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EDITORIAL

Biochemical and pathophysiological properties of polyamines

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Preface

The history of polyamines dates back to the fifteenth century when spermine was discovered by Antonie van Leeuwenhoek [born in Delft, Holland (1632–1723)], but it took several decades before scientists got interested in understanding and unraveling the role(s) of spermine and other polyamines in the biology of living cells. Mammalian cells contain significant amounts of polyamines and these molecules, which are polycations, play specific roles in various tissues. Although the physiological functions of these polycations have yet to be elucidated completely at the molecular level, many studies have provided a better understanding of the roles polyamines play in cell growth, proliferation, and pathophysiological processes. At the 5th International Conference on Polyamines: Biochemical, Physiological and Clinical Perspectives held in Taiwan, in 2018, special attention has been given to the role of polyamines in carcinogenesis and in developing new approaches for cancer therapy and other diseases.

The issue is a tribute and dedicated by internationally recognized experts to the memory of Professor Seymour S. Cohen, a prominent scientist in polyamine research. The manuscripts included in this special issue range from biochemistry to pharmacology, chemistry, genetics, molecular biology and clinical science on the current state of knowledge regarding the physiological, biochemical, and therapeutic actions of polyamines, and should be of use to the old and the new generation of researchers in the polyamine field.

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Editorial

This special issue of Amino Acids brings together 17 peer-reviewed manuscripts that provide the essence of the lectures and posters presented at the above-mentioned conference held in Taipei (Taiwan) in 2018 on the biological and physiological roles of polyamines. Also, a few other manuscripts are authored by international experts who were unable to attend the said conference. Short overviews of a few important concepts and notions in the subject matter are also presented; these represent tools that new investigators can benefit from in this field. The manuscripts project the role of polyamines in cell growth and differentiation, cell cycle regulation, gene expression, and signal transduction in animals, plants, and microorganisms as well as under several pathophysiological processes including carcinogenesis and other diseases. All the articles represent high-class research data obtained until the mid-2019.[1]

Cellular polyamine concentrations are highly regulated. Their accumulation at high extracellular concentrations or deregulation of the systems that control polyamine homeostasis can induce programmed cell death (or apoptosis) in various cell types. The polyamines spermidine and spermine are substrates for several enzymes that generate cytotoxic metabolites, via the action of monoamine oxidase (MAO), polyamine oxidase (PAO), spermine oxidase (SMOX), or copper amine oxidases (CuAOs) (Ohkubo et al. 2019; Fratini et al. 2019; Agostinelli et al. 2014). Amine oxidases (AOs) regulate the levels of these polycations. Mono-, di- and polyamines, as well as several *N*-acyl amines, are oxidatively deaminated by AOs in a reaction consuming O_2 and H_2O. In fact, cytotoxicity in vitro can be induced in several human tumor cell lines using purified bovine serum amino oxidase (BSAO), a CuAOs, in the presence of exogenous spermine or endogenous polyamines (Amendola et al. 2014; Agostinelli et al. 2014). It can also be achieved via the injection of the enzyme into the tumor in vivo (Averill-Bates et al. 2005). Amine oxidases preferentially use polyamines (spermine and

[1] All manuscripts in this special issue were subjected to external peer reviewing according to the policy of this journal.

spermidine) as substrate to generate the reactive oxygen species (ROS), H_2O_2, and aldehyde(s). Spermidine and spermine exist in cells as an RNA–polyamine complex to regulate protein synthesis (Igarashi and Kashiwagi 2015). When cells are damaged, polyamines are released from RNA, especially from ribosomes, and acrolein is produced by spermine oxidase, one of the polyamine-metabolizing enzymes (Pegg 2013). Interestingly, recent research has shown that phytohormones affect polyamine metabolism/homeostasis via impact on polyamine biosynthesis and catabolic genes (Anwar et al. 2015). Also, it seems apparent that in plants polyamines can interact with nitrous oxide (NO) and H_2O_2 to program cellular senescence (Mattoo and Sobieszczuk-Nowicka 2018).

