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Potassium in Solid Cancers

Jessica Iorio, Lisa Lastraioli and Elena Lastraioli

Abstract

Electrolyte disorders are a frequent finding in cancer patients. In the majority of cases the etiologies of such disorders are common to all cancer types (i.e. diuretic-induced hyponatremia or hypokalemia). Sometimes, electrolyte disorders are caused by paraneoplastic syndromes or are due to cancer therapy. Potassium is one of the most important electrolytes of the human body since it is involved in the regulation of muscle contraction, maintenance of the integrity of the skeleton, blood pressure and nerve transmission as well as in the normal function of cells. Potassium homeostasis is strictly regulated since the gap between the recommended daily dietary intake (120 mEq/day) and the levels stored in the extracellular fluid (around 70 mEq) is huge. Alterations of potassium homeostasis are frequent in cancer patients as well alterations in potassium channels, the transmembrane proteins that mediate potassium fluxes within the cells. The present chapter is focused on the clinical significance of potassium homeostasis and potassium channels in patients with solid tumors.

Keywords: potassium, electrolyte homeostasis, solid cancers, potassium channels, channelopathies

1. Introduction

Potassium has a great importance within the cell as it is one of the main determinants of membrane potential in nervous and muscle cells (both skeletal and cardiac). Therefore, it is not surprising that in humans potassium blood levels are strictly controlled and even slight deviations from the physiological range can cause severe clinical conditions.

The amount of potassium in the human body is 3000–4000 mEq (corresponding to 50–55 mEq/Kg). Potassium levels in the extracellular fluid are quite low (roughly 70 mEq corresponding to 2% of the amount absorbed through the intestine) while the majority of K^+ (98%) is stored in the body tissues under a tight hormonal control. This great gap between extracellular fluid and tissues is responsible of the restricted range of K^+ levels in the plasma (3.5–5.5 mEq/L) that is maintained through the following mechanisms:

- Activity of Na-K ATPase. The Na-K pump actively extrudes three Na^+ from the cells exchanging them with two K^+ that enter the cells against gradient [1]. Such mechanism makes it possible the preservation of the physiological electrolyte concentration as well as the maintenance of the normal volume of extracellular

fluid. It is also essential for the solute passage through renal and intestinal epithelia.

- Elimination of potassium dietary intake through feces and urine.

A scheme of potassium intake, absorption and elimination is reported in **Figure 1**. Potassium intake from diet is mainly due to the consumption of K^+ -rich food such as bananas, avocados, grapes and salmon, among others. Once introduced in the body as food, potassium is rapidly conveyed towards intestine, where it is absorbed for its majority (90%). It has been suggested that absorption in the intestine is a passive process, guided by electrochemical gradients differently from the one taking place in the kidney [2].

Insulin is one of the main regulators of potassium homeostasis, modulating the exchange between extracellular fluid and tissues such as muscle, through the activation of the Na- K ATPase [3]. Moreover, in muscular tissue during exercise, a rise in potassium levels causes the stimulation of Na-K ATPase thus enhancing K^+ uptake [4], although the primary upregulation of the ATPase is due to adrenergic stimulation.

From the extracellular fluid, K^+ is also conveyed towards kidney where in physiological conditions it is partly reabsorbed and for the major portion eliminated with urine (90%) in the distal renal tubule, directed by mineralocorticoids and Na-K ATPase. The mechanisms of K^+ renal reabsorption are outside the scope of this chapter and can be deepened in several reviews (see for example [5]).

K^+ distribution across plasma-membranes is regulated by pancreatic hormones, acid–base homeostasis alterations and by the autonomous nervous system.

Figure 1.
Schematic diagram of K^+ intake, fluxes, storage and elimination.

Moreover, potassium itself regulates somehow its own excretion and redistribution through the stimulation of insulin and aldosterone secretion as well as the increase of Na-K ATPase activity in the distal nephron. On the whole, K^+ homeostasis is due to the interaction of two different systems, one based on K^+ cellular uptake and the other based mainly on renal excretion and, at a minor extent, on gastrointestinal elimination. These two systems have an important difference since the redistribution of potassium between intra- and extra-cellular compartments occurs rapidly (it takes minutes) while renal response to K^+ variations in plasma is quite slow (it takes hours to be activated and days to be completed). Moreover, since the biological effects depend on the ratio between the external and the internal K^+ concentration, the regulation of the internal distribution must be extremely efficient. A tight association exists between pH and kaliemia, therefore acidosis causes an increase of potassium plasma level while alkalosis induces hypokalemia. Another pathological condition that might cause hyperkalemia is the increase of osmolarity (due to hyperglycemia and hypernatremia).

