously thought, MGO synthase being a very common enzyme. Yet, its role remains enigmatic (Dickmanns et al. 2018; Shin et al. 2017).

Given the highly reactive nature of MGO, its half-life in a biological environment is short and, at the time and site of production, local MGO concentrations have been estimated to be fairly large (in the range of the upper µM to low mM concentrations). Furthermore, and as just stated, a great many cells possess a specific MGO synthase (that makes MGO directly from DHAP), which implies that this must be an important reaction despite the MGO intrinsic toxicity. In order to avoid these toxic effects, cells possess different detoxifying mechanisms such as the glyoxalase, aldose reductase, aldehyde dehydrogenase and carbonyl reductase pathways. The glyoxalase system consists of two enzymes, glyoxalase I (Glo-1 or GlxI) and glyoxalase II (Glo-2 or GlxII), and can be found in the cytosol and organelles like mitochondria and ubiquitously distributed in all forms of life (Allaman et al. 2015). This pathway produces D-lactate, a metabolite which is much less abundant than the standard L-lactate end product of glycolysis. Many bacteria and certain yeasts possess the enzyme D-lactate dehydrogenase, which converts D-lactate into pyruvate (end product of glycolysis), thereby making the MGO bypass an alternative to glycolysis under certain physiological conditions. The glyoxylase system detoxifies MGO using reduced glutathione (GSH) as the co-factor for direct inactivation of the highly reactive aldehyde. Glo-1 converts the

hemithioacetal formed by the non-enzymatic reaction of GSH with MGO, to *S*-D-lactoylglutathione (Fig. 2). This compound is then converted to D-lactate [often metabolized by non-standard dehydrogenases (Jiang et al. 2017; Welchen et al. 2016), but this considerably depends on the organism (Jia et al. 2018), in contrast to L-lactate, which is rapidly processed by a large variety of dehydrogenases] by Glo-2, recycling GSH in the process. In general, despite its critical role, the origin and fate of D-lactate and L-lactate—quite variable in different organisms—is still under much exploration [see for example the discussion in Goncalves et al. (2019)]. To be sure, the MGO detoxifying pathway in trypanosomes and *Leishmania* uses a specific thiol carrier, and yields L-lactate, not D-lactate (Wyllie and Fairlamb 2011).

Remarkably, this process is consistently tied up to K^+ metabolism, as recognized in Bacteria (Ferguson et al. 1993), fungi (Barreto et al. 2012), plants (Hoque et al. 2016, 2012) and animals (Wang et al. 2019; Yang et al. 2012). In *E. coli*, detoxification of MGO is carried out by the products of the unlinked *gloA* and *gloB* genes, through their integration with the GSH adduct-gated KefGB K^+ export systems (Ozyamak et al. 2010). KefGB and KefFC are structurally related K^+ efflux systems, the activity of which is prevented by the binding of GSH (activation is triggered by binding of specific GSH adducts). Activation