In this issue, it is reaffirmed (Igarashi et al. 2020) that acrolein (CH_2=CH–CHO) produced from spermine is more toxic than reactive oxygen species ($O_2^{-\cdot}$, H_2O_2 and $^{\cdot}OH$) (Igarashi et al. 2018). The authors also correlate several diseases with acrolein. In brain infarction and dementia, incipient patients with high sensitivity and specificity were identified by measuring protein-conjugated acrolein (PC-Acro) in plasma, together with IL-6 and CRP in brain infarction and $A\beta_{40/42}$ in dementia. The level of PC-Acro in plasma and saliva also correlated with the seriousness of renal failure and Sjögren's syndrome, respectively. Thus, scavenging acrolein is of great importance in maintaining the QOL (quality of life) of the elderly. Polyamines are often present at high concentrations in growing tissues as well as in the rapidly dividing tumor cells and likely activate hyperproliferative diseases such as various cancer cells. Therefore, special attention has been paid to their involvement in carcinogenesis and in developing new approaches to cancer therapy and other diseases. Amine oxidases (AOs) regulate the levels of polyamines and generate cytotoxic metabolites (Ohkubo et al. 2019; Agostinelli et al. 2014). Interestingly, spermine oxidase (SMOX), a FAD-containing enzyme, specifically oxidizes spermine (Spm) and its dysregulation alters polyamine homeostasis, leading to aetiology of several pathological conditions, including cancer (Casero and Pegg 2010). Direct mechanistic links between inflammation, SMOX activity, ROS production, and carcinogenesis have been demonstrated (Goodwin et al. 2008; Fratini et al. 2019). Main biochemical, cellular, and physiological processes in which SMOX is involved have been highlighted (Cervelli et al. 2012). In the last decade, a number of studies have demonstrated that polyamine metabolism is deregulated in brain diseases such as epilepsy, the fourth most common neurological disorder (World Health Organization WHO 2019). The mouse model Dach-SMOX, overexpressing the spermine oxidase (SMOX) in the brain, is highly susceptible to excitotoxic injury induced by kainic acid (Cervelli et al. 2013; Cervetto et al. 2016; Pietropaoli et al. 2018). In this issue, Leonetti et al. (2020) report that Dach-SMOX mice is more vulnerable to a different epileptic model, pentylenetetrazole, and emphasized the involvement of the SMOX catalytic product hydrogen peroxide during epilepsy. In this context, the mouse model can be considered a suitable genetic model to study epilepsy.

An interesting investigation performed by Stump et al. (2020) has shown that the ultraviolet-B (UVB) radiation is carcinogenic causing non-melanoma skin cancer (NMSC) (Bowden 2004). The mammalian targets of rapamycin complex 1 (mTORC1) and ornithine decarboxylase (ODC) are upregulated in response to UVB (Nowotarski et al 2018). However, the interplay between these two pathways after UVB exposure remains unclear. The studies described in this article compare mRNA stability between normal human keratinocytes (HaCaT cells) and HaCaT cells with low levels of Raptor to investigate whether the induction of ODC by UVB is dependent on mTORC1. These data suggest that ODC mRNA stability is regulated in human keratinocytes, in part, by an mTORC1-dependent mechanism after UVB exposure. Latour et al. (2020) summarize the role of polyamines in macrophage activation and function. $Odc^{\Delta mye}$ mice with myeloid-specific deletion of ornithine decarboxylase (ODC) have been developed. These mice had exacerbated inflammation and M1 macrophage activation (Hardbower et al. 2017) when infected with the gastric bacterial pathogen *Helicobacter pylori.* Further, they attributed this effect to histone modifications favoring gene transcription; the enhanced innate immune response attenuated bacterial burden in the stomach. Putrescine-based impairment in M1 response was found abrogated by Odc deletion. $Odc^{\Delta mye}$ mice were protected from colitis-associated colon tumorigenesis (Singh et al. 2018). Previously, upstream arginase activity was connected to the regulation of polyamine metabolism in *H. pylori* infection (Hardbower et al., 2016).

