# Growth Factors and Their Receptors:

## Genetic Control and Rational Application

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## Genetic Control and Rational Application

Proceedings of an Abbott-Cetus-Genentech-Smith, Kline, & French-UCLA Symposium
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The table of contents does not necessarily follow the pattern of the plenary sessions. Instead, it reflects the thrust of the meeting as it evolved from the combination of plenary sessions, poster sessions, and workshops, culminating in the final collection of invited papers, submitted papers, and workshop summaries. The order in which articles appear in this volume does not follow the order of citation in the table of contents. Many of the articles in this volume were published in the Journal of Cellular Biochemistry, and they are reprinted here. These articles appear in the order in which they were accepted for publication and then published in the Journal. They are followed by papers which were submitted solely for publication in the proceedings.

# Preface

The UCLA Symposium on *Growth Factors and Their Receptors: Genetic Control and Rational Application* brought together a diverse array of scientists who presented many exciting new findings on growth factors and their receptors. The outcome was a gamut of chemical, biological, and clinical studies that melded together to create a stimulating meeting on the mechanisms of tissue and cellular growth control. The conference began with a keynote address that set the stage for the week with a thoughtful and provocative discussion of the complexity of the signals controlling cell proliferation and differentiation, and the multistep nature of carcinogenesis. With regard to the latter issue, oncogenes such as *ras* cause the initial loss of growth control associated with carcinogenesis but rarely induce a complete oncogenic phenotype. This was illustrated by the properties of v-*ras*-transformed keratinocytes, which, although tumorigenic by themselves, do not form tumors when inoculated together with dermal fibroblasts. However, if the v-*ras*-transformed keratinocytes acquire another oncogenic perturbation (e.g., a v-*myc* gene), they form tumors even when mixed with the "suppressor" dermal fibroblasts.

As the signals for controlling the growth and differentiation of cells are being identified, it is becoming clear that tissue homeostasis is an extremely complex process. The four presentations on the structure of the receptor for platelet-derived growth factor (PDGF) illustrated some of the difficulties we are facing. Since the initial description of the structure for the PDGF A-B heterodimer, which is composed of one A and one B chain, two homodimer forms of PDGF (A-A and B-B) have been identified. Recombinant forms of all three PDGF dimers have been prepared, and from receptor binding studies with these forms it appears that there are two PDGF receptors which have different affinities for each dimer. The two types of PDGF receptor may be displayed on the same cell (e.g., osteosarcoma cells) or separately, as in some uterine cells.

The critical structural determinants for several growth factor receptor interactions were presented in both poster and symposium sessions. Using chimeric human and chicken epidermal growth factor (EGF) receptors, it is possible to define a region between the cysteine-rich domains as the ligand-binding site on the EGF receptor. Interestingly, human transforming growth factor $\alpha$ (hTGF$\alpha$) binds tightly to the chicken EGF receptor, whereas hEGF binds only weakly, suggesting that the so-

called EGF receptor may really be the TGFα receptor. Studies analyzing the effects of site-directed mutation on the functions of growth factor receptors with protein-tyrosine kinase activity were reported. There is general agreement that protein-tyrosine kinase activity is intimately involved in the process of ligand-induced downregulation of receptors and is absolutely required for mitogenic activity. However, a mutant of the PDGF receptor from which the long insert in the middle of the protein kinase domain has been eliminated is not able to sustain a mitogenic response, even though it retains PDGF-stimulated protein-tyrosine kinase activity and can induce many of the characteristic early growth factor mediated events such as phosphatidylinositol turnover. This implies that protein-tyrosine kinase activity is necessary but not sufficient for mitogenic signalling by the PDGF receptor.

Another important theme was that many growth factor molecules appear to be designed for multiple interactions. For example, the activity of acidic fibroblast growth factor (FGF) is stimulated more than a hundredfold by heparin sulphate to which it binds. This heparin dependence can be overcome by specific structural mutations in acidic FGF. It is clear that the interaction between growth factors and the extracellular matrix elements must be considered if we are to understand the action of growth factors in tissues.

