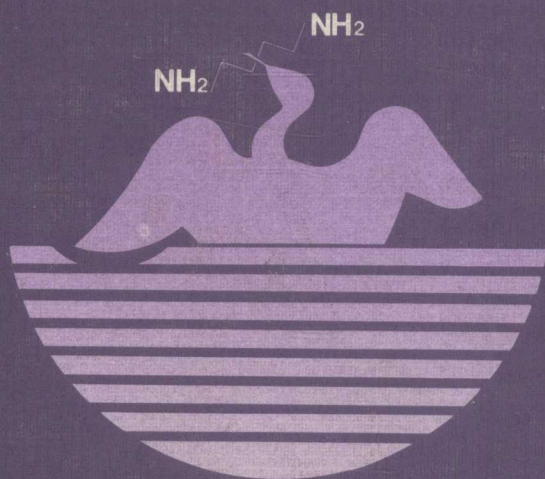


POLYAMINES

BASIC AND CLINICAL ASPECTS



Editors: K. Imahori, F. Suzuki, O. Suzuki
and U. Bachrach

POLYAMINES: BASIC AND CLINICAL ASPECTS

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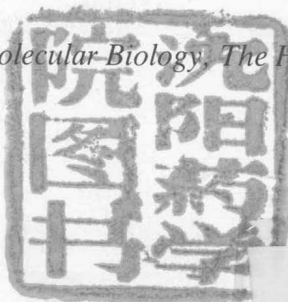
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POLYAMINES: BASIC AND CLINICAL ASPECTS

PREFACE

Although the history of polyamines goes back to the 15th century, it has been paid little attention for many years. Recently, however, the importance of polyamines has been recognized because of its close relationship to cell proliferation and carcinogenesis. In Japan too, research on polyamines has been conducted actively. Accordingly it was our sincere desire to invite the International Symposium on Polyamines to provide Japanese researchers with an opportunity to exchange ideas with eminent scholars from all over the world. It was very fortunate that we were able to realize our hopes on the occasion of the 3rd International Congress on Cell Biology as its Satellite Symposium.

The Symposium was held on 22-24 August 1984 at Nagaragawa Hotel, Gifu, Japan. About 150 participants attended and we were able to count more than 30 overseas visitors among them. Twenty-six papers were read and 32 posters were presented. This book represents the Symposium as its Proceedings; we hope that readers can feel the exciting atmosphere that prevailed.

Finally the Editors would like to express their hearty appreciations to VNU Science Press for its enormous efforts dedicated to publishing this volume. Our sincere thanks are also due to Professor T. Nagatsu and Dr T. Matsumoto of Nagoya University School of Medicine for their kind cooperation in editing the manuscripts and also for their kind advice.

K. Imahori

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CONTENTS

Preface	ix
Organizing committee	x
List of participants	xi
Metabolism of polyamines	
Evidence that an elevated level of ornithine decarboxylase may be essential to tumor promotion by phorbol esters <i>M. Takigawa, R.K. Boutwell and A.K. Verma</i>	1
Induction of ornithine decarboxylase in guinea pig lymphocytes: possible involvement of Ca^{2+} -activated, phospholipid-dependent protein kinase and calmodulin <i>S. Otani, I. Matsui, A. Kuramoto and S. Morisawa</i>	9
Induction of ornithine decarboxylase in mouse tissues <i>in vivo</i> by a factor produced by a macrophage cell line <i>Y. Endo, R. Suzuki and K. Kumagai</i>	17
Ornithine decarboxylase activity and cell proliferation <i>H. Nishino, T. Hasegawa, E. Naitoh and A. Kinugasa</i>	25
A human neuroblastoma cell line with altered form of ornithine decarboxylase which is stable <i>in vivo</i> and <i>in vitro</i> <i>H. Pösö, E. Karvonen, H. Suomalainen and L.C. Andersson</i>	33
Ornithine decarboxylase of <i>Tetrahymena thermophila</i> : general characteristics and its resistance to α -difluoromethylornithine <i>K.M. Yao, W.F. Fong and S.F. Ng</i>	41
Changes in ornithine decarboxylase-mRNA activity in the liver of thioacetamide-treated rats <i>T. Kameji, K. Fujita, T. Noguchi, M. Takiguchi, M. Mori, M. Tatibana and S. Hayashi</i>	49
Induction of ornithine decarboxylase and spermidine/spermine N^1 -acetyltransferase by parathyroid hormone in rabbit costal chondrocytes in culture <i>I. Matsui, S. Otani, S. Morisawa, M. Takigawa, M. Enomoto and F. Suzuki</i>	57
Distribution of spermidine synthase in leaf protoplasts of Chinese cabbage <i>R.K. Sindhu and S.S. Cohen</i>	65
Acylpolyamine deacylase from microorganisms and its application to the assaying of urinary polyamine <i>M. Okada, Y. Yoshimura and K. Imahori</i>	73
Purification of hypusine-containing protein from rat liver <i>A. Sano</i>	81
Partial purification and properties of soybean seedling amine oxidase <i>O. Suzuki and T. Matsumoto</i>	89
Regulation of polyamine metabolism by 5'-deoxy-5'-methylthioadenosine in a mouse T cell line <i>M. Kubota, O. Kajander and D.A. Carson</i>	97