Activation of the intrinsic apoptosis pathway is linked to mitochondrial membrane permeabilization. Although many aspects of this complex process are not completely understood, the steps involve permeabilization of the mitochondrial outer membrane (MOMP) and opening of the mitochondrial permeability transition pore (MPTP). Both processes are tightly regulated by several components belonging to Bcl-2 family proteins that have attracted increasing interest as possible targets for the treatment of some diseases and, in particular, of cancer (Green and Kroemer 2004). In this context, naturally occurring polyamines have received increasing attention. AGM, a product of Arg decarboxylation, is a substrate for agmatinase for the synthesis of putrescine and other polyamines and it is transported in mitochondria. Martinis et al. (2020) observed in rat liver mitochondria the selective release of pro-apoptotic factors induced by AGM, an evidence for the complex effect on mitochondrial pathophysiology. This release takes place under conditions of mitochondrial membrane energization

and involves the pro-apoptotic factors localized in the intermembrane space, cyt c and Smac-DIABLO by leading to the caspase-dependent apoptosis. Instead, AIF, another pro-apoptotic factor, also present in the intermembrane space, but inserted in the inner membrane, is not released out of mitochondria, by preventing the caspase-independent apoptosis induction. This effect is ascribable to the induction of MOMP, a mechanism controlling cell death, taking place under physiological conditions (Green and Reed 1998). By activating the Bcl-2 protein, BAX, AGM favors the interaction with VDAC leading to the opening of a channel on the outer membrane responsible of pro-apoptotic factors release (Renault and Manon 2011; Westphal et al. 2011). This investigation opened an intriguing survey on intrinsic apoptosis induction. In addition, many efforts have been addressed to elucidate neuroprotective effects of agmatine at low concentrations. Furthermore, several lines of evidence showed that AGM plays a role in the excitotoxicity and its effect was mediated by interaction with NMDA and NO production (Kotagale et al. 2019; Mun et al. 2010). A mechanism hypothesized suggested that biogenic amine may be involved in the neuroprotection by scavenger effects on oxygen radicals to prevent oxidative stress (Condello et al. 2011). In this issue, Ferlazzo and coauthors (2020) have evaluated differentiated SH-SY5Y cells exposed to rotenone, as cellular model of Parkinson's disease (PD), in particular, to test whether AGM effect could be associated with a mechanism involving mitochondrial function. Consequently, the authors have evaluated the possible relationship between AGM neuroprotective effects and changes in the activation of hypoxia-inducible factor 1 alpha (HIF-1α), a transcription factor, which may be able to control cellular response to mitochondrial dysfunction. These authors also relate to whether HIF-1α inhibitor influences the effects of AGM against rotenone induced damage.

The physiological importance of agmatine (AGM) in mammals and its potential for therapeutic application were largely ignored for more than 80 years, mainly due to the difficulties in detecting low arginine decarboxylase (ADC) activity in mammals (Piletz et al. 2013), suggesting that a large portion of the AGM is supplemented from diets and gut microbiota (Galgano et al. 2012). Akasaka and Fujiwara (2020) have studied the therapeutic and nutraceutical potential of agmatine, and its enhanced production using a filamentous fungus *Aspergillus oryzae*, used widely for Japanese rice wine (Sake) and a wide range of fermented foods (Akasaka et al. 2018). Continuous intake of fermented foods, including those produced with *A. oryzae*, would be beneficial to health and aging with improved quality of life. In the manuscript, the authors also provide an approach for enhancing AGM production using *A oryzae*.