The presentations on the cellular responses to growth factors emphasized the complexity of cytoplasmic biochemistry and emphasized the need for caution in attempts to probe the relevant events triggered (or sustained) by growth factors. There were several examples of indirect stimulation of proliferation where a "mitogen" such as IL-1 is capable of inducing the production of an array of growth factors (G-CSF, GM-CSF, and IL-6). These secondary signals my be responsible for the proliferative and differentiative responses to the primary agent (e.g., IL-1) on bone marrow progenitor cells. Similarly, one of the PDGF-inducible gene products (KC) is identical to a potent melanoma growth-stimulating activity (MGSA) capable of inducing autocrine proliferation of melanoma cells. The expression of the same protein has also been associated with the transformed phenotype of some cells. Indeed, although many of the new gene products detected after growth factor stimulation will be needed for the induction of DNA synthesis and/or division, it appears that a significant number will be connected with intercellular signalling.

The candidate molecules on the critical pathways for mitogenic signalling continue to multiply. However, the substrates for growth factor receptor and intracellular protein-tyrosine kinases still proved a strong focus of attention for scientists investigating the growth factor stimulated cascades leading to mitosis. Protein kinase C, phospholipase C, and the adenylate cyclase enzyme systems all act in close juxtaposition to the cell membrane. The interaction of the type I phosphatidylinositol kinase with the polyoma virus middle T antigen/pp60$^{c\text{-}src}$ complex, pp60$^{v\text{-}src}$, and the PDGF receptor revealed a new phosphatidylinositol product (phosphatidylinositol-1, 3-diphosphate) that could provide a novel mitogenic-signalling pathway. Bombesin and PDGF are capable of both stimulating protein kinase C and activating adenylate cyclase. To what extent either or both of these events are involved in mitogenesis is

still not understood. The activation of secondary protein kinases by the primary signalling protein kinases was well documented, and the idea that there are protein kinase cascades involved in signal amplification and arborization is rapidly being converted from fantasy into fact.

Growth factors induce rapid changes in the transcription rates for a number of genes associated with proliferation and differentiation. For instance, transcription of the c-*fos* and c-*myc* genes is induced by mitogen treatment of many cell types. Several new members of this "immediate early" family of genes were described. These genes fall into two classes. As discussed above, some of these genes encode secreted proteins that may be growth factors. In the other category are genes encoding nuclear proteins, such as c-*myc* and c-*fos*, which appear to be general transcriptional activators. Two new members of this family, *jun*B and a protein with three predicted "zinc fingers," seem likely to be sequence-specific transcription factors. Presumably these nuclear proteins are themselves involved in regulating expression of a secondary set of genes needed for progression through $G_1$ into S phase. Evidence was presented that this is the case for the c-*fos* protein.

The role of growth factors in tumorigenesis and/or normal cell production is not yet defined in detail. However, it is now known that most of the growth factors characterized by their ability to stimulate cells in culture also have potent effects on cell differentiation and proliferation in vivo. The hemopoietic growth factors (HGF) are powerful inducers of the production of a range of white blood cells. The chronic overproduction of one of the HGFs is associated with tissue macrophage infiltration and damage (e.g., in GM-CSF transgenic mice). Promising results of clinical trials with several HGFs were reported, and realization of the therapeutic potential of HGFs may be near at hand. Fibroblast growth factor, EGF, and PDGF appear to be excellent candidate molecules for accelerating the repair of both full-thickness wounds and the religation of nerve axons. Activated macrophages produce a range of growth factors as well as potent biological response modifiers including the HGFs, the interleukins, TGFα, PDGF, and tumor necrosis factor (TNF). Overexpression of these growth factors by endothelial cells and macrophages may be responsible for both rheumatoid arthritis and atherosclerosis.