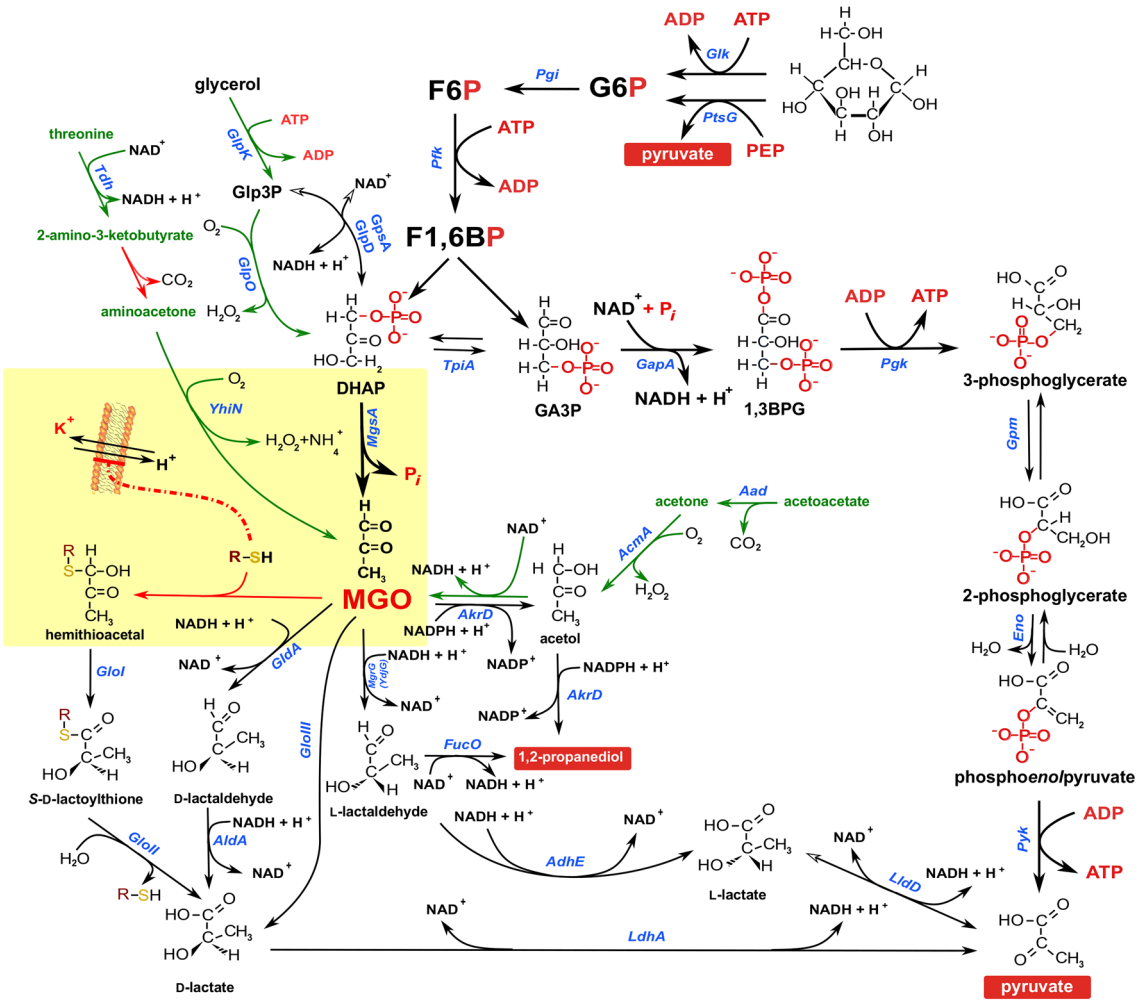

Fig. 2 Methylglyoxal metabolism. Synthesis of methylglyoxal (MGO) is an inevitable consequence of the activity of enzymes in the glycolytic pathways. Green arrows display examples of other sources of MGO, essentially derived from oxygen-related metabolism. Note that many other reactions, not displayed in the figure, also end up producing MGO. Red arrows correspond to spontaneous reactions (such reactions are however usually taken up by specific enzymes, unknown at this time). Glutathione and related compounds (R–SH) control efflux of potassium and influx of protons in relevant cell compartments. Spontaneous reaction of these thiols with MGO are expected to alleviate inhibition of potassium transport, and result in influx of protons that act against spontaneous reactions of MGO with amines, thiols and related chemical groups, thereby protecting against its toxicity. The abbreviations used for the metabolites in the figure are as follows: G6P, glucose-6-phosphate; F6P, fructose-6-*P*; F1,6BP, fructose-1,6-bisphosphate; DHAP, dihydroxyacetone-*P*; GA3P, glyceraldehyde-3-*P*; 1,3BPG, 1,3-bisphosphoglycerate; Glp3P, glycerol-3-*P*; and PEP, phosphoenolpyruvate

of the systems leads to rapid K^+ efflux, which is in turn quantitatively affected by several parameters: the external K^+ concentration, the activity of K^+ uptake systems, the expression level of *kefGB* and *kefFC* and the intracellular concentration of the GSH adduct effector. The K^+ efflux is accompanied by influx of H^+ (or Na^+), and the availability of protons in the cytoplasm due to rapid H^+ influx critically affects protection against MGO, via a mechanism the details of which are still poorly understood (Ferguson et al. 1998) but points out a critical role of the flux of protons for the control of cell activity. In particular, increasing the cytoplasmic proton availability may slow the reaction of MGO with guanine residues in the DNA as well as with other macromolecules (Krymkiewicz 1973).

