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Polyamines: metabolism to systems biology and beyond

Minireview Article

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Summary. Polyamines and the metabolic and physiopathological processes in which they are involved represent an active field of research that has been continuously growing since the seventies. In the last years, the trends in the focused areas of interest within this field since the 1970s have been confirmed. The impact of "-omics" in polyamine research remains too low in comparison with its deep impact on other biological research areas. These high-throughput approaches, along with systems biology and, in general, more systemic and holistic approaches should contribute to a renewal of this research area in the near future.

Keywords: Polyamines – Systems biology – Functional genomics – Proteomics – Metabolomics – Sematic web

Abbreviations: ADME/Tox, absorption, distribution, metabolism, excreton and toxicity; HTML, hypertext markup language; HTTP, hypertext transfer protocol; SAM, S-adenosyl methionine; siRNA, small interferent RNA

Introduction

Polyamines (putrescine, spermidine and spermine) are aliphatic polycations present in almost all living species, the exceptions being two orders of Archaea, namely, Methanobacteriales and Halobacteriales (Hamana and Matsuzaki, 1992). Their ubiquity and conservation across evolution point to their importance for cell biology. In fact, polyamines have pleiotropic effects with relevant regulatory roles in macromolecular synthesis and cell proliferation rates (Cohen, 1998; Thomas and Thomas, 2001; Medina et al., 2003).

Although the prehistory of polyamine research can be drawn back to the famous letter from Antonie van Leeuwenhoek to the Royal Society of London in 1678, the history of the scientific study of polyamines does begin in the last quarter of the 19th century, with the identification of spermine (1878), cadaverine (1886) and putrescine (1889). Discovery and synthesis of spermidine was achieved in 1927 (Cohen, 1998). The evolution of this research topic along the last 86 years of its history is depicted in Fig. 1, showing a continuous increase in the publication rate, with a steady rise in the number of publications in the last 35 years. Two key cornerstone references clearly show the evolution of polyamine research in this last period of time: the monographic *Polyamines* volume of *Methods in Enzymology* edited by Herbert and Celia White Tabor in 1983 and the comprehensive *A Guide to Polyamines* written in 1997 by Seymour Cohen and published in 1998 (Tabor and Tabor, 1983; Cohen, 1998). According to the seach criteria used in Fig. 1, up to 1970 around 500 references on polyamines had accumulated, meaning a mean value of 7 new references per year. From 1971 to the date of publication of the volume *Polyamines*, the publication rate drastically increased to more than 300 new references per year. From 1984 to the date of publication of *A Guide to Polyamines* there was a further increase in the publication rate up to more than 500 references per year. Since then up to the moment of writting this review, the rate has suffered a new increase to more than 600 new references per year. The growing accumulated number of references containing data on polyamines is currently around 18,000 ref-

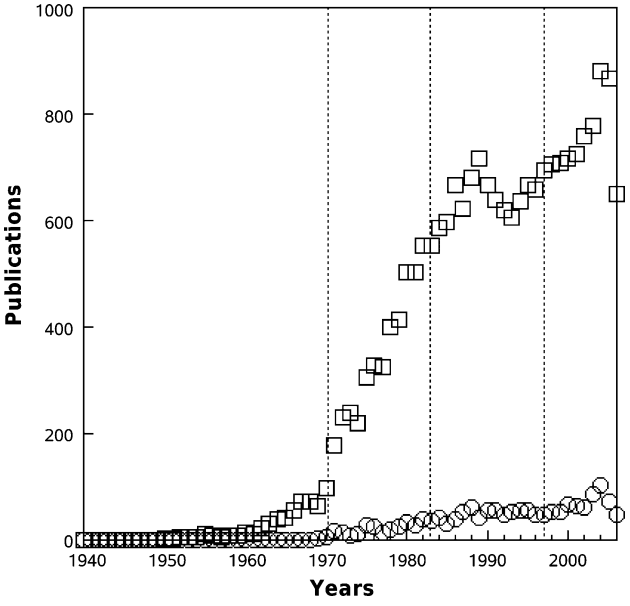

Fig. 1. Evolution of the rate of publication within polyamine research since 1940. Data are the total number of publications (squares) and the number of reviews (circles) per year, according to a search within the PubMed database using the unrestricted query ''polyamine* OR putrescine OR spermidine OR spermine''

erences according to the search criteria used in Fig. 1 (increased to 70,000 references according to a general search using ''polyamine'' as a keyword).