Distribution of polyamines in prokaryotes, algae, plants and fungi <i>K. Hamana and S. Matsuzaki</i>	105
Unusual long polyamines in a thermophile <i>T. Oshima and M. Senshu</i>	113
Effect of polyamines of cellular metabolism	
Effects of polyamine depletion on ribonucleotide concentrations and transcriptional activity in early chick embryos <i>H. Emanuelsson, B. Löwkvist, E. Egyházi, J. Sjöberg and O. Heby</i>	119
Preferential stimulation of the <i>in vivo</i> synthesis of Mr 62K protein and $\beta\beta'$ subunits of RNA polymerase by polyamines <i>K. Igarashi, K. Mitsui, T. Kakewaga, R. Ohnishi and S. Hirose</i>	127
Polyamine-DNA interactions and cancer therapy <i>L.J. Marton</i>	135
Changes in DNA precursor pools due to inhibition of polyamine biosynthesis <i>O. Heby, S.M. Oredsson, M. Kanje and B. Nicander</i>	143
Isolation of a cDNA clone encoding S-adenosylmethionine decarboxylase from bovine lymphocytes <i>M. Mach, M.G. Neubauer, J.L. Degen, C.E. Seyfried and D.R. Morris</i>	155
Effects of catecholamines on polyamine metabolism and DNA synthesis in cultured rat parotid explants <i>H. Inoue, N. Arakaki, K. Takigawa and Y. Takeda</i>	165
Polyamines and opiates <i>U. Bachrach and D. Benalal</i>	173
Putrescine-macromolecule complexes detected <i>in vivo</i> by carbon-13 nuclear magnetic resonance <i>B. Frydman, R.B. Frydman, C. De Los Santos, D. Alonso Garrido, S.H. Goldemberg and I.D. Algranati</i>	187
The study of a polyamine responsive protein kinase in the mouse mammary gland <i>L.J. Leiderman and T. Oka</i>	195
The role of polyamines in restoration of the differentiated phenotype of chondrocytes from de-differentiated cells pretreated with retinoic acid and a tumor promoter <i>M. Takigawa, T. Takano, K. Fukuo, E. Shirai, M. Enomoto and F. Suzuki</i>	207
Prolactin receptor coupling to polyamine biosynthesis in human peripheral blood lymphocytes is selectively inhibited by cyclosporine <i>D.H. Russell, R. Kibler, D.F. Larson, B. Poulos, B.E. Magun and J.G. Copeland</i>	215
Intercellular pH changes and lysosomal swelling induced by high concentrations of extracellular polyamines <i>W.F. Fong and T.T. Loh</i>	227
AMP deaminase reaction as a control system of glycolysis in yeast. Role of polyamines in the stimulation of glycolysis <i>K. Murakami and M. Yoshino</i>	235
Inhibitors of polyamine metabolism and their clinical relevance	
Inhibition of tumor growth and metastasis by a spermidine synthase inhibitor, N-chlorosulfonyl-dicyclohexylamine <i>H. Hibasami, T. Tsukada and K. Nakashima</i>	243