A similar process is present in many bacteria of different clades, where glutathione is replaced by other thiol-containing effectors/substrates such as bacillithiol in *B. subtilis* and other Firmicutes (Chandrangsu et al. 2018), or mycothiol in Mycobacteria (Liu et al. 2014). Likewise, GSH is substituted by trypanothione (Wyllie and Fairlamb 2011) in Protozoa. Once more, we note that the role of potassium in these homeostatic processes is linked to co-transport of protons, which have the key role in cell metabolism—and not to the intrinsic nature of the cation. Thus, despite its omnipresence, this mechanism cannot be seen as a driving force for the specific picking up of potassium in living cells.

In plants, MGO acts as a biochemical marker of abiotic stress (Hoque et al. 2016). This carbonyl aldehyde is known to modulate plant stress responses by regulating stomatal opening and closure, formation of ROS, cytosolic Ca^{2+} concentration, activation of inward-rectifying K^+ channels and the expression of stress-responsive genes. In particular, the uptake of K^+ into guard cells accompanies light-induced stomatal opening, and inward-rectifying K^+ (Kin) channels play important roles in regulating K^+ uptake. The KAT1 K^+ transporter of *Arabidopsis thaliana* is present in stomatal guard cells, and plants with a dominant negative mutation in the corresponding gene show a significant reduction of Kin channel currents, which results in a limited ability in regulating K^+ ion flow and suppression of light-induced stomatal opening (Kwak et al. 2001). It has also been demonstrated that MGO interferes with light-induced stomatal opening in *Arabidopsis* in a concentration-dependent manner, and that this interference involves inhibition of Kin channel currents in guard cells, partially due to suppression of KAT1 channel activity (Hoque et al. 2012). Finally, MGO has been recently found to be a direct inhibitor of the Na^+/K^+ ATPase via a direct chemical interaction of the aldehyde with amino acids residues in the pump, resulting in the formation of N^{ε}-(carboxymethyl)lysine (Svrckova et al. 2017). Again, the role of the potassium ion in this process appears to be linked to its ubiquitous presence in cells, not to its specific physicochemical properties.

Yet, a specific attribute of potassium might play a role in MGO detoxification, namely its kinship with ammonium (as documented later on). To be sure, a variety of hypotheses have been proposed to account for the ubiquitous presence of MGO in cells. Among those, an imbalance between carbon and nitrogen metabolism—in particular, an excess of ammonium availability—results in an increase in glycolytic activities (hence, an increase in toxic phosphorylated three-carbon metabolites) coupled to an interference with K^+ import and export, mediated by a variety of properties that are common to K^+ and NH_4^+. For example, potassium deprivation in *Saccharomyces cerevisiae* has a considerable impact on gene expression, leading, in particular, to a toxic influx of ammonium through the Trk1 transporter (Barreto et al. 2012). Remarkably, K^+ depletion in this organism was coupled to a role in translation, another important potassium-related feature that we now explore before investigating its relationship with nitrogen metabolism.

Potassium in the Structure and Function of RNA-Based Processes

Splicing

Ribozymes are proposed to have played a critical role during the RNA-metabolism stage that preceded the RNA-genome stage of the RNA world [see discussion in Danchin (2017b)], catalysing splicing and peptide synthesis. Understanding the role of potassium in splicing is therefore particularly relevant. Binding of potassium ions to RNA has been observed since the beginning of the study of nucleic acids, with specific K^+ binding sites observed in group I introns. Generally speaking, the rate of intron splicing was increased by a high concentration of monovalent cations. The splicing rate in a K^+-containing solution was faster than with NH_4^+, than with Na^+, and finally faster than with Li^+ (Partono and Lewin 1991). We note again a proximity of NH_4^+ to K^+ that is more significant in the splicing process than Na^+ is. More precisely, metal binding to the group I intron P5b loop, in particular at the GG·UU metal binding site, displayed specific binding for $Co(NH_3)_6^{3+}$ (hexaamminecobalt acting as an analogue of Ca^{2+}) or K^+, but not for Zn^{2+}, Cd^{2+} or Mg^{2+} (Fan et al. 2005; Stahley et al. 2007).