The contents of the monographic *Polyamines* volume of *Methods in Enzymology* edited by Herbert and Celia White Tabor (1983) show that the main topics of polyamine research were as follows: a) Analytical and preparative methods for amines and metabolically related compounds. b) Physiopathological and metabolic studies on the effects of polyamine treatments or genetic manipulation of their metabolism. c) Isolation and kinetic characterization of the enzymes involved in polyamine metabolism, including the study of inhibitors. d) Study of analogs and derivatives.

According to the contents of *A Guide to Polyamines* by Seymour Cohen (1998), the previously mentioned research topics remained in the mainstream, but it can also be observed a renewed interest for the study of: 1) polyamine metabolism in mammals, other animals, plants, fungi and bacteria; 2) the role of polyamines in cancer; and 3) the interactions of polyamines with macrobiomolecules (proteins, RNA and DNA).

The rest of this minireview is devoted to analyse the trends of polyamine research since the publication date of *A Guide to Polyamines* and to describe future prospects.

What has been published for the last 9 years concerning polyamines?

A selective search (by adding new restriction criteria) within the more than 6,000 references found to be published since the publication date of *A Guide to Polyamines* allows to depict a classification of current research trends (Fig. 2). Some clear trends deserve to be commented:

1. The trends mentioned for the previous period (1984–97) confirm their prevalence within the preference of the polyamine researchers.
2. More than 2/3 of the published work is devoted to some aspects of metabolism.
3. Enzyme studies have still a remarkable yield (30% of total production). Within this area, more than 40% of papers are devoted to kinetic aspects. Ornithine decarboxylase remains the most popular enzyme. The number of studies devoted to this enzyme exceeds by 4-fold that of papers concerning spermidine, spermine acetyltransferase and by 5-fold that of papers devoted to study antizyme. The relative number of papers on S-adenosyl methionine decarboxylase and polyamine oxidases remains low.
4. The transport of polyamines remains a topic full of uncertainties (Medina et al., 2003) and emerges as a rapidly growing research subarea (more than 10% of polyamine research total production within this period of time).
5. The enzymologic, metabolic, physiological and pharmacological studies concerning polyamine analogs and derivatives remain in the mainstream.
6. Genetic manipulation with transgenic mice and modified cell lines provides new valuable information on the pathophysiological roles of polyamines and the enzymes involved in their metabolism. This subarea is continuosly growing. It is noteworthy that in the last three years the use of the potent technologies of siRNA has entered with strength in the polyamine field, providing the first thirty-something papers based in the use of this technology (see, for instance, Choi et al., 2005; López-Contreras et al., 2006).
7. Another strong subarea of research is that related to the study of the interactions of polyamines with nucleic acids or proteins, yielding more than 150 new papers.
8. Finally, in relation with pathophysiological processes, the connection of polyamines with cancer remains the most productive topic, yelding almost the 15% of newly released papers. Inflammation, neurodegenera-

