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Reviews

From protein structure and function to molecular pathology

The editors wish to thank E.E. Di Iorio for having coordinated this review.

The section on proteins in Lehninger's well-known textbook of biochemistry begins, 'Almost everything that occurs in the cell involves one or more proteins'. One might add that – at least in animals – the structure and the form of cells and organisms are also dependent on these macromolecules. This review brings together a number of contributions presented at a symposium held on the occasion of the 60th birthday of Kaspar Winterhalter. They cover a wide range of the functions of proteins, from the support and development of structures to the control of metabolism – and, in the case of Gaucher's disease, the disastrous effect on the whole organism of the absence of a protein. Kaspar Winterhalter carried out pioneering work on the structure of hemoglobins, so it is not surprising that a number of speakers discussed oxygen-binding proteins. Ernesto Di Iorio, who organized the symposium, contributes a personal introductory note.

Introductory Note

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My longstanding friendship with Kaspar Winterhalter was what initiated my decision to organize this symposium. The choice of speakers was difficult only because I wanted to put together a programme in which all Kaspar Winterhalter's scientific interests were represented. However, of all the people I initially invited, only two answered negatively because of other commitments. This made the organization very easy. The organization of a symposium of this type is inevitably linked to the risk of forgetting people who should have been invited. I tried to avoid this, but I am sure I did not fully succeed. I wish to express my apologies to those who were not included.

I am highly indebted to all the speakers for the enthusiasm with which they participated, and especially to the three chairmen, Jürgen Engel, Robert W. Noble and Dimitri Loukopulos. The abstracts and short papers which follow do not require any comment from my side. Instead, I think it is important to say a few words about the pleasant atmosphere that characterized the symposium, and the enthusiasm of the many old friends, colleagues and former students of Kaspar's who accepted the invitation. At the very end of the symposium, Max Perutz came up to me and said, 'Ernesto, you wanted an abstract of my talk. Here it is' and handed me a neatly hand-written manuscript. I should like to thank him and all the others who not only contributed to the symposium but promptly sent me their contributions in written form for this publication.

List of contributions

The roles of collagen genes in skeletal development and morphogenesis

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Abstract

Molecular genetic analyses of osteochondrodysplasias in mice and humans have recently led to the identification of mutations in genes encoding structural proteins[1] growth factor receptors[2,3] and sulphate transporters[4]. Further analyses of such inherited disorders, using rapid techniques for gene mapping, positional cloning and mutation detection, will undoubtedly uncover other genes that are important for skeletal development. Together with studies of transgenic mice, in which specific genes that are expressed in the skeleton are mutated, these analyses will provide insight into genes that are essential for skeletal morphogenesis.

A good example of the usefulness of the molecular genetics approach for studies of skeletal morphogenesis, is the identification of the mutation causing autosomal recessive chondrodysplasia (*cho*) in mice[5]. Homozygous *cho/cho* mice have severe defects in the cartilage of limbs, ribs, mandible and trachea[6]. They are born with cleft palate, shortened snouts, protruding tongues, short limbs, and die at birth, probably because of asphyxia as a result of tracheal collapse and/or lung hypoplasia[7]. Previous studies have shown that epiphyseal growth plates in *cho/cho* mutants do not show the normal columnar arrangement of chondrocytes as they go through maturation towards hypertrophy and contain fewer hypertrophic chondrocytes than normal growth plate cartilage[8]. Finally, *cho/cho* cartilage is mechanically abnormal in that it is completely without cohesive strength, and the proteoglycan aggregates are unusually extractable. Thus, the *cho* mutation results in abnormalities both in cellular differentiation, cellular organisation and the mechanical properties of the extracellular matrix.

Since several attempts during the past 20 years to identify that *cho* gene were unsuccessful, we decided to determine the chromosomal locus of the mutation by linkage analysis. The results of such analysis showed the *cho* locus to be on mouse chromosome 3, close to the Amy1, Amy2 locus[5]. The gene encoding the α1(XI) chain of the quantitatively minor fibrillar collagen XI was localised to the same region, thus making *Col11a1* a candidate gene for *cho*.

To test the possibility that the *cho* abnormality could be the result of a mutation in *Col11a1*, polyclonal antibodies against a peptide epitope within α1(XI) collagen were used to examine extracts of wild-type and *cho-cho* cartilage by Western-blotting and for immuno-histochemistry. Wild-type extracts showed, as expected, the presence of α1(XI) collagen while no reaction was seen with *cho/cho* extracts, and wild-type cartilage was positive with the anti-α1(XI) antibodies while *cho-cho* cartilage was not. We concluded therefore that the *cho* mutation leads to loss of α1(XI) collagen in cartilage.

Amplification of α1(XI) cDNA by RT-PCR from normal and *cho/cho* RNA, followed by nucleotide sequenc-