Mitochondrial Sirtuins in Cancer: Emerging Roles and Therapeutic Potential
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Abstract
The past few decades have witnessed a furious attention of scientific community toward identifying novel molecular factors and targets that could be exploited for drug development for cancer management. One such factor is the sirtuin (SIRT) family of nicotinamide adenine dinucleotide (NAD⁺)-dependent deacetylases. The role of SIRTs in cancer is extremely complex, with dichotomous functions depending on cell contexts. Mammalian SIRTs (SIRT1–7) differ in their cellular localization and biologic functions. Among these, SIRT3, -4, and -5 are located in the mitochondria and are being carefully investigated. These mitochondrial SIRTs (mSIRTs) regulate multiple cellular and physiologic processes, including cell cycle, gene expression, cell viability, stress response, metabolism, and energy homeostasis. Recent research suggests that mSIRTs influence tumors by regulating the metabolic state of the cell. Although the research on the role of mSIRTs in cancer is still in its infancy, studies have suggested tumor suppressor as well as tumor promoter roles for them. This review is focused on discussing up-to-date information about the roles and functional relevance of mSIRTs (SIRT3, -4, -5) in cancers. We have also provided a critical discussion on our perspective on their dual roles, as tumor promoter versus tumor suppressor, in cancer. Cancer Res; 76(9); 2500-6. ©2016 AACR.

Introduction
Cancer is a cluster of diseases with an underlying common feature of the development of abnormal cells that propagate out-of-control to travel and target almost every organ of the body to make it dysfunctional. According to American Cancer Society, it is expected that, the global cancer burden will nearly double by 2030, with 21.4 million cases and 13.2 million deaths (1). The last few decades have seen tremendous progress toward identifying the genes and pathways in cancer development and progression. The members of the Sir2 (silent information regulator 2) family, or sirtuins, have been widely investigated for their role in a variety of biologic processes and disease conditions.

The sirtuins (SIRT) belong to a family of class III histone deacetylases (HDAC) enzymes, which are highly conserved enzyme homologs of the yeast Sir2 protein, with nicotine adenine dinucleotide (NAD⁺)-dependent protein deacetylases and/or mono ADP ribosyltransferase activities (2). They are also known for regulating posttranslational acyl modifications in organisms ranging from bacteria to human (3, 4). Mammalian SIRTs make up a superfamily of seven SIRTs (SIRT1–SIRT7). Among these, SIRT1 is predominantly nuclear and SIRT2 is localized mainly in the cytoplasm. However, they have the ability to shuttle between the nucleus and cytoplasm. SIRT3, SIRT4, and SIRT5 are primarily mitochondrial proteins, whereas SIRT6 and SIRT7 are nuclear sirtuins (5).

The SIRT family of proteins is becoming increasingly interesting and important due to the seemingly dichotomous role of this enzyme family in cancer biology, with both tumor promoter and tumor suppressor functions suggested in different cancers. In this review, we have focused on the role of mitochondrial sirtuins (mSIRT) in cancer. Indeed, mitochondrial cell signaling is extremely critical for cancer cells to grow and proliferate, and metabolic imbalances and enhanced resistance to mitochondrial apoptosis are well-established hallmarks of cancer cells.

Discovery of Sirtuin Family of Enzymes: An Important Class of HDACs
The founding member of sirtuin family, Sir2, was first discovered as regulators of aging in the budding yeast Saccharomyces cerevisiae. In the late 1990s, a study led by Matt Kaebelrein verified that Sir2 overexpression prolongs yeast lifespan and deletion of Sir2 reduces yeast lifespan (6). However, a study by Imai and Guarente showed, for the first time, the true enzymatic activity of Sir2, as a NAD⁺-dependent histone deacetylase and gave a possible description of the mechanism by which Sir2 controls yeast aging (7). The evolutionarily conserved orthologs of Sir2 are shown to be found in most forms of life, including eukaryotes and prokaryotes (8). Structurally, the sirtuins members (SIRT1–SIRT7) share a conserved catalytic core of approximately 275 amino acids that is flanked by N- and C-terminal sequences of variable length. A small zinc-binding domain and a large Rossmann-fold domain endow all SIRTs with the specificity to bind NAD⁺ as a cofactor. SIRTs enzymatic activities have been linked to a variety of cellular processes such as stress response, differentiation, metabolism, apoptosis, and cell survival due to their ability to deacetylate both histone and numerous non-histone targets (9). Although SIRTs have been studied for over a decade, the scientific community is still struggling to establish their complex role in cancer.
Mitochondrial SIRTs: The Master Regulators of Metabolic Homeostasis

