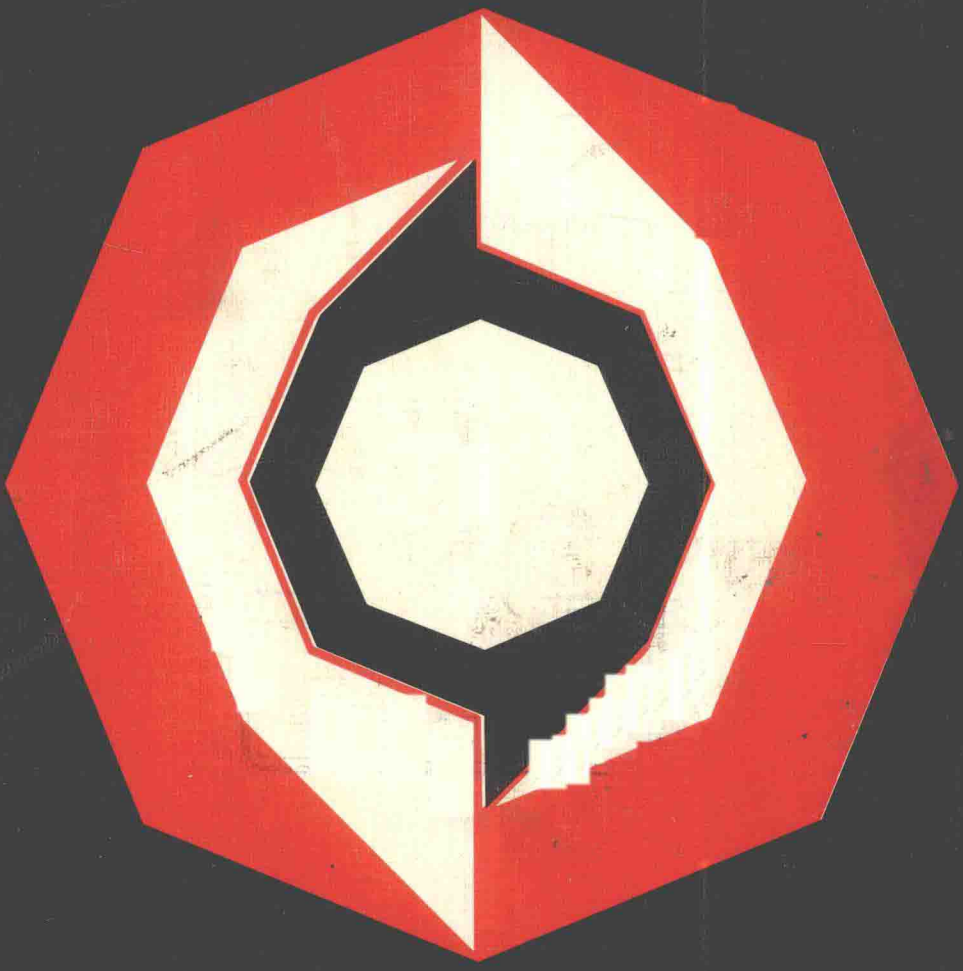
The Organization and Expression of the Mitochondrial Genome

A. M. Kroon and C. Saccone Editors

Developments in Genetics - Volume 2



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THE ORGANIZATION AND EXPRESSION OF THE MITOCHONDRIAL GENOME

Proceedings of the 12th International Bari Conference on the Organization and Expression of the Mitochondrial Genome held in Martina Franca, Italy, 23-28 June, 1980

Editors
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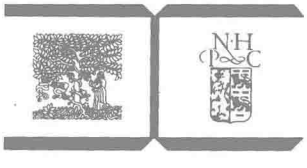
and
C. SACCONE



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DEVELOPMENTS IN GENETICS
Volume 2

Volume 1 Plasmids of Medical, Environmental and Commercial Importance
K.N. Timmis and A. Pühler editors

Volume 2 The Organization and Expression of the Mitochondrial Genome
A.M. Kroon and C. Saccone editors