This role of K^+ extends to other introns as well. Group II introns are ribozymes that can catalyse their own splicing out of the molecule in which they are inserted, religating the intron into a lariat form. They share common structural features and are evolutionarily related to the eukaryotic « spliceosome » [or koptosome (Iliopoulos et al. 2019)] RNA components (Smathers and Robart 2019). Hence, group II introns are excellent model systems for understanding the mechanism of RNA splicing in gene expression. Again, K^+ binding displays specificity in the group II intron

self-splicing pathways. Recent advancement of structural studies has provided X-ray structures at different stages (pre-hydrolytic, post-hydrolytic and free intron) of the splicing pathway, revealing the presence of heteronuclear metal ion clusters (two potassium ions and two magnesium ions) in the active site as a common structural feature. It is believed that these four metal ions are critical for catalysis. K^+ is especially important for the function, as buffers containing only Na^+ will inactivate the splicing function of group II introns (Kumar and Satpati 2018).

The Ribosome, Translation and Protein Folding

The ribosome, the largest RNA-containing macromolecular nanomachine in the cell, requires metal ions not only to maintain its three-dimensional fold but also to perform protein synthesis. Despite the vast biochemical data regarding the importance of metal ions for efficient protein synthesis and the increasing number of ribosome structures solved by X-ray crystallography or cryo-electron microscopy, the assignment of metal ions location within the ribosome remains elusive, mostly because of methodological limitations (Rozov et al. 2019). Yet, K^+ certainly binds ribosomal RNA at specific positions, as demonstrated, for example, with 5S ribosomal RNA (Auffinger et al. 2004). Furthermore, K^+ ions play a key role in the architecture of the essential functional regions of the ribosome and, in particular, in its decoding centre. Two potassium ions serve as coordinators of important conformational rearrangements in the decoding centre upon binding of loaded tRNA. This role took some time to be identified because both these ion-binding sites were previously assigned to magnesium binding. A general discussion of the role of potassium, in particular suggesting a likely preference of K^+ over Na^+, can be found in Rozov et al. (2019).

The K^+ ion is further involved in critical functions related to the translation process (Danchin and Fang 2016; Fritz et al. 2018; Voigt et al. 1974). This pivotal process requires a variety of GTPases that are used both for mechanochemical polypeptide synthesis and management of accurate information transfers during the mRNA decoding process (Perez-Arellano et al. 2013). This involvement also holds for the very construction of the translation machinery, in particular the synthesis of ribosomes and active tRNAs. As a case in point, a remarkable K^+-dependent GTP-hydrolysis mechanism is exerted by MnmE, an enzyme required for 5-methylaminomethyl-2-thiouridine (tetrahydrofolate-dependent) modification of certain tRNA molecules at anticodon position U34, as well as other GTPases of related structure.