As aforementioned, there are three known mtSIRTs (SIRT-3, -4, -5) shown to regulate a variety of cellular processes. SIRT3, a 45 kDa protein, is located on chromosome 1p15.5 having an N-terminal mitochondrial targeting sequence that is cleaved off after import into the mitochondria, leaving an enzymatically active 28 kDa protein. SIRT4 is 35.2 kDa protein located on chromosome 12q24.31, whereas SIRT5 (33.9 kDa)-like pseudogene is present on chromosome 1p31.2-32.1 (8). Most of their functions are recently reviewed by Shih and colleagues (10). SIRT3 has a strong deacetylase activity, whereas SIRT4 has ADP ribosyltransferase activity, lipoamidase and biotinidase activities in mitochondria (11). SIRT5 has protein lysine desuccinylase, demalonylase, deglutarylase, and weak deacetylase activities. In addition, SIRT3 deacetylates carbamoyl phosphate synthetase 1 (CPS1), an enzyme catalyzing the initial step of the urea cycle for ammonia detoxification and disposal (12). All these three SIRTs are metabolically active in tissues like kidney, liver, adipose, heart, and brain.

The important role of mtSIRTs in cancer is not surprising owing to the fact that the process of cancer development and progression involves major alterations in cellular metabolism and mitochondrial energetics. Moreover, cancer cells are metabolically active and consume more cellular fuel than normal cells (13). Otto Warburg first proposed the theory in 1920s that defects in energy metabolism, particularly in mitochondrial function, may be the root cause of cancer. The proposed “Warburg effect” suggests that cancer cells prefer glycolytic breakdown of glucose for energy, rather than mitochondrial oxidative phosphorylation (14). Mitochondria is considered as the energy provider and regulate various homeostatic processes, such as cell proliferation, apoptosis, oxidative stress, and calcium homeostasis. Understanding the mechanisms that link cellular energy metabolism and regulation of gene expression is of fundamental importance that could potentially be exploited for the management of various diseases, including cancer. The mtSIRTs are critical for the maintenance of cellular and mitochondria homeostasis through regulating mitochondrial metabolism and protecting cells against oxidative stress via regulating reactive oxygen species (ROS) generation, a critical mechanism in cancer. Utilizing the mitochondrial NAD pool, the mtSIRTs can deacetylase targets implicated in the regulation of both glycolysis and cellular oxidative stress.

A more detailed discussion of mtSIRTs, including SIRT5, is elegantly provided in a very recent article by Kumar and Lombard (15). A brief account of mtSIRTs and their biologic functions, especially relevant to cancer pathophysiology, is provided below.

SIRT3

SIRT3 is most well characterized and studied mtSIRT that has been shown to regulate almost every major aspect of mitochondrial biology (16–18). Not surprisingly, SIRT3 is reported to contribute to the age-related diseases, metabolic, cardiovascular, neurogenerative diseases, and cancer (19). SIRT3 deacetylates key mitochondrial proteins, including acetyl-coenzyme A synthetase 2, isocitrate dehydrogenase 2 (IDH2), and glutamate dehydrogenase (GDH; refs. 20, 21). Recently, SIRT3 is found to deacetylate and increase pyruvate dehydrogenase activity in cancer cells, which can increase both mitochondrial bioenergetics and glycolysis (22). Furthermore, SIRT3 binds to and deacetylates mitochondrial pyruvate carrier 1 (MPC1) to promote its function, thereby inhibiting colon cancer cell growth (23). SIRT3 functions as a downstream target of peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α) and decreases cellular ROS production and stimulate mitochondrial biogenesis (17). Indeed, PGC-1α, a transcriptional coactivator of genes involved in energy homeostasis, including PPARs, estrogen-related receptor (ERR), and nuclear respiratory factors (Nrf), is a master regulator of metabolism and mitochondrial biogenesis.

