

Hox genes: past, present and future of master regulator genes

Guest Editors

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Preface

Four decades of Hox gene investigation and many more to go

Forty years ago, Ed Lewis established for the first time the organization of homeotic genes along the chromosome and its importance in embryo patterning. To celebrate this seminal discovery, the *International Journal of Developmental Biology* decided to launch a Special Issue. It is with honor, pleasure, but also humility that we accepted the challenge of acting as guest editors for this Special Issue. We entitled the issue *Hox genes: past, present and future of master regulator genes* since despite four decades of amazing discoveries, numerous questions remain unanswered, which open new avenues of research. This is well-acknowledged by Robb Krumlauf and Jacqueline Deschamps in the Introductory articles. The high-level reviews and original research reports collected in this Special Issue also reflect the wide-range and important topics that are still in the spotlights including the origins of *Hox* genes, the regulatory events controlling their expression, the mechanisms driving the action of HOX proteins, and their multiple roles in normal development and pathogenesis.

Origin and regulation

Hox clustered organization is fundamental for the collinear spatial or spatio-temporal regulation and the function of each gene. Forty years after their discovery, the evolutionary and regulatory aspects of *Hox* collinear organization and expression remain the subject of exciting research, as attested by the authors of five papers in this Special Issue (Fig. 1). The evolution of the *Hox* arrangement throughout animal life is reviewed by Gaunt. Gentile and Kmita present an overview of long-range regulatory mechanisms of *Hox* gene expression implying chromatin architecture, insulators and protein complexes, whereas Casaca *et al.*, report the different transcriptional and post-transcriptional layers that control *Hox* expression. An example of the complexity of *Hox* gene regulation is provided by Lalonde and Akimenko, who



explain how conserved and diverging regulatory processes of *Hox* gene expression participate in the fin-to-limb transition during evolution. Lastly, in an original research report, Gaunt proposes a cell culture alternative to progress in the characterization of regulatory sequences in *Hox* genes.

HOX protein characteristics and action

It is well-established that HOX proteins are acting as transcription regulators of the expression of target genes after binding specific DNA

Fig. 1. Authors and coauthors of papers on the origin and regulation of Hox genes.

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Fig. 2. Authors and coauthors of papers on HOX protein characteristics and action.

sequences via their homeodomain. However, their characteristics and the molecular mechanisms involved are still an outstanding question in the field, as tackled by several authors in this Special Issue (Fig. 2). Indeed, the role of HOX proteins appears to be broader and more complex than just transcriptional regulators, as explained by Carneseccchi *et al.* HOX proteins are also modified at the post-translational level, which may impact on their action as reviewed by Draime *et al.* In their research paper, Liu *et al.* present data showing that unlike its DNA-binding homeodomain, the transcriptional activation determinants of the Ubx protein have substantially evolved. Finally, while only a few functional domains have been identified so far in HOX proteins, Rinaldi *et al.* report analyses supporting the presence of multiple Short Linear Motifs (SLiMs) susceptible to define interaction interfaces and functional modules contributing to HOX action.

Biological and pathological functions of HOX proteins and co-factors

Over the last decades, the crucial role of *Hox* genes in developmental processes and the implication of their misregulation in pathogenesis have been clearly established. And yet, despite years of successful studies regarding their functions in development, recent data still uncover new and fascinating aspects of their roles, which is well exemplified by the work of the authors of the following articles (Fig. 3). Gosh and Sagerström revisit the roles of HOX proteins in the developing hindbrain, while Gordon presents a complete description of the function of the *Hoxa3* gene in the formation of the pharynx and associated organs. Holzman *et al.* describe the expression of HOXA5 in somites and lateral plate mesoderm derivatives unveiling potential new roles for this protein in musculoskeletal morphology. In their review, Pérez-Gómez *et al.* update our current understanding of the function of *Hox* genes in digit patterning and spacing, while Gofflot and Lizen discuss new data supporting the multiple and successive involvement of HOX proteins in the assembly of neuronal circuitry, including synapse formation and maturation. As HOX protein activity is also dependent on transcriptional cofactors including those belonging to the Three Amino acid Long Extension (TALE) homeoprotein family, two



Fig. 3. Authors and coauthors of papers on the biological and pathological functions of HOX proteins and co-factors.

papers from Purushotaman and Blasi and from Sicouri *et al.* are devoted to the numerous developmental roles of PREP1. The increasing recognition of the association of *Hox* genes and human pathologies is illustrated in the reviews of Lescroart and Zaffran targeting heart development and diseases and of Collins and Thompson focusing on hematopoiesis. In their research article, Clemenceau *et al.* describe the presence of genetic variants in the *HOXB* cluster that may participate in lung cancer, while Jia *et al.* present a comparative analysis of *HOX* and *TALE* expression in human cancers.

To summarize, despite forty years of intense and productive investigations, the variety of papers collected in this Special Issue demonstrate that many aspects of *Hox* biology still deserve attention and research. As important and fascinating have been these studies so far, there is still place for exciting research in the *Hox* field. The enthusiasm of the authors who contributed to this Special Issue illustrates the great interest of the “*Hox* community” for these new questions and is a promise for many more decades of stimulating discoveries.

Acknowledgments

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Further Related Reading, published previously in the *Int. J. Dev. Biol.*

The significance of Hox gene collinearity

Stephen J. Gaunt

Int. J. Dev. Biol. (2015) 59: 159-170

Hox collinearity - a new perspective

Antony J. Durston, Hans J. Jansen, Paul In der Rieden and Michiel H.W. Hooiveld

Int. J. Dev. Biol. (2011) 55: 899-908

The Hox Complex - an interview with Denis Duboule

Michael K. Richardson

Int. J. Dev. Biol. (2009) 53: 717-723

The evolution and maintenance of Hox gene clusters in vertebrates and the teleost-specific genome duplication

Shigehiro Kuraku and Axel Meyer

Int. J. Dev. Biol. (2009) 53: 765-773

Initiation, establishment and maintenance of Hox gene expression patterns in the mouse

J Deschamps, E van den Akker, S Forlani, W De Graaff, T Oosterveen, B Roelen and J Roelfsema

Int. J. Dev. Biol. (1999) 43: 635-650

5 yr ISI Impact Factor (2016) = 2.421