MnmE is a homodimeric multi-domain GTPase required for tRNA modification. In this system, the GTPase activity rests on K^+-dependent homodimerization of its G domains (Fislage et al. 2016). The cation plays a role analogous to that of the « arginine finger » of the Ras-RasGAP system, and accelerates the otherwise slow GTP-hydrolysis rate (Rafay et al. 2012). In this and related proteins, two conserved asparagine residues and a « K-loop » control K^+-mediated GTPase activity (Prado et al. 2013). A remarkable feature of the MnmE enzyme is that, while it belongs to a very large class of enzymes [the so-called P-loop NTPases (Verstraeten et al. 2011), that make up to some 18% of all proteins], a critical peptide is absent and its role is substituted, in a decisive way, by K^+ (Shalaeva et al. 2018). Other GTPases, such as Era in *E. coli* (Razi et al. 2019) or Nug1 in Eukarya (Manikas et al. 2016), exhibit a similar K^+-mediated activation of GTP hydrolysis. This is also the case of the ribosome assembly bacterial ribosome biogenesis protein RbgA that functions to properly position protein L6 on the ribosome, prior to the incorporation of protein L16 and other late assembly proteins (Corrigan et al. 2016). In *B. subtilis*, GTPase RgpH(YqeH) and ribosome-binding ATP/GTPase EngD(YchF) [present in Eukarya as well (Tomar et al. 2011)] utilize a similar mechanism, in association with ribosomal protein S5, to proceed in ribosomal 30S subunit assembly. While the catalytic machinery is similar in both, mechanistic differences arise depending on the way they are set out. In summary, it appears that a K^+-driven mechanism was used to stabilize the transition state and hydrolyze GTP in a subset of GTPases, such as the HAS-GTPases (Anand et al. 2010), possibly replaced by the more versatile role of a peptide loop in non-K^+-dependent enzymes. Another important feature of this requirement in several potassium-dependent GTPases acting in translation is that, in general, NH_4^+ can replace K^+ (Kuhle and Ficner 2014), yet another feature that links potassium to nitrogen metabolism (see below).

Molecular Chaperones

Polypeptide synthesis during translation does not consistently lead to a properly folded protein. Adequate protein folding further asks for the action of a family of proteins with activities collectively known as molecular chaperones. NTP-dependent chaperones illustrate a critical feature of living cells, which channels information into a meaningful process or structure: a proper functioning requires identification of a specific conformation among a large number of possible ones. Living cells require that, for each new bit of information created, a quantum of energy is dissipated. Typical examples of creation of information are discrimination of a class of objects—proper folding is a case in point—among similar ones, identification of a space position, and identification of a precise timing, among other processes. This input of information implies that the agent (here, a molecular chaperone) performs the sequence of actions required by Landauer's principle: (i) setting a reversible link between

information and a source of energy (typically, at this stage, non-hydrolyzable NTP analogues can replace NTPs) and (ii) once information is used (the protein is properly folded), energy is dissipated (the NTP is hydrolyzed) to reset the agent to its ground state (Landauer 1961). Embodiment of such an informational (abstract) process at 300 K in a world where objects have a mass has to compete with thermal noise. It becomes therefore essential to associate any gain of information to a significant signal-to-noise ratio. This is where phosphate bonds (with their metastability in water) come into play, allowing material systems to associate hydrolysis of one phosphate bond to gain one bit of information, while coupling information gain to mechanical movements [see discussion in Boel et al. (2019)].

Many molecular chaperones require K^+—again—for this critical function. As an example, the GroEL chaperonin in complex with GroES is a tetradecameric protein composed of two stacked heptamers with a large central cavity. Its activity is stimulated by Mg^{2+} and possibly other divalent metals such as Mn^{2+}, and it has an absolute requirement for K^+ (Gruber and Horovitz 2016). NH_4^+ and Rb^+ can partially substitute for K^+, but Li^+, Na^+ or Cs^+ are inactive. The crystal structure of GroEL bound to ATP revealed that Mg^{2+} and K^+ act together to assist binding of ATP to the protein (Viitanen et al. 1990). In the same way, two K^+ ions associate to a Mg^{2+} ion to allow catalysis mediated by the molecular chaperone Hsc70 (Wilbanks and McKay 1995). This chaperone, which again requires ATP hydrolysis for activity, is another member of the heat shock family of proteins involved in the folding/refolding of polypeptides. As with GroEL, the ATPase activity of Hsc70 requires the presence of K^+, which cannot be substituted by Na^+. Analysis of the crystal structures of a fragment of Hsc70 allowed investigators to decipher how its activity proceeds (Flaherty et al. 1990). The phosphate moiety of ADP in the active binding site has a distorted position when K^+ is replaced by Na^+ (Gohara and Di Cera 2016).