A key metabolic enzyme that is directly regulated by SIRT3 in mitochondria is manganese superoxide (MnSOD) that protects the cells by detoxifying ROS (24). SIRT3 promotes antioxidant activity of MnSOD via direct deacetylation, and loss of SIRT3 increases acetylation of MnSOD to enhance ROS, which stabilizes hypoxia-inducible factor 1-alpha (HIF1α), thereby facilitating tumor development (25). Conversely, Cui and colleagues found that overexpression of SIRT3 increases lactate production, ATP production leading to increased glycolysis, which together with increased MnSOD activity, decreased ROS level to promoted cell proliferation of gastric cancer cells (26). In glioma cells, SIRT3 maintains the mitochondrial DNA integrity through its ability to deacetylate 8-oxoguanine-DNA glycosylase 1 (OGG1), thus preventing apoptosis and promoting carcinogenesis (27). Also, SIRT3 has been recently shown to deacetylate glutamate oxaloacetate transaminase (GOT2) that regulates the malate-aspartate NADH shuttle to control the growth of pancreatic tumor (28). Mitochondrial impairment and ROS production have been implicated in the development of insulin resistance and linked with diabetes. Consistent with this framework, decreased level of SIRT3 along with its associated transcription factor, forkhead box O3 (FOXO3a) was observed in mouse 3T3L1 adipocytes and C2C12 myotubes upon chronic arsenic exposure (29). This decrease in SIRT3 caused enhanced ROS generation and mitochondrial membrane damage, leading to insulin resistance (29). Another study shows SIRT3–deficient mice when fed a chronic high-fat diet showed accelerated obesity, insulin resistance, and steatohepatitis compared with wild-type mice (30).

SIRT4

SIRT4 has also been shown to regulate cellular metabolism by a variety of mechanisms. Glutamine metabolism is important for mitochondrial functions and macromolecular synthesis and could play an important role in cancer progression. SIRT4 has been shown to act as a tumor suppressor by regulating glutamine metabolism, suggesting a potential therapeutic use in glutamine-dependent neoplasms, such as B-cell lymphoma (31). In addition, C-terminal–binding protein (CtBP)-mediated suppression of SIRT4 and enzymatic modification of GDH has been shown to promote glutaminolysis, in breast cancer cells (32). Also, mTOR complex 1 (mTORC1) promotes mitochondrial glutamine metabolism by stimulating GDH1 and repressing the transcription of SIRT4 regulator cAMP-responsive element binding 2 (CREB2), and SIRT4 overexpression reduces proliferation and transformation of tuberous sclerosis 2 mutant cells and tumor development in a xenograft model (33). Besides, SIRT4 has also been implicated in other mitochondrial dysfunction–related disorders like insulin secretion, obesity, and cardiovascular diseases (34–36). Therefore, on the basis of published studies, SIRT4 appears to have a tumor suppressor function.
SIRT3
Phylogenetically most closely related to prokaryotic sirtuins, SIRT3 is predominantly mitochondrial, with some evidence of existence of functional extra-mitochondrial protein. Limited number of studies has examined the role of SIRT3 in cellular metabolic functions. SIRT5-mediated lysine desuccinylation has been shown to modulate a number of diverse metabolic pathways (37). Probably, the first clue suggesting the role of SIRT5 in metabolism and cancer comes from the observation that SIRT5 desuccinylates SOD1 and eliminates ROS thereby inhibits lung cancer cells growth (38). In addition, SIRT5-mediated deacetylation of FOXO3 is shown to play an essential role in protecting epithelial cells from cigarette smoke extract–induced apoptosis (39). As described in a very recent review, SIRT5 deacetylates, desuccinylates, demalonylates, and/or deglutarylates multiple metabolic enzymes to activate or inhibit a variety of metabolic/cellular processes, including glucose oxidation, ketone body formation, fatty acid oxidation, ammonia detoxification, and ROS management (15).

Mitochondrial SIRTs and Their Molecular Targets: Relevance to Cancer

The research on mtSIRT’s role in cancer and its downstream targets has gained a lot of momentum in the recent years. A wide variety of molecular targets are associated with the different biologic functions modulated by SIRTs. Some of these important targets are described below.