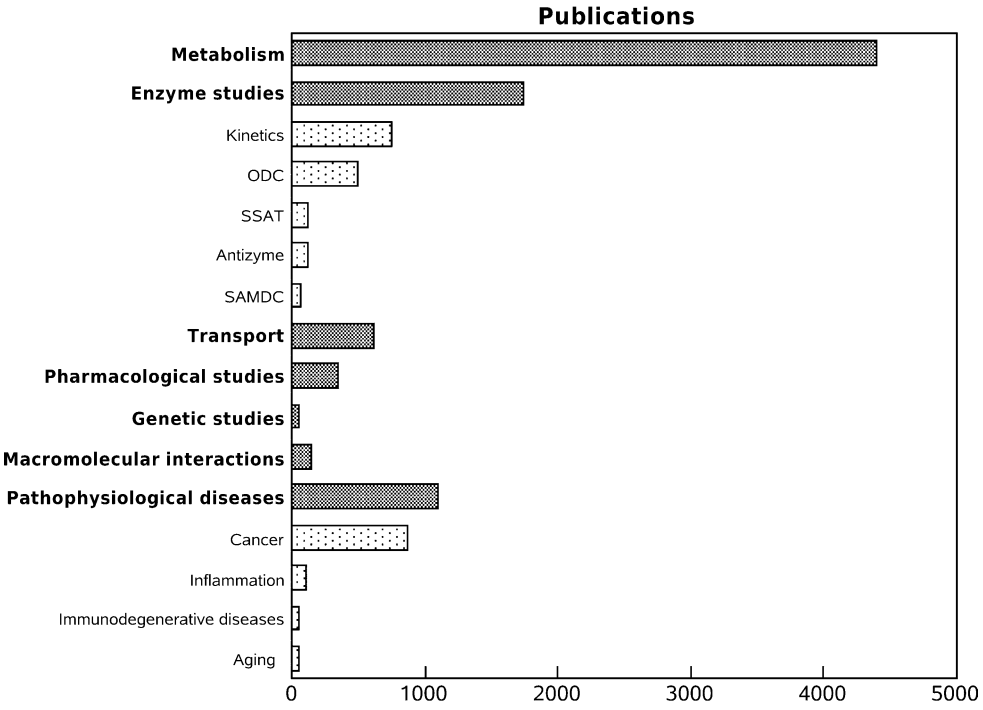

Fig. 2. A simple classification of current research trends within the polyamine field, according to the number of publications devoted since the date of publication of *A Guide to Polyamines* to different areas and subareas. The query used in Fig. 1 was restricted by the addition of a keyword (describing the area or subarea) to the original query by the connecting Boolean "AND"

ive diseases and aging are the following topics and the study of connections of polyamines with angiogenesis emerges as a new topic of interest, with 33 articles published in this period of time.

An especial mention should be given concerning review papers. Almost a 10% of all the new references containing data on polyamines are reviews. Among the 132 review articles containing the words "polyamine", "putrescine", "spermidine" or "spermine", the general trends mentioned above are confirmed. Table 1 contains a selection of representative reviews related to the different subareas mentioned above.

Table 1. Representative reviews published in the last years and focused on some of the different subareas within the polyamine research topic

Metabolism	Seiler (2004)
Enzyme studies	Binda et al. (2002)
ODC	Kubota (1999)
Antizyme	Mangold (2005)
SAMDC	Pegg et al. (1998)
Transport	Reguera et al. (2005)
Pharmacological studies	Liang et al. (2006), Bienz et al. (2005) and Seiler (2005)
Genetic studies	Jänne et al. (2005) and Pegg et al. (2003)
Macromolecular interactions	D'Agostino et al. (2006) and Bachrach (2004)
Pathophysiological processes	Mionard et al. (2005)
Cancer	Samejima (2006), Gerner et al. (2004) and Bachrach (2004)
Inflammation	Satriano (2004)
Immunodegenerative diseases	Jeevanandam et al. (2001)
Ageing	Wu et al. (2000)

What about the "-omics" world?

The launch of genome projects in the last decade of 20th century marked the beginning of the "-omics" era within biological research. Genomics, functional genomics, transcriptomics, interactomics, metabolomics and other "-omics" pervade current biochemical and molecular biology research. It has been claimed that the advent of this new "-omics" technologies will contribute to the identification of new polyamine-regulated genes (Wallace et al., 2003) and, in general, it is expected that these approaches will contribute to a new burst of additional data concerning polyamines. In high contrast with these expectations, it is remarkable that up to the moment the "-omics" approaches have had only a testimonial presence in the production within polyamine research area.

Within the more than 6,000 references published since the publication date of *A Guide to Polyamines*, only six papers are rescued when "proteomics" is added as a key-

word, and only two of them are research papers focused on polyamines in bacteria and plants (Franceschetti et al., 2004; Pessione et al., 2005). The situation is even worst for ''functional genomics'', yielding eight papers and none of them is a research paper focused on the study of polyamines. Concerning ''metabolomics'', only two references are rescued, both of them corresponding to metabolic profiling studies carried out in plants, and only one of them yielding some relevant results related to polyamines (Parr et al., 2005).

This scarcity of research papers devoted to study some aspects of polyamines with the tools of the different new ''-omics'' clearly points to a delay in the general incorporation of these tools by polyamine research groups. This situation should change deeply in the near future. Our research group is contributing within this issue with a first functional genomics approach to the study of polyamine/histamine metabolic cross-talk (Chaves et al., 2007).