Yet, the role of potassium in NTP-dependent informational NTPases is not universal. As cases in point, EngB or HflX, which also behave as Maxwell's demons (Danchin and Fang 2016), do not depend on this ion for activity. However, the very fact that potassium has been selected to improve the activity of core functions of the cell, possibly replacing a polypeptide loop in a large family of enzymes (Shalaeva et al. 2018), has been taken as a strong argument to propose that the ion was present during the very first steps of the development of life (Dibrova et al. 2015; Mulkidjanian et al. 2012).

Miscellaneous Activities Linked to Potassium

With features highly reminiscent of those of the GTPases explained above, the ferrous transporter FeoB, present in Archaea and Bacteria, is also endowed with a GTPase domain displaying a structure similar to that of those discussed previously (Hagelueken et al. 2016; Shin et al. 2019). Here, GTP hydrolysis appears to be connected to the discriminative sensing of the Fe^{2+} ion under conditions where many competing divalent ions are present. Again, this GTPase activity depends on the presence of potassium (Ash et al. 2011). The relevant domain of the protein is thus likely to be discovered in a variety of information requiring functions other that the process of translation (Rafay et al. 2012).

Over the years, the activity of quite a few enzymes has been found to depend on the specific presence of the potassium cations (Gohara and Di Cera 2016; Page and Di Cera 2006). Among those, we find (non limitative list), aldehyde dehydrogenase (Garza-Ramos et al. 2013) and pyruvate kinase (Nowak and Suelter 1981)—key enzymes involved in carbon metabolism. K^+ is essential in the activation of pyruvate kinase, but the strong preference of K^+ over Na^+ as an activator remains puzzling because the Na^+-bound structure does not display significant changes in the architecture of the active site (Gohara and Di Cera 2016). This occurrence could be due to a water-related entropy contribution (see our previous discussion of the comparative properties of Na^+ and K^+). Another example of potassium dependency discussed by Gohara and Di Cera (2016) is pyridoxal kinase, a member of the ribokinase superfamily involved in the ATP-dependent phosphorylation of pyridoxal to provide pyridoxal-5′-*P*. This enzyme requires K^+ and Zn^{2+} as absolute cofactors, and K^+ stabilizes the enzyme–substrate complex through interactions with a negatively charged phosphate moiety.

Finally, potassium has been occasionally described as a second messenger, used to monitor stress or carbon/nitrogen imbalance conditions (Lee et al. 2007; Shabala 2017). Again, this potential regulatory property of K^+ does not appear to be linked to an original feature of the potassium ion physico-chemical properties, its similarity to NH_4^+ aside, as now discussed.

Potassium and Nitrogen Metabolism

The coupling between nitrogen and carbon metabolism has been explored for a long time, and a variety of high-level control systems were found to play a key role in the process [see for a recent study (Li et al. 2019)]. As previously discussed, it was not unexpected that a key element of carbon transport, the PTS system, was involved in this control via the phosphoenolpyruvate-dependent phosphorylation of a regulatory protein [$EIIA^{Ntr}$, PtsN (Cases et al. 2001, 1999; Powell et al. 1995)]. As a case in point, PtsN was shown to be involved in the control of potassium transport in *E. coli* via regulation of TrkA (Lee et al. 2007). This observation matches yet another interference of potassium with nitrogen

metabolism. We stressed that the ammonium ion has properties extremely close to those of K^+, precluding, for instance, discrimination against potassium when ammonium is abundant. Hence, K^+ will interfere directly with metabolic pathways that consume or produce NH_4^+ (Deuschle et al. 2015; Deutscher et al. 2014; Lee et al. 2015; Luttmann et al. 2015; Muriel-Millan et al. 2017; Wolf et al. 2015).

A further interaction with nitrogen metabolism comes from an interference of potassium with the metabolism of polyamines. A general role of monovalent ions, as stated previously, is to maintain interactions with nucleic acids to counteract their inherent negative electric charge (Auffinger et al. 2016). These ions act in competition with the much more selective positively charged polyamines (Iacomino et al. 2012; Lightfoot and Hall 2014). For organisms that live at very high temperature, the role of specific polyamines is particularly important to maintain proper nucleic acids structure, as reflected by their role in translation (Dever and Ivanov 2018) or in viral infection (Mounce et al. 2017). Polyamines are linked to nitrogen availability and this requirement will create a functional coupling between polyamines and potassium.