Polyamine analogues were previously designed, synthesized, and tested as anticancer agents (Casero and Woster 2009) as well as in neurodegenerative processes (Minarini et al. 2010), antiparasitic compounds, neurotransmitter receptor neuroprotectants, and multitarget-directed ligands for multifactorial diseases. The polyamine metabolism has been widely employed during the last decades for the search of therapeutic approaches for cancer treatment (Damiani and Wallace 2018; Murray-Stewart et al. 2018a). Generally, the activation of PA catabolism is associated with the formation of cytotoxic products and cancer cells death (Murray-Stewart et al. 2018b). Several compounds are known to induce PA catabolic enzymes (Di Paolo et al. 2019). Syatkin et al. (2020) report the investigation of structure–activity relationship of polyamine-targeted synthetic compounds from different chemical groups. The aim of this work was to explore if low molecular compounds could activate them directly and how their structure determines their action using docking simulations. The strongest activators were found among halogenated aniline derivatives and azafluorene derivatives. The docking revealed a distinction in the mode of binding of both activators and inhibitors with the enzyme via Asp211 and Tyr204. These results may be useful for structure-based drug design (Di Paolo et al. 2019). Dysregulation of epigenetic control of gene expression is a common feature in the initiation and progression of cancer. DNA methylation and covalent modification of histones collaborate to function as epigenetic regulators of gene expression. Polyamine derivatives acting as epigenetic modulators have also been studied since these polyamine-based pharmacologically active molecules are promising tools in anticancer therapy (Pasini et al. 2013). In this issue, Soda (2020) has described a mechanism of life span extension induced by polyamine-rich diet. Aging is associated with decreases in enzymatic activities for polyamine synthesis and regulation of DNA methylation and with enhancement of aberrant DNA methylation. Long-term increased polyamine intake elevated blood spermine concentrations in humans and mice, and lifelong intake of high-polyamine chow-inhibited aging-associated aberrant DNA methylation and extended life span of mice (Soda et al. 2009). In in vitro studies, spermine supplementation re-activated DNA methyltransferases that regulate DNA methylation and reversed aberrant methylation induced by decreased polyamine synthesis (Fukui et al. 2019). As aberrant DNA methylation is closely associated with aging-associated pathologies, the biological background of life span extension by polyamine is discussed in Soda's overview. Bollenbach et al. (2019a) provided evidence that enzymatic methylation and citrullination of the guanidine (N^G) group of Arg residues in proteins are abundant. Arg and its homolog L-homoarginine (hArg), Lys and Orn are involved in many other biochemical processes including the L-arginine:glycine amidinotransferase (AGAT) pathway. hArg emerged in recent years as a cardiovascular risk factor, but the underlying mechanisms are still undefined

(Bollenbach et al. 2019b). hArg is likely to be metabolized to the polyamine homoagmatine (hAgm), which has not been measured in humans thus far. These ramifications give rise to elucidation of unexplained biological activities of polyamines, hArg, and N^G-methylated and citrullinated Arg proteins (Hanff et al. 2020). Gas chromatography-mass spectrometry (GC–MS) methods were developed, validated and used to measure serum spermidine, putrescine and hArg in both seropositive and seronegative *Helicobacter pylori* subjects (Bollenbach et al. 2019a, b; Hanff et al. 2020) and of hAgm in rat organs (Tsikas et al. 2020).

Interesting data on the metabolic peculiarities of parasites with respect to glutathione and trypanothione (bis-glutathionyl spermidine) metabolism were previously reported in *Leishmania* (Colotti and Ilari 2011). *Leishmania* parasites possess a unique polyamine-based redox metabolism, in which trypanothione replaces many of the antioxidant functions of glutathione in mammals (Colotti and Ilari 2011). Ilari et al. (2012) solved the crystal structure of *Leishmania infantum* trypanothione reductase (TR) in complex with Sb(III), Ag(I) and with auranofin, an anti-rheumatic organo-gold drug. Saccoliti et al. (2017) solved the X-ray structure of trypanothione reductase (TR) from Leishmania in complex with the diaryl sulfide compound RDS 777 (6-(sec-butoxy)-2-((3-chlorophenyl)thio)pyrimidin-4-amine), which impairs the parasite defense against the reactive oxygen species by inhibiting TR with high efficiency binding to the catalytic site (Saccoliti et al. 2017; Ilari et al. 2017). On the basis of the RDS 777–TR complex, Colotti et al. (2020) designed and synthesized a new class of diaryl sulfide TR inhibitors able to compete for trypanothione binding to the enzyme and to kill the promastigote in the micromolar range. One of these compounds (RDS 562) inhibits selectively Leishmania TR, reduces trypanothione concentration in the parasite, while it does not inhibit the human homolog glutathione reductase. Little is known about the function of polyamines in parasites. To address this question, Perdeh et al. (2020) assessed the effect of polyamine depletion in *Leishmania donovani* mutants lacking ornithine decarboxylase (Δ*odc*) or spermidine synthase (Δ*spdsyn*). Putrescine depletion in the Δ*odc* mutants led to cell rounding, immediate cessation of proliferation, and loss of viability, while putrescine-rich Δ*spdsyn* mutants displayed an intermediate proliferation phenotype and were able to arrest in a quiescent-like state for 6 weeks. Thus, putrescine is not only essential as precursor for spermidine formation but also critical for parasite proliferation, morphology, and viability.