The enthusiasm and energy of the five hundred conference participants and the opportunity to meet with colleagues investigating a range of peptides and proteins initiating cell proliferation or accelerating differentiation made for an exciting week for all of us. The joint sessions with the concurrent meeting on growth inhibitors provided a reminder that growth control not only requires stimulatory molecules but also inhibitory molecules. As the scientific organizers, we found the conference most enjoyable and we would like to thank all involved—session conveners, presenters, and organizers—for making our task so rewarding.

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# Contents

**Contributors** ..... xiii

**Preface**
Tony Burgess, Tony Hunter, and Russell Ross ..... xix

**I. FIBROBLAST GROWTH FACTOR**

**Immunological Study of Acidic Fibroblast Growth Factor (aFGF) Distribution in the Eye**
D. Caruelle, R. Groux-Muscatelli, A. Gaudric, C. Sestier, G. Coscas, J.P. Caruelle, and D. Barritault ..... 95

**Modulation of Mitogenic Activity and Cellular Binding of Basic Fibroblast Growth Factor by Basic Proteins**
M.C. Dauchel, J. Courty, A. Mereau, and D. Barritault ..... 163

**Characterization of Tumors Produced by Signal Peptide-Basic Fibroblast Growth Factor-Transformed Cells**
Snezna Rogelj, Robert A. Weinberg, Paul Fanning, and Michael Klagsbrun ..... 83

**Structure and Activities of Acidic Fibroblast Growth Factor**
K.A. Thomas, J. DiSalvo, S. Ortega, G. Conn, M.-T. Schaeffer, G. Gimenez-Gallego, D. Soderman, T. Mellin, B. Busch, J. Capparella, J. Menke, L. Kelly, and D. Linemeyer ..... 253

**II. RECEPTORS**

**Forces Involved in Epidermal Growth Factor Receptor Binding**
Kevin H. Mayo ..... 283

**Biochemical Evidence for Multiple Classes of Platelet-Derived Growth Factor Receptor**
Charles E. Hart, John W. Forstrom, James D. Kelly, Robert A. Smith, Russell Ross, Mark J. Murray, and Daniel F. Bowen-Pope ..... 297

**Cell Type and Tissue Distribution of the Fibroblast Growth Factor Receptor**
Bradley B. Olwin and Stephen D. Hauschka ..... 195

**Colony-Stimulating Factor-1 Receptor (c-*fms*)**
Charles J. Sherr, Martine F. Roussel, and Carl W. Rettenmier ..... 29

**Characterization of a Bombesin Receptor on Swiss Mouse 3T3 Cells by Affinity Cross-Linking**
James Sinnett-Smith, Ian Zachary, and Enrique Rozengurt ..... 57

**Retroviruses Expressing Different Levels of the Normal Epidermal Growth Factor Receptor: Biological Properties and New Bioassay**
Thierry J. Velu, Laura Beguinot, William C. Vass, Ke Zhang, Ira Pastan, and Douglas R. Lowy. . . . . 131

**Epidermal Growth Factor-Stimulated DNA Synthesis Requires an Influx of Extracellular Calcium**
Timothy D. Hill, Henrik Kindmark, and Alton L. Boynton. . . . . 21

**Ligand-Induced Association of Epidermal Growth Factor Receptor to the Cytoskeleton of A431 Cells**
P.M.P. van Bergen en Henegouwen, L.H.K. Defize, J. de Kroon, H. van Damme, A.J. Verkleij, and J. Boonstra. . . . . 207

III. SIGNALLING

**Cascade of Autophosphorylation in the β-Subunit of the Insulin Receptor**
Morris F. White and C. Ronald Kahn. . . . . 181

**Evidence for Autocrine Activation of a Tyrosine Kinase in a Human Gastric Carcinoma Cell Line**
Silvia Giordano, Maria Flavia Di Renzo, Radha P. Narsimhan, Luca Tamagnone, Elena V. Gerbaudo, Loredana Chiadó-Piat, and Paolo M. Comoglio. . . . . 49