Systems biology enters into scene

Much of last century biology was an attempt to reduce biological phenomena to the behavior of molecules. In spite of the great success of this approach, most biological functions arise from interactions among many components, yielding nonlinear behavior that has been fine tuned by natural selection to achieve specific functional properties (Hartwell et al., 1999; Alberghina et al., 2004). Therefore, a comprehensive understanding of biological functions requires new systemic approaches, as those provided by systems biology. In fact, systems biology uses to be described as the analysis of the relationships among the elements in a system in response to genetic or environmental perturbations, with the goal of understanding the system as a whole (Weston and Hood, 2004; Yang et al., 2005). Systems biology approaches are hypothesis-driven and involve iterative rounds of model building, prediction, experimentation, model refinement and development (Kitano, 2001, 2002a, b; Weston and Hood, 2004). Within this framework, computational biology contributes with former and newly designed tools for both knowledge discovery (or data-mining) and model-and-simulation-based analysis.

During the last years, we have been claiming for more holistic approaches to characterize the biological roles of biogenic amines and – in particular- polyamines (Medina et al., 2003, 2005; Sánchez-Jiménez et al., 2007). Due to the pleiotropic and important roles of polyamines, their metabolism has long been the focus of biochemical studies that have provided extensive and detailed information concerning each of the enzymes and metabolites of the pathway (Wallace et al., 2003; Pegg et al., 2003; Pegg, 2006). However, most of this information is very disperse and not integrated in a comprehensive, systemic framework. On the other hand, many therapeutic strategies based on the specific inhibition of one of the key enzymes of polyamine metabolism have failed, mostly due to the presence of compensating mechanisms in polyamine metabolism that contribute to the buffering of those effects elicited when only an enzyme is the target (Medina et al., 2005). The structure of the reaction diagram of polyamine metabolism in mammals is relatively complex, consisting of a bi-cycle having two required entrances (ornithine and S-adenosylmethionine) and several alternative outwards. For most of the reactions, both activities and turnover rates of enzymes depend on polyamine concentrations in a non-linear way. Therefore, the behavior of the full pathway in response to genetic and environmental perturbations cannot be easily deduced from the reaction diagram itself. Nevertheless, if the behavior of the elements of a system is known, they can be assembled in a model to acquire a global knowledge of the system. This is known as bottom-up approach. In this case, the global behavior of polyamine metabolism taken as a biomodule (Hartwell et al., 1999) can be investigated with a mathematical model, which describes the reactions and interactions among its components. We have recently described the first basic mathematical modeling of polyamine metabolism in mammals based on available experimental metabolite concentrations and kinetic data (Rodríguez-Caso et al., 2006). In this work, we show that polyamine homeostasis is not only controlled by the key enzymes but also acetyl-CoA and S-adenosylmethionine (SAM) availability, suggesting metabolic connections with other biological processes, as aerobic glucose (and fatty acid) consumption and processes involving SAM as a methyl donor (including gene regulation by DNA/histone methylation). New metabolic modules will be added to this first model, and we are working on this line (Montañez et al., 2007). This and other systemic approaches to the study of polyamines will allow to ascertain whether potential strong modulators of polyamine metabolism are expected to induce relevant effects administered either alone or in combination.

Systems biology can also be used for the prediction or determination of absorption, distribution, metabolism, excretion and toxicity (known as ADME/Tox in pharmacology jargon) properties of compounds before they reach the clinic (Ekins et al., 2005). This emergent area of re-

search could be applied for the study of new modulators of polyamine metabolism with potential pharmacological interest. This has been the case of previously described metabolically programmed polyamine analog antidiarrheals (Bergeron et al., 1996).

