Expression of Growth Factors and Their Receptors in Development

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A. Introduction

The discovery and characterization of growth factors and their receptors has led to considerable interest in the roles these molecules play in early development. The relatively recent cloning of cDNAs for many of these molecules has meant that efforts to understand the developmental functions of growth factors need no longer be limited to in vitro studies. Information gained from these analyses can now be weighed in the light of detailed knowledge of their developmental expression. Thus, our aim in writing this review has been to integrate data gleaned from studies of the effects of various growth factors on fetal tissues and cells in vitro with those aimed to analyzing their expression in vivo. The inevitable limitations of space have prompted us to concentrate on the latter.

Development is a complex process in which a single cell, the zygote, grows and differentiates into a multicellular organism. This process is dependent on both genetic and epigenetic influences on the developing embryo. In higher animals, development occurs in utero where the fetal and maternal circulatory systems are linked by a specialized organ, the placenta. Thus, development may not be regulated only by fetal gene products, but may also be influenced by humoral factors derived from maternal tissues and/or placenta. However, it is important to recognize that development does not end with parturition. Most, if not all, tissues and organs continue to develop in postnatal life. Thus our review will emphasize, but will not be restricted to, the role of growth factors during embryonic and fetal development.

A number of themes will hopefully emerge from what follows. An important one is that growth factors should not be thought of simply as "mitogens." Many growth factors have both growth-promoting and growth-inhibiting activities, depending on the biological context. In addition, growth factors can influence the differentiation of animal cells in culture, and there is increasing evidence from studies of lower animals that growth factors (or growth factor-related molecules) can act as inductive signals in early differentiation events. Examples include the findings that: (a) segregation of products to the animal and vegetal poles is essential for normal polarization of the embryo, and a transforming growth factor (TGF-β)-related molecule, Vg-1, is one of the products localized to the amphibian vegetal pole (Weeks and Melton 1987); (b) two mammalian growth factors, fibroblast growth factor
(FGF) and embryonal carcinoma-derived growth factor, will mimic amphibian mesoderm induction signals (SLACK et al. 1987); (c) the Notch locus, expression of which is essential for neurulation of the Drosophila embryo, encodes a molecule related to the epidermal growth factor (EGF) precursor (WHARTON et al. 1985); and (d) expression of lin-12, which also encodes an EGF-related molecule, is required for normal cell fate switching in the development of the nematode reproductive system (GREENWALD 1985). Thus, the classical definition of "growth factor" may be too narrow, and this confounds attempts to interpret function simply based on the location and ontogeny of expression.

A second major theme relates to the distinction that growth factors, unlike the classical endocrine hormones, are produced by a wide range of separate and anatomically distinct cell types. Furthermore, many of these same cells also produce the appropriate receptor. This has given rise to the notion that growth factors are not limited to endocrine actions, but can also act through paracrine and autocrine mechanisms (SPORN and TODARO 1980). Indeed, given the potency of growth factors and the ubiquitous distribution of many of the growth factor receptors, it seems likely that mechanisms must exist whereby the actions of these molecules can be highly localized – for example, during development when inductive signals are passed between relatively small numbers of cells. Hence, it may be significant that a number of growth factors including all members of the EGF family, CSF-1, and possibly a developmental form of the platelet-derived growth factor (PDGF) A-chain are synthesized as integral membrane precursors. Assuming that these membrane-anchored "precursors" are biologically active (see the discussion of TGF-α below), this might provide a form of cell-cell interaction in which paracrine actions are limited to contiguous cells. It should also be considered that the biological activities of these larger, transmembrane molecules may differ from those of the smaller secreted growth factors.

We are, undoubtedly, entering an exciting period in terms of efforts to understand the role of growth factors in development. The realization that analogous molecules are expressed during the development of lower eukaryotes allows for greater manipulation, including the use of genetics. In addition, a number of new and improving technologies hold great promise. For example, polymerase chain reaction (PCR) amplification now allows the detection of specific transcripts in single cells, and this has already been applied to the study of growth factor expression in preimplantation embryos (RAPPOLEE et al. 1988). Methodologies for localizing growth factor expression in embryos by in situ hybridization and immunocytochemistry are improving, and the ability to study in transgenic animals expression of heterologous genes which have been divorced from their normal regulatory elements may provide new insights. Finally, a new approach on the horizon, namely that of inactivating genes through homologous recombination, may ultimately provide a powerful quasigenetic means by which to address the function of growth factors in development.