CHAPTER 1

The Multifunctional Nature of Peptide Growth Factors

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A. Introduction

It might seem paradoxical, perhaps even capricious and quixotic, to introduce this first comprehensive treatise on peptide growth factors with a statement that in reality there is no such thing as a peptide growth factor. Indeed, this treatise does concern itself with an extremely potent set of regulators of cell growth, all of which are peptides, many newly discovered. However, at the beginning of these two volumes, it is important to emphasize that all the peptides considered here actually are elements of a complex biological signaling language, providing the basis for intercellular communication in multicellular organisms. Thus, the “peptide growth factors” that are the topic of this treatise in reality are peptide signaling molecules. They often promote cell growth, but they also can inhibit it; moreover, they regulate many other critical cellular functions, such as control of differentiation and many other processes that have little to do with growth itself. Like the symbols or alphabet of a language or code, the meaning of the action of these peptide signaling molecules can only be understood in context with other symbols. Thus, all peptide growth factors act in sets, and to understand their actions, one must always consider the biological context in which they act.

Historically, because of interest in a particular problem, investigators have attempted to purify and characterize specific peptides associated with specific biological activities. However, the original context of the discovery of any signaling peptide has seldom indicated the extent of its diverse range of action. Thus, interest in defining a peptide in human urine which suppressed gastric acid secretion ("urogastrone") antedated by many years (for a review, see GREGORY and WILLSHIRE 1975) the identification of this substance as the mitogen presently called "epidermal growth factor" (EGF). By now it is also known that this same molecule has potent antimitogenic activity on hair follicle cells, which has led to it use as a defleecing agent for sheep (PANARETTO et al. 1984). Furthermore, although EGF was originally isolated and purified by its ability to cause premature eruption of incisor teeth in mice (COHEN 1962), it has recently been shown that the teeth of newborn mice treated with EGF are abnormally small (RHODES et al. 1987). Most recently, it has been shown that EGF has direct and immediate contractile effects on isolated arterial tissue, which interestingly may be either agonistic or antagonistic, depending on the context of the other effectors acting on the artery (GAN et al. 1987).
Is EGF a growth factor? Clearly it is a very important one in certain situations, while in others it is not. In all situations, however, EGF acts as a peptide signaling molecule by binding to its own receptor. Thus, the highly specific fit of this peptide ligand with its glycoprotein cell membrane receptor has provided a modular regulatory element that the evolutionary process has repeatedly used in many cell types for diverse purposes. One cannot consider control of epidermal growth without considering EGF, but it is also apparent that the biological actions of this peptide extend far beyond its name.

After the initial identification of any peptide growth factor, better methods for purification, and the availability of recombinant material in particular, have always expedited the investigation of its biological activity. The results have been quite startling: for any single amino acid sequence, new activities, including new target cells, have been repeatedly found. In this regard, almost all peptide growth factors considered in these two volumes are "mis-named", in that their biological activities are now known to extend far beyond the original context of their discovery. Thus, as examples, "platelet-derived" growth factor (PDGF) is made by many cells other than platelets, including smooth muscle cells, endothelial cells, and normal and malignant glial cells; "fibroblast" growth factor (FGF) is made by numerous and diverse cell types and has an exceptionally wide range of target cells; "transforming" growth factor-β (TGF-β) has many actions that bear no relationship to its ability to cause phenotypic transformation of rat kidney fibroblasts; many of the "interleukins" (originally defined as signaling molecules controlling activities of cells within the immune system) have profound effects on nonimmune cells as diverse as keratinocytes, chondrocytes, fibroblasts, mesangial cells of the kidney, neuroblasts, and glial cells; "tumor necrosis" factor-α (TNF-α) is a mediator of many phenomena, such as angiogenesis, having nothing to do with tumor necrosis; and inhibins and activins have now been shown to have many actions which do not pertain to control of secretion of pituitary hormones (see the respective chapters on these peptides).

Even the parent molecule for the development of the entire field of peptide growth factors, namely "nerve" growth factor (NGF) has recently been shown to be multifunctional. Modern studies with peptide growth factors began when it was shown that extracts of tumors and salivary glands promoted neurite outgrowth from cultured nerve ganglia (LEVI-MONTALCINI and HAMBURGER 1953; COHEN 1960). NGF was named for this activity, purified to homogeneity, and then sequenced (ANGELETTI and BRADSHAW 1971). Assay of neurite outgrowth has been the classical method for measuring NGF activity. However, the concept that NGF functions solely as a neurotrophic agent is no longer tenable. New studies have shown that NGF can promote human hematopoietic colony growth and differentiation (MATSUDA et al. 1988), and that mRNA for its receptor or immunohistochemically detectable receptor is present on fibroblasts, lymphocytes, and many other cells of mesenchymal origin, unrelated to neural lineage (ERNFORS et al. 1988; BOTHWELL et al. 1989). The recent finding of NGF mRNA and protein in the testis and