2. Electrolyte disorders in human cancer

Cancer patients are characterized by complex alterations encompassing the whole organism. Among them electrolyte disorders represent quite frequent complications in such patients [6, 7] and are mainly due to alterations of sodium, potassium, calcium and magnesium plasma levels. In the majority of the patients these unbalances are asymptomatic but in some subjects they can contribute to worsen the clinical conditions and therefore must be treated. The electrolyte derangements adversely affect survival [8] and can disrupt cancer treatment [9–11]. There are many potential causes of electrolyte derangements in cancer patients that might be related either to a particular cancer or to any specific therapy. Actually, the picture might be even more complicated since these electrolyte disorders can be primary or secondary and active treatment can improve prognosis.

3. Potassium homeostasis alterations in human cancer

In cancer patients both a reduction (hypokalemia) or an increase (hyperkalemia) in potassium levels might be observed.

Hypokalemia is a condition of low K^+ plasma levels (< 3.5 mEq/L) that might have different causes in cancer patients. The principal causes of hypokalemia are reported in **Table 1**.

In cancer patients, the main cause of hypokalemia is a reduced K^+ intake due to malnutrition and malabsorption. In particular cases (i.e. Neuroendocrine Tumors), hypokalemia could be provoked by secretive diarrhea that causes potassium losses [12, 13]. Other tumors cause hypokalemia with the ectopic secretion of hormones (cortisol, ACTH and mineralocorticoids) [14].

In other cases, hypokalemia could be a secondary effect of cancer therapy, since some agents might cause diarrhea or vomiting thus leading to K^+ loss. Different cancer therapy agents (such as cisplatin, anti-EGFR agents and mTOR inhibitors, for instance) could induce renal damage associated to hypokalemia due to K^+ loss caused by tubular toxicity. For this reason, before starting therapy, renal function should be evaluated in order to prevent additional renal damage [15].

Decreased K ⁺ intake	Starvation			
	Clay ingestion			
Redistribution into cells	Acid-Base			
	Metabolic alkalosis			
	Hormonal			
		Insulin		
		β2 adrenergic agonists		
		α adrenergic antagonists		
	Anabolic state	Vitamin B12 or folic acid		
		Granulocyte-macrophage colony stimulating factor		
		Total parenteral nutrition		
		Other	Pseudo-hypokalemia	
	Hypothermia			
	Hypokalemic periodic paralysis			
	Barium toxicity			
Increased loss	Nonrenal	Gastrointestinal loss (diarrhea)		
		Integumentary loss (sweat)		
	Renal	Increased distal flow (diuretics....)		
		Increased K⁺ secretion	Mineralocorticoid excess	
		Distal delivery of non-reabsorbed anions (vomiting, nasogastric suction....)		
		Other	Amphotericin B	
	Liddle's syndrome			
	Hypomagnesemia			
	<i>The causes primarily represented in cancer patients are indicated in bold.</i>			

Table 1.
Main causes of hypokalemia.

Also, the simultaneous treatment with different agents (for example thiazide diuretics and glucocorticoids) might lead to hypokalemia because they promote potassium renal losses. Finally, the concomitant presence of endocrine dysfunctions might cause hypokalemia due to glucocorticoids or mineralocorticoids excess [14, 16].

Hyperkalemia is a condition of increased K⁺ plasma levels (> 5.5 mEq/L). The principal causes of hyperkalemia are reported in **Table 2**.

The main causes of hyperkalemia in cancer patients are represented by reduced renal elimination caused by renal failure and redistribution within extracellular compartment.

In cancer patients there are different conditions than can induce hyperkalemia [1]. For instance, highly proliferative tumors can develop lysis syndrome after anticancer therapy, thus causing hyperkalemia. As in the case of hypokalemia, also treatment

Renal failure	
Decreased distal flow	
Decreased K ⁺ secretion	
	Impaired Na ⁺ reabsorption
	Primary hypoaldosteronism
	Secondary hypoaldosteronism
	Resistance to aldosterone
Enhanced Cl ⁻ reabsorption NCC channel at the distal tubule	Gordon's syndrome
	Cyclosporine

The causes primarily represented in cancer patients are indicated in bold.

Table 2.
Main causes of hyperkalemia.

with chemotherapeutic agents such as platinum compounds might lead to hyperkalemia due to renal injury. Patients treated with a combination of drugs (i.e. potassium sparing diuretics, NSAIDs, angiotensin-converting enzyme inhibitors) might develop hyperkalemia. Also, the occurrence of concomitant disease (i.e. diabetes mellitus, sepsis, renal failure) or the need of parenteral nutrition might cause hyperkalemia [17, 18]. An important cause of hyperkalemia is represented by Tumor Lysis Syndrome, a serious condition characterized by hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia and hyperazotemia (**Figure 2**).