Potential of antitumor activity of α -difluoromethylornithine by interferon and interferon inducers <i>P.S. Sunkara</i>	251
Polyamine antimetabolites as antiproliferative agents: the urgent need for combinations <i>J. Jänne, L. Alhonen-Hongisto, P. Seppänen, A. Kallio, K. Kontula and O.A. Jänne</i>	263
Novel combined anti-tumor therapy with polyamine biosynthetic inhibitors and mitomycin C <i>R.D. Shrestha, S. Fujimoto, K. Igarashi and K. Okui</i>	277
Antitumor effect of α -difluoromethyl ornithine (DFMO) and ornithine decarboxylase activity in a human tumor transplanted into nude mice <i>H. Takami, S. Umemoto, S. Kodaira, K. Ishibiki and O. Abe</i>	285
Effect of canavalmine on proliferation and differentiation of murine erythroleukemia cells in culture <i>S. Fujihara, T. Nakashima and Y. Kurogochi</i>	293
Qinghaosu, a potent antimalarial, perturbs polyamine metabolism in human malaria cultures <i>J. Whaun, N. Brown, W. Milhous, C. Lambros, J. Scovill, A. Lin and D. Klayman</i>	301
Steroid-like anti-inflammatory effects of arcaine and spermidine analogues <i>Y. Öyanagui, J. Hiroi and S. Kishi</i>	311

Application to diagnosis and prognosis

Simple enzymatic assays for diamines and polyamines in human materials <i>T. Matsumoto, T. Furuta, M. Asai, Y. Kurokawa, N. Hayakawa, Y. Nimura and O. Suzuki</i>	319
A routine application of a simple enzymatic assay to urinary total polyamines in cancer research <i>N. Ohsawa, S. Kubota and M. Okada</i>	327
Formation of polyamine oxidases by fungi and application to differential determination of polyamines <i>K. Isobe, Y. Tani and H. Yamada</i>	333
A new enzymatic differential assay for diamines, spermidine and spermine and their clinical correlations with cancer <i>S. Otsuji, Y. Soejima, K. Isobe, H. Yamada, S. Takao and M. Nishi</i>	341
Acetylpolyamines in urine and polyamines in erythrocytes as biochemical markers of cancer <i>T. Nagutsu, K. Shinpo, K. Kawai, M. Shinzato, S. Ito, T. Matsui, K. Nakamura, Y. Kitagawa, M. Hirano, M. Ito and K. Fujita</i>	349
Determination of polyamines in plasma and erythrocytes of digestive cancer patients. <i>T. Furuta, T. Matsumoto, M. Asai, Y. Kurokawa and Y. Nimura</i>	357
Effect of intravenous nutritional therapy on erythrocyte polyamines in tumor-bearing hosts <i>K. Nishioka, V.B. Grossie, Jr., D.M. Ota and D. Patenia</i>	367
Levels of free and acetylated polyamines in human colorectal tumors <i>S. Takenoshita, G. Nakano, H. Kimura, H. Hoshi, H. Shoda, R. Kato, T. Nakamura and S. Matsuzaki</i>	375

