Gene Families of Collagen and Other Proteins

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GENE FAMILIES OF COLLAGEN AND OTHER PROTEINS

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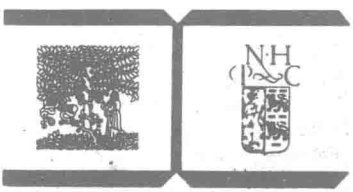

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INTRODUCTION

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The initial impetus for this conference was simple: Several of us who had worked on collagen for some time were convinced that this protein was now a prime target for study using the new technologies of recombinant DNA. There were a variety of reasons for this conviction, including the preeminent status of collagen as the major structural protein of higher organisms, its critical roles in both development and evolution, and the fact that the synthesis of collagen appears to be an intrinsic function of most eukaryotic cells in culture. Among the most important reasons, however, was that within the past few years our information about the chemistry and biochemistry of collagen had reached a high level of sophistication, and we now had a large fund of basic chemical and biological information which could be used as a basis for understanding of the structure and regulation of its genes. The aim for the conference, from the outset, was therefore to create a forum in which leaders in the field of recombinant DNA could effectively interact with collagen biochemists to the mutual benefit of both groups. In considering this aim, it was immediately obvious that the usual format of a scientific meeting---with a series of prepared talks and slide presentations---would not suffice. The range of expertise and technical language was simply too broad. Luckily, a member of the Department of Biochemistry of CMDNJ-Rutgers Medical School, Dr. Bjørn Olsen, had recently attended one of the Dahlem Conferences which Dr. Silke Bernhard has been conducting in West Berlin for several years. Bjørn's enthusiastic account of the conference quickly convinced us that we wanted to employ the format of the Dahlem Conferences. We contacted Silke and were pleased to learn that she was enthusiastic about our carrying out what would be the first trial in the U.S. of the conference format she had developed. Also, we were very pleased that she was willing to serve as a consultant for our own conference.

The format and organization of the Dahlem Conferences have been described elsewhere (1). In essence, it is truly a workshop conference in which about 50 invited participants are asked to work intensively to define the status of current research in a field and suggest future lines of investigation.

There are no formal presentations and no slides are permitted. No more than a third of the participants are investigators who work in the field which is the focus of the discussions; the rest are from related areas. All participants are informed about current research topics relevant to the conference by a series of "Background Papers" which are circulated before the conference. During the conference itself the participants are divided into four groups which, over the course of a week, are asked to develop a paper on a topic which relates to the over-all goal of the conference but which they can largely re-define and explore as they see fit. The discussions are guided by a Moderator and the group report is written by an individual selected as a Rapporteur.

We began developing this format for our conference in the summer of 1979 by selecting a Planning Committee which consisted of Nigel Godson, Brian McCarthy, George Martin, and Sidney Pestka. The seven of us, including Silke, met on a week-end in October. It quickly became apparent that the work of the Planning Committee was crucial in developing the conference and we are very much indebted to its members for providing substance for what up to that point was still only a vague plan of how to proceed. One of the critical ideas adopted by the Planning Committee was the suggestion, made by Brian McCarthy, that we could perhaps capture a broad conceptual framework for the conference if we considered collagen as an example of a "gene family." Another important contribution by the Planning Committee was to select topics for the four Discussion Groups which were broad enough to encompass general concepts yet specific enough to allow a meaningful discussion. A third contribution by the Planning Committee was in selecting the Moderators, Rapporteurs, Authors and members of the four groups. The selection of these oustanding scientists, on the basis of their ability to adapt to the unusual format of the meeting as well as their research achievements, was obviously of over-riding importance.

How successful was the meeting? What were its achievments? In our opinion, the major criterion for answering this question will be how much the meeting influences future research on collagen, related structural proteins, and the genes for these proteins. Therefore the conference should be judged primarily by the usefulness which you, our readers, find in the enclosed Group Reports and Background Papers.

In reviewing these reports we feel that in the aggregate they speak, as well as it is now possible, to the question which expressed the overall goal of the conference: How can we determine the genetic factors regulat-

ing the synthesis, structure and function of collagen and other proteins? At the same time, it was clear from the first day of the meeting that each group developed its own modus operandi and that each defined its task in a manner that reflected both the composition of the group and the specific topic it examined.

Group I, Gene Families and Their Expression, undertook the challenging problem of systematically analyzing the information currently available about genes which, on the basis of common structural or regulatory features, can be considered as members of discrete families. Here they faced a basic question: to what extent can we draw general conclusions about gene families and to what extent must each still be regarded as unique? Their final report, in our opinion, presents an outstanding synthesis of current data on a topic of vast scope and with broad implications for all future research in biology.

Group 2, Genetic Diseases, centered its discussions on the question of how much the new technologies of recombinant DNA have transformed our ability to study genetic diseases in man. In its initial meeting, the members of the group were divided in their opinions in that several felt that many investigators were far too enthusiastic and uncritical about the potential applications of recombinant DNA. Because of the differences in opinion and because the discussion was still unfocused at the end of the first day, a special unscheduled session was held that evening during which the issues were thoroughly and loudly debated. This session proved to be a highly productive one and thereafter the group moved toward the consensus about the appropriate roles of different experimental strategies, as reflected in their report.