**Identification of Tyrosine-Phosphorylated Colony-Stimulating Factor 1 (CSF-1) Receptor and a 56 Kilodalton Protein Phosphorylated in Intact Human Cells in Response to CSF-1**
Richard D. Huhn, Mary Elizabeth Cicione, and A. Raymond Frackelton, Jr. . . . . 107

**Effects of Platelet-Derived Growth Factor and Fibroblast Growth Factor on Free Intracellular Calcium and Mitogenesis**
Robert W. Tucker, David T. Chang, and Kimberly Meade-Cobun. . . . . 117

IV. HEMATOPOIETIC GROWTH FACTORS

**Clinical Applications of Hematopoietic Growth Factors**
David G. Nathan and Colin A. Sieff. . . . . 259

**Aberrant Expression of a Murine Hematopoietic Growth Factor (Granulocyte Macrophage Colony Stimulating Factor) in Transgenic Mice**
Ashley R. Dunn, Richard A. Lang, R. Andrew Cuthbertson, and Donald Metcalf. . 219

**Recombinant Human Granulocyte-Colony Stimulating Factor and Recombinant Human Macrophage-Colony Stimulating Factor Synergize In Vivo to Enhance Proliferation of Granulocyte-Macrophage, Erythroid, and Multipotential Progenitor Cells in Mice**
Hal E. Broxmeyer, Douglas E. Williams, Scott Cooper, Giao Hangoc, and Peter Ralph. . . . . 11

**Transforming Growth Factor β: Possible Roles in the Regulation of Normal and Leukemic Hematopoietic Cell Growth**
Jonathan R. Keller, Garwin K. Sing, Larry R. Ellingsworth, and Francis W. Ruscetti. . . . . 153

**Mechanisms in Interleukin-3 Dependent Growth of Factor-Dependent Myeloid Leukemia Cell Lines**
Robert J. Isfort, Robert Abraham, W. Stratford May, Don A. Stevens, A. Raymond Frackelton, Jr., and James N. Ihle. . . . . 229

## V. STUDIES OF mRNA IN CELLS

**Novel Method for Studying mRNA Phenotypes in Single or Small Numbers of Cells**
Daniel A. Rappolee, Alice Wang, David Mark, and Zena Werb. . . . . 71

**Structure and Expression of *lck* Transcripts in Human Lymphoid Cells**
Roger M. Perlmutter, Jamey D. Marth, David B. Lewis, Richard Peet, Steven F. Ziegler, and Christopher B. Wilson. . . . . 1

**Cyclin mRNA and Protein Expression in Recombinant Interleukin 2-Stimulated Cloned Murine T Lymphocytes**
P.M. Shipman, D.E. Sabath, A.H. Fischer, P.G. Comber, K. Sullivan, E.M. Tan, and M.B. Prystowsky. . . . . 39

**Overexpression of the c-*erb*B-2 Protein in Human Breast Tumor Cell Lines**
Nancy E. Hynes, Heinz A. Gerber, Suzanne Saurer, and Bernd Groner. . . . . 145

**Growth Factor Modulation of Melanoma Growth Stimulatory Activity mRNA Expression in Human Malignant Melanoma Cells Correlates With Cell Growth**
R. Bordoni, G. Thomas, and A. Richmond. . . . . 173

**Nuclear Factor Binding Sites and Requirements for Initiation and Attenuation of Murine c-*myc* Transcription**
Claude Asselin, Alain Nepveu, Jian-Qing Yang, and Kenneth B. Marcu. . . . . 239

**Growth, Differentiation, and Neoplastic Transformation of Human Bronchial Epithelial Cells**
Curtis C. Harris, Brenda Gerwin, Yang Ke, Tohru Masui, Masao Miyashita, Andrea Pfeifer, Roger Reddel, Vincent L. Wilson, and John F. Lechner. . . . . 269

**Index**. . . . . 307