Conclusion and Perspectives

With all the information collected in the works described here, the question raised by the ubiquitous presence of potassium in living organisms remains largely open. A popular scenario proposed that the origin of life is associated to hydrothermal vents. Yet they are bathed by ocean water, where K^+ concentration was (and still is) lower than Na^+ concentration. This view has been replaced in recent times by scenarios where life started in pools/lagoons on emerged continents around volcanoes where a variety of ionic conditions prevail, depending on the location (Deamer 2017; Natochin et al. 2012). If life had started in the bulk of ocean water, there would need to have been a process concentrating chemicals for reactions to occur because the organic molecules therein would have been too dilute. One possible way to concentrate organic molecules could have been to freeze most of the oceans [see Bada et al. (1994) and Levy et al. (2000)]. This scenario would lead to high concentrations of salts, with Na^+ likely dominating, implying that the specificity of K^+ in biological processes would have led to its selective enrichment within cells in the course of early evolution. A few authors have argued that this would be insufficient to explain its omnipresence, suggesting that it remains as an archive of the historical past of life (Dibrova et al. 2015; Mulkidjanian et al. 2012). Thus, in contrast with the involvement of phosphorus, which is certainly linked to the particular chemical properties of phosphates (Westheimer 1987), K^+—despite its variety of important physico-chemical traits—may not display enough unique properties that warrant its involvement in biological processes.

Besides the chirality of proteinogenic amino acids, which is likely to have been selected by chance, the involvement of potassium could result from the place where prebiotic chemistry developed into a living metabolism. This contention has the important consequence that it would assume that life emerged in terrestrial aquatic environments that were well stocked in potassium-rich minerals (Deamer 2017; Natochin et al. 2012). As expected, this view should face considerable challenge (Maurer 2017). Various alternatives have been proposed, often discussed in the context of possible life on planet Mars (Cavalazzi et al. 2019). In particular, it has been suggested that surface hydrothermal vents provide a natural bridge between a continental scenario for prebiotic chemistry and the probable first habitat for early biology. Such vents express a rich chemical diversity, with changes in composition and temperature with depth and time, which means a wealth of prebiotic and early biotic environments may exist in superposition in such extreme environments (Rimmer and Shorttle 2019).

Yet, a noteworthy argument might plead in favour of a selective process leading to potassium enrichment in cells. Following a line of reasoning similar to the one that explains how L-amino acid stereochemistry drove the selection of D-carbohydrates (Danchin 2017b), potassium enrichment could have been positively selected against sodium as a major component of the cells' cytoplasm, because it stabilized critical RNA structures. In turn, the dialogue between Na^+ and K^+ endowed the cells with a rich panel of electrochemical potential management. Interestingly, both the physico-chemical constraint hypothesis and the history-based scenario can be reconciled. This possibility has been suggested by authors who explored the comparative role of sodium and potassium in peptide formation. Potassium appears to be significantly more efficient than sodium in the process (Dubina et al. 2013). If this scenario is retained, the omnipresence of potassium in cells asks for understanding primitive metabolism at the bottom of oceans, where it seems established that sodium was already dominating over potassium (Rubey 1951). Several further features of potassium are at odds with the purely historical view, among which is the possible unique role of potassium in water-driven cellular processes that would account for its selection as a long-range modifier of water structure in a way consistent with its similarity with the ammonium ion. Further experimental evidence is needed to substantiate this hypothesis—and the role and relevance of K^+ in biological systems makes it urgent to revisit our current understanding of the activity of many enzymes when assayed in vitro, as indicated in previous sections of the article. One way or another, the many roles of metallic cations in the cells are becoming more and more explicit as the analytical techniques to study

biological systems to an unprecedented degree of detail are becoming accessible.

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Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

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