Figure 2.
Schematic diagram of tumor lysis syndrome.

TLS generally occurs within 72 hours from the therapy beginning and it is due to necrosis and subsequent release of cell content into the bloodstream [19]. In particular, there is an increase of potassium, phosphate and uric acid plasma levels while calcium levels are reduced. As a consequence, calcium phosphate precipitates in renal tubules, thus causing kidney injury and failure. Renal injury causes a worsening of metabolic disorders and hyperkalemia that can lead to arrhythmias, seizures, weakness and muscle cramps. Some cancer patients have a higher risk of developing TLS: for example, patients with a large tumor burden, rapidly growing tumors and tumors highly responsive to therapy (either standard chemotherapy, hormonal, radiation and targeted therapy). All these factors should be carefully evaluated before starting the treatment [20]. TLS generally occurs after a week of treatment but it can also develop spontaneously, for example in childhood cancers [21]. Moreover, patients suffering from additional renal dysfunctions have a higher risk of developing TLS.

Other causes of hyperkalemia in cancer patients are represented by adrenal insufficiency (Addison's disease) due to metastases in the adrenal gland especially in patients with advanced tumor of the breast and lung. Nevertheless, although the frequency of adrenal metastases is high, adrenal failure is rare due to the use of corticosteroids [22].

3.1 Potassium in paraneoplastic syndromes

According to the National Cancer Institute (NCI, Dictionary of Cancer Terms, <https://www.cancer.gov/publications/dictionaries/cancer-terms>) a paraneoplastic syndrome is defined as follows: “A group of symptoms that may develop when substances released by some cancer cells disrupt the normal function of surrounding cells and tissue”. This definition implies that a cancer patient may develop symptoms that are not directly attributable to tumor invasion or compression [23]. Paraneoplastic syndromes may have impact on different organs, such as endocrine, neurologic, hematologic, rheumatologic and dermatologic systems. Such group of disorders may be due to the ectopical secretion of hormones and peptides (endocrine paraneoplastic syndromes) or immune cross-reactivity (neurologic paraneoplastic syndromes) [24].

The only endocrine paraneoplastic syndrome involving K⁺ alteration is Cushing syndrome, characterized by hypercortisolism [25]. The syndrome is caused by the secretion of adrenocorticotrophic hormone or corticotropin-releasing factor from tumor cells [26, 27] followed by cortisol secretion from the adrenal glands. The main features of Cushing syndrome are reported in **Table 3**.

Clinical features	Laboratory findings	Associated tumors	References
Muscle weakness; Peripheral edema; Hypertension; Weight gain; Centripetal fat distribution	Hypokalemia (<3.0 mEq); High cortisol baseline level (>29 µg/dL); Urinary free cortisol level > 47 µg/24 h Midnight ACTH level > 100 ng/L	Neuroendocrine lung tumors; Small cell lung cancer; Thymoma; Medullary thyroid cancer; Gastrointestinal tract cancer; Ovarian cancer; Pancreatic cancer; Adrenal cancer	[26–29]

Table 3.
Main features of Cushing syndrome.

In contrast to other paraneoplastic syndromes (i.e. syndrome of inappropriate antidiuretic hormone secretion and hypercalcemia), patients often develop Cushing syndrome's symptoms before cancer is diagnosed. Moreover, the reappearance of Cushing syndrome may precede tumor recurrence [24].

4. Potassium channels

The multi-gene family of potassium channels is made of several subfamilies (**Figure 3**): calcium-activated channels, voltage-gated channels, inward rectifiers and two-pore domains (reviewed in [30, 31]).

Calcium-activated potassium channels are represented by two classes of proteins: “small- and intermediate- conductance” (SK) and “high-conductance” (BK) potassium channels. SK channels assemble as tetramers and each monomer is composed by six transmembrane domains (S1-S6) with a central pore in the S5-S6 region. Similarly, BK channels are organized as tetramers with α and β subunits; in this case the pore is formed by α subunits.

Voltage-gated potassium channels are composed by four subunits (each constituted by six transmembrane domains termed S1-S6) surrounding an aqueous pore. In these channels, the pore (P) is formed by a loop between S5 and S6. S4 domain acts as voltage sensor.

Inward rectifier potassium channels are tetramers, with each monomer characterized by only two transmembrane domains linked by a P-loop.

The last subfamily is represented by Two-pore domains channels, made of four transmembrane domains with two regions forming the aqueous pores.

4.1 Potassium channels in human cancer

Among ion channels, those selective for K^+ channels are the most frequently deregulated in cancers. Several reports have been published over the years, highlighting

Figure 3.
Potassium channels subfamilies.