Group 3, Post-Translational Modification, systematically examined the post-translational modification of collagen and of other proteins. In the process they developed a series of specific and general questions which are still unanswered and which should serve as an important guide for future research in this area.

Group 4, Structural Molecules, considered a vast amount of biological and chemical data about these proteins. Like Group 1, they were faced with the basic question of how much we can generalize from the data we now have about different systems and how much we must consider each as an isolated example. Their report contains therefore not only a review of our knowledge about fibrous proteins, but also a valiant attempt to resolve a basic tension intrinsic to most biological research——the tension generated by the pressing need to develop general concepts and the ever-present danger of straying

too far from the facts in scientific fields which are still largely experimental and empirical.

Obviously, a number of groups and individuals have greatly contributed to the conferences. The costs of the conference were shared more or less equally by the National Institute of Arthritis, Metabolism and Digestive Diseases, and by the Foundation of the College of Medicine and Dentistry of New Jersey. We are grateful to both of these organizations.

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SOME ASPECTS OF THE BIOLOGY OF THE EXTRACELLULAR MATRIX*

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Much will be written and said at this meeting about the composition and structure of collagen, precursors, types, biosynthetic mechanisms and fibrils. Therefore in this brief attempt at an "overview" I shall not address these items except perfunctorily and in context with other things. I believe that the major important questions lying ahead deal with how tissues with specific and multiple functions are created and organized from cells, macromolecules and supramolecular assemblies. How do the unique tissue architectures, cellular, chemical and structural, relate mechanistically to their function? How are the cells synchronized in their various functions both spacially and temporily in building a tissue or organ? How do they communicate in order to coordinate their activities? How do signals from extracellular macromolecules reach the genetic apparatus and manipulate the regulatory processes?

No doubt the current exciting studies on gene transcription and regulation of collagen synthesis when combined with new knowledge from cell biology will answer the last question fairly soon. This will be a big step forward. However I will try here to discuss briefly some subjects which bear in a selective glancing manner, on the first questions dealing mainly with morphogenesis.

The plan of organization of all multicellular animals consisting of heterogeneous cell populations includes some form of organized solid or semi-solid matrix between the several cell types. This may consist of nothing more than a continuous, (or transiently, discontinuous) basement lamina, although in most instances there is more or less additional matrix material.

The morphology and physical properties of the connective tissues of both vertebrates and invertebrates vary enormously, from the liquid, slightly viscous synovial fluid to the rigid, highly ordered structure of bone. In the cornea and integument of most aquatic animals the organization of fibrils in orthogonal arrays resembling plywood could be considered quasi-crystalline in

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its degree of perfection whereas loose areolar tissues such as those between skin and deep fascia seem nearly random in the arrangement of structural elements. Each of the different connective tissues, i. e. the fascia tightly encasing muscle fibers, the basement laminae between epithelial cells and mesenchymally derived tissues as in skin, liver, the eye, neuromuscular synapses, the highly ordered arrays of dense collagen fibrils in tendon, cornea, ligaments, etc. vary significantly one from the other in terms of the differ ent types of connective tissue macromolecules, their arrangement in structural units, their relative proportions, rates of synthesis and turnover, physiologic function and cell of origin.

EVOLUTION AND DIVERSITY OF FUNCTION

Perhaps the most intriguing early function of the extracellular matrices may have been the development of multicellularity. The earliest animal and plant cells were probably unicellular organisms moving individually and freely in a fluid environment. However, they had to be clustered in groups of relatively high density for survival and perpetuation. Some of these flagelated or ciliated protozoa developed jelly-like extracellular matrices, forming a wide range of coherent colonies of the most varied (and beautiful) forms[1b]. One such organism described in 1880 by W. Saville Kent[1a] called proterospongia (also protospongia) is a particularly instructive model for dreaming about posible ways in which extracellular matrix may have played a significant role in the development of multicellularity. This colonial protozoan consists of individual choanoflagellates held together at the periphery of a transparent gelled mafrix with flagellae facing outwards, giving the entire structure its motility. The gel layer is populated with a second amoeboid, non flagellated cell form (Figure 1).

The proposition that the metazoa evolved from protozoa in the colonial form was proposed and vigorously debated by Metchnikov and later by Saville Kent[1a] in the last century. To elaborate this viewpoint -- let us conjecture that free swimming individual choanoflagellates with the capacity for making a gelled extracellular matrix (of which there are many known examples[1]) and its progeny, coalesced to form a coherent colony embedded in a common extracellular jelly, either by migration or excessive matrix secretion, lost their flagellae and converted to an amoebod form. In fact, Saville Kent observed this phenomonon[1a]. An existant mode for such behavior is represented by that of the well known amoebo-flagellate, Nagleria gruberii, a flagellated protozoan in the free swimming form which loses its flagellum, and rigid pellicle within minutes on