The identification of potentially relevant regulatory elements will establish the interconnections among amine-related proteins and genes, as well as the transcription factors that control their regulation. This can be assessed by the use of algorithms to analyze the amine-related macromolecules in combination with experimental approaches (e.g. expression microarrays, proteomics, and other experimental methods to assess protein–protein interactions and/or coexpressions). The topological approaches provided by graph theory is a suitable approximation to extract valuable information from cellular interaction networks. The first efforts have been done on the human transcription factor network (Rodríguez-Caso et al., 2005). Similar studies can be carried out for other aspects of the intracellular and intercellular communication network involving polyamines. To improve the efficiency of this task, development of new tools for automatic integration of the information are very helpful and it is one of our current priorities. From the analysis of the state of the art on the polyamine field, we detect the following needs that could be solved by systems biology technologies:

1. Development and validation of new computational tools for integration of biochemical and molecular information stored in public databases containing properties of individual elements (metabolites, proteins, genes), as well as for assessed interactions among them.
2. Development of a new database containing bibliographic information on biochemistry, molecular biology and physiopatological roles of biogenic amines and related compounds by using text mining techniques.
3. New bioinformatic tools for structural and functional predictions on the molecules and pathways related to amine metabolism and biological missions.

To contribute to fulfill these purposes, we have announced (Medina et al., 2007) and started the so-called ''Amine System Project'' (www.asp.uma.es). This project combines our most recent efforts (mentioned above) in development of predictive models (item 3), with our present aims for development of a prototype system for integration of metabolic and functional data concerning biogenic amine-related molecules and pathways (items 1 and 2). Since most of the control mechanisms of the essential processes for any biological system (maintenance of the genetic material, gene expression and signalling) are supported on protein–protein interactions, the automated search and integration of protein–protein interactions concerning the polyamine field is another goal of our project in the long-term. To achieve a maximum efficiency in this automated search and integration, an optimum system should be able to reach a high degree of integration among any information repository, as well as the maximum interoperability among the different data analysis tools. Furthermore, it should avoid redundant information, discriminate (to detect and to score) a confidence degree for each interaction, and provide the user with a solution vector compatible with as much independent graphic tools as possible. Finally, an additional facility could be obtained by integration of a minimum algorithm set to the system to carry out some graph theory calculations (for instance, connectivity and clustering). In our opinion, development of ontology-based systems could help to advance in development of new and better information integration services. Ontologies provide a formal representation of the real world, shared by a sufficient amount of users, by defining concepts and relationships among them. In order to provide semantics to web resources, elements (instances) of such concepts and relationships are used to annotate them. These annotations over the resources are the foundation of the Semantic Web. Semantic Web technologies provide a natural and flexible solution for combining two levels of abstraction, the data level and the knowledge level, which are related by means of metadata. Thus, ontologies provide necessary elements to make explicit the database semantics, allowing the management of great amounts of knowledge distributed among different databases. According to the World Wide Web inventor Tim Berners-Lee, the Semantic Web could be the key to unlocking scientific data that's sequestered by disparate applications' formats and organizational limitations, and could allow scientists to harness computations full power. Furthermore, Berners-Lee (who also invented key components of the World Wide Web such as HTTP – Hypertext Transfer Protocol – and HTML – Hypertext Markup Language – in the late 1980s) thinks that life scientists in particular could find the Semantic Web a useful tool, and in so doing, ''provide leadership to lots of other fields'' in implementing this next-generation Web technology.

...And beyond: the need for more systemic and holistic approaches to polyamines in biology

Nowadays, in our opinion, systems biology is a controversial forum of open and active discussion, mostly due to

the many different interpretations of its aims and tools. In the wikipedia, systems biology is defined as ''*an academic field that seeks to integrate different levels of information to understand how biological systems function*''. The identification of systems biology as an ''academic field'' (namely, an additional speciality of biology) is suspicious. In fact, since the objects of study of biology (cells, organisms, populations, ecosystems) are all of them complex systems, should not the whole biology be considered as a ''systems biology''? We are afraid that most of the scientists ''converted'' to systems biology make an instrumental use of it to manage the huge amount of information provided by new ''-omics'' technologies and bioinformatics. Although this instrumental approach is indeed also required, this cannot surpass the limitations of reductionism. It is our understanding that an authentic holistic and systemic view of biology should be based on the analysis of the relationships among elements of a biological system in a given steady-state, as well as along the response of the system against any perturbation of its environment, with the final aim to know not only the system itself but also its dynamics. To achieve this goal, the approaches provided by the general theory of systems, the theory of dynamical systems and, in general, the new sciences of complexity should be applied. ''Complexity'' is a keyword, which was identified as one of the three main challenges of biology (the others are ''consilience'' and ''communication'') for the incoming century in an influential editorial published in *BioEssays* (1999).

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