K⁺ channels' relevance in human solid cancers [31]. For example, in colorectal cancer the presence of the transcripts of *KCNA3*, *KCNA5*, *KCNC1*, *KCNH1* [32–34], *KCNH2* [35] and *KCNK9* [36] was reported.

KCa1.1 channels (also indicated as BK channels) are encoded by the *KCNMA1* gene, located in 10q22, and belong to the high conductance subgroup of the calcium-activated subfamily. For these channels a clinical relevance in breast and prostate cancer has been demonstrated [37–41]. In breast cancer, *KCNMA1* gene amplification occurs in invasive ductal tumors, and it is associated with high grade, high stage and unfavorable prognosis [37]. Moreover, *KCa1.1* expression positively correlates with estrogen receptors [41] and the channel is expressed at higher levels in breast cancers developing metastases to brain [38]. Similarly, in prostate cancer *KCNMA1* is more frequently amplified in late-stage tumors [39] and represents a promising diagnostic biomarker since it is over-expressed in tumors with Gleason score equal to 5–6 [40].

KCa3.1, encoded by the *KCNN4* gene, is another member of the calcium-activated subfamily that is frequently upregulated in high grade breast cancers [42], small cell lung cancer [43], colorectal cancer [44] and pancreatic ductal adenocarcinomas [45]. In small cell lung cancer, *KCNN4* hypomethylation was shown to be a negative prognostic factor [43].

Kv1.3 (also named *KCNA3*) is a channel belonging to the voltage gated subfamily that was shown to be overexpressed in Gleason score 5–6 prostate cancer samples with respect to Gleason Score 8–9 patients [46], being down-regulated in high grade tumors [47]. In pancreatic cancer *Kv1.3* is down-expressed with respect to healthy pancreas and such downregulation could be due to the methylation of the promoter of the gene and it was also associated with the development of metastases [48].

Kv7.1 (also named *KCNQ1*) was shown to be over-expressed in lung tumors and to regulate cell proliferation and migration [49].

Kv10.1 (*KCNH1*) was shown to be expressed in esophageal squamous cell carcinoma and it was proposed as an independent negative prognostic factor [50]. *Kv10.1* is highly expressed also in colorectal cancers where it is associated with lymph node metastasis, tumor size, Dukes staging and was therefore proposed as a prognostic marker [51]. Also in gastric cancer it was demonstrated that high *Kv10.1* expression is associated with lymph node metastasis and higher stage [52].

Kv11.1 (*KCNH2*) was found to be expressed in a high percentage of esophageal squamous cell carcinoma samples with respect to healthy esophageal squamous epithelium [53]. Similarly, in esophageal adenocarcinomas it was shown that *Kv11.1* as well as the corresponding gene are expressed [54] and more recently it was shown that preneoplastic lesions expressing high levels of *Kv11.1* have a significantly higher risk to progress towards adenocarcinoma [55]. *Kv11.1* is also associated with TNM stage, grading, serosal and venous invasion, Lauren intestinal type and VEGF-A expression in gastric cancer [56, 57]. In colorectal cancers, the overexpression of *Kv11.1* regulates cell invasion [35]. Moreover, in TNM I and II samples *Kv11.1* presence associated with Glut-1 absence represents an independent negative prognostic factor [58]. More recently, it was shown that the concomitant expression of *hERG1* and *HIF-2α* represents a prognostic biomarker and it can be used to select metastatic CRC patients suitable to be treated with Bevacizumab [59]. In pancreatic cancer *Kv11.1* is associated to aggressive behavior and poorer prognosis [60].

Kir3.1 (*KCNJ3*) channels belong to the inward rectifier subfamily and it was shown that they positively correlated with lymph node metastases in breast cancer [61].

Several members of the Two Pore Domain family have been shown to be overexpressed in human tumors [62]. Quite recently, **K2P6.1** (KCNK6) was shown to be expressed in breast cancer and to promote proliferation, migration and invasion [63]. The gene encoding for **K2P9.1** (KCNK9, located on 8q23.4) was proven to be amplified in breast cancer [64]. Another member of the same family, **K2P5.1** (KCNK5) is induced by estrogens in ER-positive breast cancer cells [65]. *K2p 2.1* is overexpressed in prostate cancer, where it regulates cell proliferation [66].

5. Conclusion

Potassium is one of the most important mineral for humans, therefore its homeostasis is under tight control. Alterations of potassium homeostasis are frequent in cancer patients as well as alterations in potassium channels, and the clinical management of such patients must take into account the possibility for the patient of developing hypo- and hyperkalemia to define a proper protocol of treatment.

Conflict of interest

The authors declare no conflict of interest.

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