Cerebrospinal fluid (CSF) polyamines as markers of meningeal metastasis <i>K. Nishioka, H.Y. Yap, B.S. Yap, H.A. Fritsche, Jr., D. Patenia and W.K.A. Yung</i>	383
A simplified method for the assay of polyamines in cerebrospinal fluid (CSF); CSF polyamines in experimental brain tumors <i>M. Miyazaki, Y. Tanaka, S. Waga and S. Shirakawa</i>	391
Clinical evaluation of urinary polyamine levels as cancer-associated markers in childhood <i>M. Kubo, H. Sakatoku, T. Matsuda, K. Kazuoka, K. Kawai, M. Kawase, H. Kamiya and M. Sakurai</i>	399
Alterations of polyamine in red blood cells, plasma, urine and amniotic fluid during normal human pregnancy <i>Y. Hiramatsu, H. Oomoto, M. Yonezawa, K. Eguchi and K. Sekiba</i>	407
Urinary polyamines in patients with urogenital cancer <i>M. Matsushima, T. Yagishita, M. Kawahara and K. Ando</i>	415
Polyamine excretion as a prognostic marker in chemotherapy (platinum- <i>cis</i> , adriamycin) of uterine cervix carcinoma <i>K. Kamiński</i>	423
Clinical values of urinary polyamines at various therapeutic stages in hematological malignancies <i>H. Nagoshi and M. Shiraishi</i>	431
Studies on the evaluation of polyamine levels in human gastric juice <i>N. Fuchita, M. Kawase, K. Yamanaka, J. Yamanaka and H. Takezawa</i>	439
Experimental studies on the significance of increased putrescine and cadaverine contents in gastric juice and saliva <i>M. Kawase, K. Yamanaka, K. Yamanaka, J. Yamanaka, N. Fuchita, H. Nakao and Y. Kamei</i>	447
Changes in polyamine levels in liver tissues and urine during rat liver carcinogenesis induced by 3'-methyl-4-dimethylaminoazobenzene <i>Y. Kurokawa, T. Matsumoto, T. Furuta, M. Asai and Y. Nimura</i>	455
Dynamics of polyamines in regenerating rat liver after biliary obstruction <i>M. Asai, T. Matsumoto, T. Furuta, Y. Kurokawa, M. Tokoro, Y. Miyazaki, M. Iwase and Y. Nimura</i>	463
Studies on the ornithine decarboxylase and polyamines in experimental intrauterine growth retardation rats <i>M. Yonezawa, Y. Hiramatsu, H. Oomoto, K. Eguchi and K. Sekiba</i>	471
Determination of free and monoacetylated polyamines in biological materials by gas chromatography with nitrogen-selective detection <i>S. Yamamoto, Y. Suemoto, T. Kobayashi, M. Kohta and M. Makita</i>	479
Polyamine stress: nonspecific component of disease? <i>R.A. Campbell and K.E. McGrath</i>	487
Synopsis by <i>U. Bachrach</i>	501
Concluding remarks by <i>F. Suzuki</i>	515
Author index	519
Subject index	521

EVIDENCE THAT AN ELEVATED LEVEL OF ORNITHINE DECARBOXYLASE MAY BE ESSENTIAL TO TUMOR PROMOTION BY PHORBOL ESTERS

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INTRODUCTION

A goal of research in chemical carcinogenesis is to learn the molecular mechanism of the process so that rational, effective procedures to prevent cancer can be developed. One of the useful model systems for studying the mechanisms that are involved in chemical carcinogenesis is the initiation-promotion protocol in mouse skin. Although this model has its unique features and all models for the carcinogenic process are clearly different in certain mechanistic aspects, there is increasing evidence for convergence in the basic mechanistic aspects of various models for studying carcinogenic mechanisms, be they chemical, physical, or viral in nature.

Initiation may be accomplished by the application to the skin of a carcinogenic hydrocarbon in a dose so small that skin tumors rarely if ever develop. No pre-cancerous lesions are an essential consequence of the initiating event (1). Yet irreversible changes have been accomplished in the initiated skin (2) so that twice

weekly applications to the same area of skin of a promoting agent, typically 12-O-tetradecanoylphorbol-13-acetate (TPA) or compounds equally active (3,4), elicit many benign skin tumors. In contrast to initiating agents, treatment with promoting agents at effective dose levels causes precancerous changes in the skin. The first tumors may appear as early as 5 weeks of promotion and by 16 to 20 weeks the number of benign, wart-like tumors may exceed an average of 20 per mouse. The number of benign tumors is dependent on the dose and duration of treatment with the promoting agent but with less of an effect on the appearance of malignant tumors (5). A second mutation-like event (treatment of papilloma-bearing mice with an initiating dose of a carcinogen) appears to be more critical to the development of malignancy (6).

THE BIOCHEMICAL MECHANISM OF PROMOTION IN MOUSE SKIN

The number of biochemical responses that can be measured in the epidermal cell layer following a single application of a promoting dose of TPA are many and are characteristic of a pleiotrophic response. The biochemical/metabolic responses include an increase in the levels of cyclic nucleotides within 2 minutes (7), increases in the levels of certain prostaglandins within 30 minutes (8), increased turnover of phosphatidyl choline (9), and the induction of ornithine decarboxylase (ODC) activity which reaches a peak between 5 and 6 hours (10). The question is, are any or all of these changes an essential part of the mechanism of tumor promotion by TPA?

In this paper, evidence will be summarized demonstrating that the induction of ODC activity and/or increased levels of putrescine or a metabolite thereof is/are essential to the biochemical mechanism of tumor promotion. Evidence for the essential nature of the induction of ODC activity is based on the correlation of the degree of enzyme induction with tumor incidence utilizing three types of studies: 1) changes in dose of TPA (5); 2) the use of congeners of TPA (11); 3) the