Transforming growth factor β (TGFβ) was first identified as a factor that could induce normal rat kidney (NRK) fibroblasts to form colonies in soft agar in the presence of epidermal growth factor (EGF) (1). Even though TGFβ has the ability to act in this classical assay for transformation, we now know that it is also a mediator of normal cellular physiology and has especially important actions in the processes of embryonic development, tissue remodeling, and wound healing (2). Almost all cells in culture synthesize TGFβ and have TGFβ receptors (3), and immunoreactive TGFβ has been found in a number of embryonic and adult murine tissues (4–5). These data suggest that TGFβ has widespread biological actions. In this chapter we review the chemistry and biology of the TGFβ family, with special emphasis on some of the biological actions of TGFβ that are most likely to be important in the function of the reproductive tract. A brief overview of the actions of TGFβ on gonadal cell types is given here; more details can be found in other chapters of this volume.

TGFβ SUPERFAMILY

Structurally, the active form of the first TGFβ cloned and sequenced (6) is a disulfide-linked homodimer with a molecular weight of 25 kD in the unreduced form. Each monomer consists of 112 amino acids. This TGFβ (TGFβ₁) is synthesized as a 390-amino acid precursor, of which the mature peptide comprises the carboxyl terminal sequence. In the past few years, four additional TGFβs have been cloned: TGFβ₂ was cloned from simian, human, and chicken libraries (7–9); TGFβ₃, from human, pig, mouse, and chicken libraries (10–13); TGFβ₄, from a chicken chondrocyte library (14); and TGFβ₅, from a frog ooocyte library (15). All TGFβs have been purified with the exception of TGFβ₄. The TGFβ monomers are all 70%–80%
identical, and there is complete conservation of the 9 cysteine residues in each TGFβ monomer. As with TGFβ1, each monomer is 112–114-amino acids long and occupies the carboxyl terminal sequence of its precursor. The proregions of the TGFβ precursors are less highly conserved between isoforms than are the mature regions. The sequences for each of the mature TGFβ isoforms are 98%–100% conserved between species; this high degree of conservation between species suggests that the TGFβs have important biological roles.

TGFβs 1, 2, 3, and 5 crossreact with the same receptor system, and in many in vitro assays, such as induction of growth of NRK cells in soft agar and inhibition of epithelial cell growth, they behave identically (16–17). Some differences in activity are beginning to be found: TGFβ1 is much more potent in inhibiting the growth of endothelial cells than is TGFβ2 (18), while TGFβ3 is most active in assays measuring mesoderm induction in amphibians (16). In vivo, there appears to be selective expression of TGFβ isoforms. For example, mouse, chick, and frog embryos express predominantly TGFβ1, 3, and 5, respectively. The TGFβ isoforms also seem to be regulated differently: Primary keratinocytes treated with retinoic acid selectively increase expression of TGFβ2 with little change in expression of TGFβ1 (19). Areas of active investigation are the significance of the expression of several TGFβ isoforms in a tissue, along with discerning the in vivo actions of different TGFβ isoforms, and the control of expression of each isoform.

In addition to five distinct TGFβs, there are now many peptides that belong to the TGFβ supergene family by virtue of their 30% to 40% amino acid homologies to the TGFβs and conservation of 7 of the 9 cysteine residues of TGFβ. The peptides are encoded as larger precursors, and the family resemblance is limited to the C-terminus of the larger precursor corresponding to the processed mature TGFβ. The C-terminus of each peptide ends in the sequence Cys-X-Cys-X. These peptides and their biological activities are listed in Table 1.

**TGFβs IN EMBRYOGENESIS**

A common feature of the biology of the peptides listed in Table 1 is their ability to regulate developmental processes. TGFβs themselves seem to play a role in development. In amphibians TGFβ3 is able to induce the formation of mesoderm from ectoderm in vitro (16), while TGFβ1 augments the ability of fibroblast growth factor (FGF) to induce mesoderm (27). Immunoreactive TGFβ5 has been localized to ectoderm and mesoderm in *Xenopus* embryos through the neurula stage (K. Flanders, unpublished). TGFβs are also present throughout development of the mouse embryo. TGFβ1 mRNA and protein appear after fertilization (28) and continue to be expressed throughout embryogenesis (4, 29). In mouse embryos of 11–18 days' gestation, TGFβ1 protein is often localized to areas of critical epithelial-mesenchymal interactions (4), as in the mesenchyme of the developing hair follicles, teeth, and submandibular gland. Regions of tissue remodeling, such as in mesenchyme underlying developing digits, heart valves, and palate, are also intensely stained.

TGFβ1 is also expressed both spatially and temporally in the developing embryo. For example, the pattern of TGFβ staining in the developing somites dem-