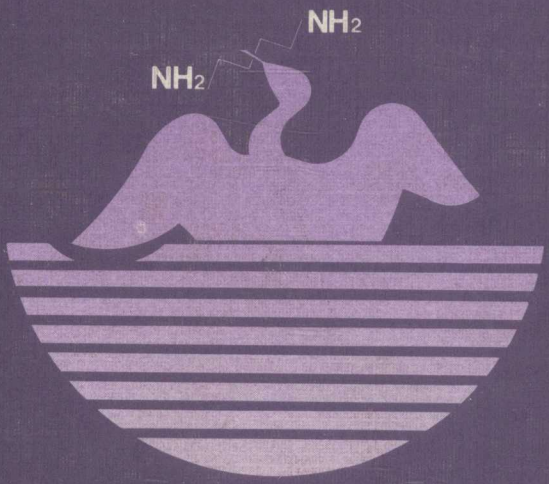
POLYAMINES

BASIC AND CLINICAL ASPECTS



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POLYAMINES: BASIC AND CLINICAL ASPECTS

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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

Application to diagnosis and prognosis

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 precancerous lesions are an essential consequence of the initiating event (1). Yet irreversible changes have been accomplished in the initiated skin (2) so that twice

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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