Symbol design on cover by Gio Pomodoro

INTRODUCTION

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It is not only a great honour, but also a great pleasure for me to introduce this book, holding the proceedings of the International Conference on mitochondrial biogenesis, held in Martina Franca from June 23 to 28, 1980. It was the fifteenth in the series of yearly meetings on aspects of mitochondrial metabolism, function and biogenesis held in Italy and the twelfth held in Bari or its surroundings. It was the fourth conference within this series concentrating on aspects of mitochondrial biogenesis. For younger scientists this probably does not mean too much but the eldest ones, some of them present at the first Bari Conference in 1965, will certainly be able to share my sentiments. In 1965, a Symposium on the Regulation of Metabolic Processes in Mitochondria was organized in Bari by E.C. Slater, J. Tager, S. Papa and myself and the proceedings were published by Elsevier, BBA Library, volume 7. At that time the study of the mitochondrion was in its infancy, and mitochondrial biogenesis considered a curiosity. Only two years later, however, the same organizers thought that it would be very interesting to hold a Round Table Discussion dedicated solely to the problem of the origin of mitochondria. In only two years the progress made in this field was so large as to justify this choice. A book on the "Biochemical Aspects of the Biogenesis of Mitochondria" was produced, containing not only the papers but also the discussions typed simultaneously. After 1967 it became quite clear that mitochondrial biogenesis represented an independent field and in some laboratories, such as my laboratory in Bari and that in Amsterdam, or Münich, just to quote some of them, the groups working on mitochondrial biogenesis split off from those concentrating on other metabolic or biophysical aspects of mitochondrial function.

The "Mitochondrial Biogenesis" after its baptism rapidly began to reach old age. At that time we felt it was necessary to put in appropriate hands the organization of the future Bari Conferences

on mitochondrial biogenesis.

In 1973 A.M. Kroon and C. Saccone organized the International Conference on "The Biogenesis of Mitochondria" in Rosa Marina, and in 1976 that on "The genetic function of mitochondrial DNA" in Riva dei Tessali. The meeting in Martina Franca was their third collaborative effort.

As an observer from outside, but still near to some aspects of this important field, such as that of the transport of proteins across the mitochondrial membranes, I wish to make some short and probably expected comments. Few fields like that of mitochondrial biogenesis have been born by putting together the results of so many disciplines such as Genetics, Biochemistry, Molecular Biology, Electron Microscopy, etc. The boundaries between them, at the beginning well-defined, are now practically erased.

Almost everybody speaks the same language and follows the same philosophy. This, in my opinion, is because mitochondrial biogenesis has, as few other fields, followed the most important progress of modern biology so closely. It has become at once one of the most modern fields of modern biology. The echos of the new discoveries about the genetic organization of mitochondria reach even the ears of the non-experts, giving rise to surprise and admiration. For this reason too I was most happy to witness the opening of the conference. Let me be proud to have been one of the first who has believed in and has supported this field.

It is not by chance that the organizers and the publisher, Elsevier-North Holland Biomedical Press, have chosen again the sign of Giò Pomodoro as the symbol of this conference. A few words of explanation. The symbol represents the mitochondrial genome. The colours, white, red and black are that of the alchemy and of the hermetic iconography. The shape is that of Castel del Monte, the castle of Frederic II which is in Puglia. How opportune that an artist has linked with this symbol our region "Puglia" with the mitochondrial genome!

The Conference of which these are the proceedings was sponsored mainly by the Consiglio Nazionale delle Ricerche (CNR) and also by the University of Bari.

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The Organization and Expression of the Mitochondrial Genome
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THE ORGANIZATION AND EXPRESSION OF THE MITOCHONDRIAL GENOME: INTRODUCTORY REMARKS AND SCOPE

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In the field of mitochondrial biogenesis the boundaries between different disciplines have been gradually dissolved in the course of time. The different topics are tending to fuse together. The present book contains the proceedings of a conference which had as the title: "The Organization and Expression of the Mitochondrial Genome". It was difficult to group the various papers into different sessions. Quite a lot of papers could find an appropriate position in more than one; sometimes in all the sessions. This clearly reflects, in our opinion, how the borders between the various disciplines have disappeared due to the emphasis put on the molecular aspects of biological processes. The proceedings[1] of the Bari Conference, organized in 1976 and entitled "The genetic function of mitochondrial DNA" were dominated by the various aspects of the "physical maps" of the mitochondrial genomes. The good correspondence between genetic and physical maps was one of the best achievements, which certainly encouraged people having different backgrounds to collaborate in common projects. In this book the main leit-motiv will be the base sequence analysis. The majority of problems has been tackled by determining directly the nucleotide sequences which, in turn, revealed a number of unexpected phenomena not only important for the specific field of mitochondrial biogenesis but for Molecular Biology as a whole. The non-universality of the genetic code is one of the best examples. However, sequence analysis is not solving all problems. We still believe that in the field of mitochondrial biogenesis it is important to pursue the study of many other aspects such as the purification of important mitochondrial enzymes, e.g. the DNA and RNA polymerases, or the purification of factors involved in protein synthesis. Assembly of the mitochondrion as well as the nucleo-

cytoplasmic mitochondrial interrelationships are, of course, among the other exciting aspects to consider. Furthermore also the role of the mitochondrial genetic system during development and differentiation requires careful experimental approach. In agreement with these considerations the book is divided into four parts: Mitochondrial gene organization; Mitochondrial gene characterization; Mitochondrial replication, transcription and translation and Developmental and regulatory aspects of mitochondrial biogenesis.