SIRT3
The fact that SIRT3 can regulate many hallmarks of the cancer cells implicates SIRT3 as a potential therapeutic target for cancer management (40). However, the role of SIRT3 in cancer is being extensively debated, with numerous evidences supporting both tumor promoter and suppressor roles for SIRT3. SIRT3 was initially suggested to act as a tumor suppressor when introduction of a single oncogene (Myc or Ras) into the mouse embryonic fibroblasts (MEF) from SIRT3-knockout mice resulted in an in vitro transformation (41). Furthermore, Yang and colleagues reported that SIRT3 was aberrantly downregulated in gastric cancer tissue samples from patients (42). Recently, decreased SIRT3 expression was found in mantle cell lymphomas and B-cell malignant cells. This SIRT3 loss was found to correlate with hyperacetylation of IDH2 and SOD2, thereby decreasing IDH2 and SOD2 activities in B-cell malignant cells (43). Another study demonstrated that SIRT3 is decreased in gastric cancer cells and its exogenous overexpression suppressed the proliferation of gastric cancer cells by downregulating Notch-1 (44). SIRT3 deacetylates and destabilizes the proto-oncogene product S-phase kinase-associated protein 2 (Skp2), and inactivation of SIRT3 leads to Skp2 acetylation and increased stability and cytoplasmic retention, causing enhanced cellular proliferation, migration, and tumorigenesis (45). Song and colleagues demonstrated that SIRT3 inhibits hepatocellular carcinoma growth via glycogen synthase kinase-3β (GSK-3β)/Bax-dependent apoptotic pathway (46). In addition, binding of SIRT3 with nicotinamide mononucleotide adenyltransferase 2 (NMNAT2) was shown to regulate cell proliferation and apoptosis in non–small cell lung carcinoma (NSCLC) cell lines, implicating the interaction between SIRT3 and NMNAT2, energy metabolism associated with SIRT3 (47). More recently, depletion of SIRT3 was shown to exert tumor-suppressive function by regulating iron metabolism in pancreatic cancer (48). Also, exogenous overexpression of SIRT3 was shown to suppress prostate cancer by decreasing ROS generation that inhibits Akt phosphorylation at Ser 473, leading to ubiquitin-mediated proteosomal c-MYC degradation (49).

In certain cancers, SIRT3 is found to be overexpressed (50–52) and associated with therapy resistance (53). Interestingly, both tumor suppressor and oncogenic function of SIRT3 have been reported in breast cancer (54, 55). Liu and colleagues have shown a transcriptional activation of SIRT3 in several radiation-treated human tumor cells and their corresponding xenograft tumors that was mediated via NF-κB and Thr150/Ser159 phosphorylation by cyclin B1-CDK1 (56). In another study, clinically, high cytoplasmic SIRT3 expression was shown to correlate with high tumor grades, positive lymph node status, and poor prognosis in colon cancer patients (57). Among 127 patients, high SIRT3 expression was seen in 71 patients and low SIRT3 expression was seen in 56 patients. The overall survival rate was 80.2% among patients with low SIRT3 expressions and 55.9% among patients with high SIRT3 expressions (log rank P = 0.002). However, the relevance of cytoplasmic SIRT3 needs to be carefully investigated in future studies. In a very recent study from our laboratory, we found that SIRT3 is overexpressed in human melanoma cells and clinical melanoma tissues (58). Furthermore, an shRNA-mediated knockdown of SIRT3 was found to impart significant antiproliferative effects in multiple human melanoma cell lines (38). Conversely, forced exogenous overexpression of SIRT3 promoted enhanced proliferative potential of Hs294T melanoma cells and normal immortalized Mel-ST melanoma (58). In addition, SIRT3 knockdown also resulted in a decrease in tumor growth in vivo in a xenograft model (58). In addition, limited information is available regarding mutation(s) in SIRT3 and its role in cancer. Chen and colleagues have found that point mutation in SIRT3 reduced its deacetylase activity promoting proliferation of oral squamous cell carcinoma cells (59). However, the exact role of mutant SIRT3 in tumorigenesis needs to be further explored.