In addition to having common polyamines (putrescine, spermidine, and spermine) found in living organisms, hyperthermophiles that grow above 80 °C synthesize two types of unique polyamines, long linear-chain polyamines (LCPAs) such as caldopentamine and caldohexamine, and branched-chain polyamines (BCPAs) such as N^4-aminopropylnorspermidine [3(3)3], N^4-aminopropylspermidine [3(3)4], and N^4-bis(aminopropyl)spermidine [3(3)(3)4]. The numbers in brackets indicate the number of methylene (CH_2) units among NH_2, NH, N, or N^+ (Oshima et al. 1983; Hosoya et al. 2004; Hamana et al. 2007). LCPAs and BCPAs contribute to the stabilization of nucleic acids such as DNA and RNA at high temperatures (Terui et al., 2005). Yamori et al. (2020) describe here that BCPAs synthesized by a BCPA synthase (BpsA) are unique polycations found in (hyper)thermophiles growing at above 85 °C (Okada et al. 2014; Hidese et al. 2017, 2019). BCPA also induce unique temperature-dependent structural changes in genome size DNA (Nishio et al. 2018). In the present study, effect of BCPA on RNAP complex was evaluated. Proteins of RNA polymerase (RNAP) core fraction extracted from *bpsA* deletion mutant were compared with those from wild type (WT). Ribosomal proteins found in WT-RNAP were not detected in the mutant RNAP, suggesting that BCPA increases the linkage between RNAP and ribosomes to achieve efficient coupling of transcription and translation. Here, Fukuda et al. (2020) report on genes expressed under the control of BCPA in hyperthermophilic archaeon *Thermococcus kodakarensis* using comparative transcriptome and proteome analyses with next-generation DNA sequencing (RNA-seq) and liquid chromatography–mass spectrometry (LC–MS), respectively. Several genes including flagellin-related proteins (FlaB2–4) and cytosolic NiFe-hydrogenase subunit alpha (HyhL) were expressed only in parental wild type KU216 but not in DBP1(Δ*bpsA*). Thus, BCPA plays a regulatory role in gene expression in *T. kodakarensis*.

The successful development of nanomaterials for biomedical applications, as delivery system, for the treatment of cancer, pain and infectious diseases, depends on the possibility of tuning the nanomaterial properties, and, in particular, of controlling the interactions at the interface with biological systems. Venerando et al. (2020) have developed peculiar magnetic nanoparticles, constituted of iron oxide, which find optimized uses for biosensing (Bonaiuto et al. 2016), targeted drug delivery (Magro et al. 2019), cell transfection (Magro et al. 2017), and cell tracking (Venerando et al. 2020). Iron oxide nano-based drug delivery systems are currently under evaluation for different pathologies. In this issue, the facile self-assembly of nanostructured ternary hybrid obtained by the combination of an aqueous colloidal suspension of SAMN@DNA with spermidine-based fluorescent quantum dots (CQDSpds) is presented. It introduces a new multifaceted tool for theranostics combining magnetic and fluorescence properties.

The last article of this issue presents the enzymatic activity and thermoresistance of improved microbial transglutaminase (TGases) variants. TGases facilitate the formation of *N*-ε(γ-glutamyl)lysine isopeptide bond between endo-γ-glutaminyl and endo-ε-lysyl protein residues, or the covalent

incorporation of diamines and polyamines in proteins (Folk 1983). Here, Böhme et al. (2020) report the optimization of the properties of the microbial and highly thermostable transglutaminase of *Streptomyces mobaraensis*. The variant TG^{16} with a specific combination of five of the seven "hot spots" previously identified shows a 19-fold increased half-life at 60 °C ($t_{1/2}$ = 38 min) compared to the wild-type enzyme ($t_{1/2}$ = 1.9 min).

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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