Mitochondrial Gene Organization and Characterization.

The mitochondrial genomes of various organisms, including the kinetoplast DNA of trypanosomes, have been intensively studied during the last five years. The mitochondrial genome of yeast remains one of the favoured model systems in which the genetic approach is still of great importance. In yeast the order of genes is now well known and more and more light is shed on the structure of various genes. It is becoming clear that some genes may have a mosaic structure and some not. An intervening sequence in the large ribosomal gene may be either present or absent. The gene model including AT spacer regions followed by GC clusters, hypothesized several years ago[2], appears to be completely valid. The recent discovery[3] that yeast mosaic genes can code for a maturase protein, an enzyme supposed to be involved in the processing (maturation) of mitochondrial transcripts, is a most exciting observation, which can throw light upon the mechanism of splicing. Detailed information on this point can be found in several contributions in this book. Petite mutants continue to give useful information and still represent a very potent tool in the study of yeast mitochondriogenesis. The petite mitochondrial (mt) DNAs are now used as probes in other systems as well.

The genetic organization of the moulds Neurospora crassa and Aspergillus niger is also well established as far as the ribosomal and transfer RNA genes are concerned. Also here intervening sequences have been observed. Whether some of the genes for the mitochondrially coded polypeptides are mosaic also in these organisms remains to be investigated. Also the order of genes is not yet known for these organisms.

It has been reported that for human mitochondrial DNA the base

sequence is known for 98%[4]. It may be expected that this will be of great help to solve many of the open questions still existing. Especially the establishment of the genetic function of the potential protein-products of so far unidentified reading frames, seems interesting. By the availability of the complete sequence the upper limit of the genetic function of mtDNA is set, the lower or actual limit has to await the characterization of all transcription and translation products. Comparison of the sequences and the latter products from different animals, from plants and from lower eukaryotes may be a firm basis for evolutionary studies. It may perhaps help answering the question whether mitochondria have developed within a cell or that they have evolved from endosymbionts.

Mitochondrial replication, transcription and translation.

The study of mitochondrial transcription is now actively undertaken in many laboratories and for various organisms. Many questions are still open. The role of the two strands of mtDNA during transcription, linked to the presence of double stranded mtRNA often reported in the literature, certainly needs elucidation. It also seems worthwhile to go back to the mechanism of action of the mtRNA polymerase, the characterization of which dates back to the 1973 Bari Conference held in Rosa Marina [5].

Agreement has been reached about the identification of mtDNA polymerase as DNA polymerase γ, at least for the vertebrate cells. The knowledge of these mitochondrial enzymes and of functionally related enzymes such as mitochondrial topisomerases or gyrases is far from complete.

Regarding mitochondrial translation, the possibility that not only a number of mitochondrial proteins synthesized in the cytoplasm and then transported, but also some mitochondrial proteins inside the organelles can be synthesized as precursors, is intriguing. This raises, of course, the problem of the role and fate of the precursors inside the mitochondrion and also in a more general context.

The role and the nature of cytoplasmic factors responsible for the activation of mitochondrial protein synthesis is also of great interest but grossly unknown.

Developmental and Regulatory aspects of Mitochondrial Biogenesis.

Several interesting problems will be treated in this respect in the fourth part of the book. The role of protein transport in the assembly and organization of mitochondria is a very fashionable topic in which great progress has been made recently. The apparent disagreements that existed a year ago seem to be solved. Transport of proteins through the mitochondrial membranes is not one standard process accompanied by proteolytic activity, but may follow various strategies.

The study of further control mechanisms in the interplay of various cell compartments during the process of mitochondrial biogenesis, is now approached from various angles. It may be expected that the combined results obtained with many different organisms, each having its special advantage for tackling part of the problem, may lead to insight into what is now still one of the most fascinating secrets of cell biology.

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MITOCHONDRIAL GENE ORGANIZATION