SIRT3 has been shown to target and deacetylate the lysine residues of not only mitochondrial proteins, but also numerous other proteins as well. An interaction between SIRT3 and tumor suppressor p53 has been shown in certain cancers. SIRT3 was shown to partially abrogate p53 activity to enact growth arrest and senescence in bladder carcinoma (60). Similarly, an exogenous overexpression of SIRT3 was found to inhibit HCC cell growth by reducing mouse double minute 2 (MDM2)-mediated p53 degradation, possibly via posttranscriptional regulation (61). Interestingly, SIRT3 overexpression upregulated p53 and its downstream factor p21 and decreased ROS level in lung adenocarcinoma cells thereby imparting proproliferative response (62). In cardiomyocytes, SIRT3 deacetylates Ku70, augmenting Ku70–Bax interactions and consequently preventing Bax translocation to the mitochondria, thus protecting these cells from genotoxic and oxidative stress-mediated cell death to promote cell survival (63). Thus, it appears that SIRT3 can have oncogenic or tumor-suppressive functions based on cancer types and both known and possibly yet unidentified downstream targets.

SIRT4
Limited information is available regarding the downstream targets of SIRT4 and its interactions with other pathways that affect metabolic reprogramming in cancer cells. As discussed above, a few reports articulate tumor-suppressive activities of
SIRT4 via its effects on mitochondrial glutamine metabolism, in part through modification and repression of GDH. In a recent study, down regulation of SIRT4 has been shown to be associated with poor prognosis in head and neck squamous cell carcinoma (HNSCC) patients (64). Tumor suppressor function of SIRT4 is also reported in colorectal cancer where SIRT4 has been shown to cause E-cadherin upregulation thereby suppressing the proliferation, migration, and invasion through inhibition of glutamine metabolism (65). Jeong and colleagues have shown that SIRT4 loss causes increased glutamine-dependent proliferation and stress-induced genomic instability, and SIRT4 knockout mice spontaneously develop lung tumors (66). Huang and colleagues have found a downregulation of SIRT4 in gastric adenocarcinoma, suggesting its tumor suppressor function (67). Thus, SIRT4 loss or inactivation seems to create a tumor-permissive environment to provide metabolic advantage, supporting cell proliferation.

SIRT5

Like SIRT4, SIRT5 is also not extensively studied and characterized, especially in context with cancer. SIRT5 has been found to be overexpressed in human NSCLC and can facilitate drug resistance in vitro and in vivo by reducing expression of Nrf2 and its downstream targets (68). Poletta and colleagues have shown SIRT5 regulation of ammonia-induced autophagy and mitophagy in breast cancer cells (69). Unlike in NSCLC, SIRT5 has been shown to be considerably downregulated in HNSCC tissues compared with noncancerous tissues, suggesting its possible tumor suppressor function (70). Guan and colleagues have identified SIRT5 as a deacetylases for the tumor suppressor promye-locytic leukemia protein (PML), suggesting a tumor suppressor function for this SIRT (71).

Thus, SIRT3 and SIRT5 have been shown to exhibit tumor suppressor as well as tumor promoter properties under different cellular conditions, tumor stage and tissue of origin. Interestingly, on the basis of limited number of studies, SIRT4 appears to have only a tumor suppressor function. However, further detailed studies are needed to dissect the downstream targets of mtSIRTs.

### Activators and Inhibitors of Mitochondrial SIRTs: Potential Uses in Cancer Therapy

Recent research has established the essential roles of mtSIRTs in a wide range of critical mitochondrial functions and cellular processes. This has spurred extensive research and efforts from scientists across multiple disciplines toward the development of small-molecule modulators (activators and inhibitors) of these SIRTs. Although considerable efforts have been made to develop sirtuin inhibitors and activators (reviewed in refs. 72, 73) in the recent past, only limited success has been achieved. Majority of the known modulators of sirtuins seem to suffer from specificity issues. To our knowledge, no specific modulators of mtSIRTs have been reported. Thus, this area of research is still in infancy and needs a concerted attention from scientists and drug companies. Table 1 provides a list of recently identified and characterized mtSIRT-modulators together with their IC_{50} values.

### Concluding Discussion and Perspective

Mitochondrial SIRTs are critical regulators of metabolic functions in the cells, which are responsible for keeping the cellular homeostasis and cellular energetics “in check.” Emerging evidence is now suggesting that mtSIRTs are important regulator of what is known as “oncometabolism,” defined as the ensemble of metabolic rearrangements that accompany oncogenesis and tumor progression (74). Increasing understanding of the function of mtSIRTs is providing an insight on their functional significance in cancer. A description of the key metabolic substrates of mtSIRTs, their biologic functions, downstream targets, and expression pattern in cancer is provided in Table 2. It seems possible that the SIRTs may be useful as novel biomarkers for cancer diagnoses and targets for development of novel strategies for cancer therapy. However, further research is needed to answer the question, why and how these sirtuins have both oncogenic or tumor-suppressive
role, in different cancer and how this dual action could be best exploited in cancer management? It seems probable that the role of sirtuins is different in cancer cells versus normal cells and/or depends on the stage of neoplastic transformation. Future research needs to address these possibilities. As discussed above, there is a need to intensify our efforts toward the development of novel specific pharmacologic activators and inhibitors of SIRTs that can serve as a tool to understand the sirtuin biology and may also possibly be useful in the management of diseases where SIRTs are dysregulated, including cancer. However, given the important role of mtSIRTs in metabolism, there is always an issue of off-target complications. This needs to be carefully investigated. Furthermore, there may be some cancers where more than one sirtuins are overexpressed (or downregulated). In these cases, the nonspecific broad sirtuin inhibitors may be more useful, rather than specific ones. On the same line, additional research is required to ascertain the functional redundancy and overlaps among different sirtuins. This is particularly important for the mtSIRTs. In conclusion, the mtSIRTs have emerged as critical regulators of diverse metabolic functions relevant to cancer. Therefore, manipulating these enzymes may have important implications in cancer management.

**Disclosure of Potential Conflicts of Interest**
No potential conflicts of interest were disclosed.

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### Table 2. mitochondrial sirtuins: Metabolic substrates, functions, downstream targets, and expression pattern in various cancers

<table>
<thead>
<tr>
<th>Sirtuin</th>
<th>Activity</th>
<th>Substrates</th>
<th>Functions</th>
<th>Downstream targets</th>
<th>Relative expression in various cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRT3</td>
<td>• Deacetylases</td>
<td>AceCS2, IDH2, GDH, MCPI, PDK, MSH5D, OGG1, GOT2, FOXO3A, Skp2</td>
<td>Metabolism/gene transcription/apoptosis/DNA repair/oxidative stress</td>
<td>PGC-1α, Notch-1, HIF1α, GSK-3β/Bax, MMNAT2, P53/Akt, NF-κB, p53, p21, Ku70</td>
<td>• Downregulated in gastric cancer, B-cell malignancies, HCC, NSCLC, prostate cancer, breast cancer, pancreatic cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Upregulated in breast cancer, melanoma, colon cancer, OSCC, lung adenocarcinoma</td>
</tr>
<tr>
<td>SIRT4</td>
<td>• ADP ribosyltransferase</td>
<td>GDH</td>
<td>Metabolism</td>
<td>E-cadherin</td>
<td>• Downregulated in B-cell lymphoma, breast cancer, HNSCC, colorectal cancer, lung tumors in mice, gastric adenocarcinoma</td>
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<tr>
<td>SIRT5</td>
<td>• Lysine deacetylase,</td>
<td>CPS1, PML</td>
<td>Metabolism</td>
<td>Nrf2</td>
<td>• Downregulated in HNSCC, leukemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Upregulated in NSCLC</td>
</tr>
</tbody>
</table>

Abbreviations: HCC, hepatocellular cancer; NSCLC, nons–small cell lung cancer; OSCC, oral squamous cell carcinoma.

*This table provides examples that have been studied in a greater detail. It is by no means a complete depiction of all the substrates, functions, downstream targets, and expression pattern in cancer.
Mitochondrial SIRTs in Cancer


Correction: Mitochondrial Sirtuins in Cancer: Emerging Roles and Therapeutic Potential

In this article (Cancer Res 2016;76:2500–6), which appeared in the May 1, 2016 issue of Cancer Research (1), there is an error in Table 1. "143 ± 3.6 mmol/L" should be "143 ± 3.6 μmol/L". The authors regret this error. The online version of the article has been corrected and no longer matches the print.

Reference

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