The mammalian uterus undergoes significant growth on a regular basis. For example, in a mouse within an estrous cycle of four days, the number of uterine epithelial cells must double within two days and return to normal levels in the next two. This process is repeated throughout the reproductive lifetime of the animal, which means that the murine uterine epithelium will be reconstituted approximately 90 times in one year. This remarkable growth potential obviously requires numerous controls. A single prime stimulus for initiation of uterine epithelial proliferation is a female sex hormone, estrogen, in the appropriate pharmacological form. Although estrogen is the apparent proximate effector of uterine epithelial cell division, the actual mechanism whereby its mitogenic signal is transduced within the uterine tissue or cell is still not completely known. Certainly, at the molecular level, the estrogen receptor (ER), functioning as a transcription factor, is involved in regulation of expression of specific genes, some of which may be involved in estrogen-induced mitogenesis; these pathways, however, remain to be established. At the same time, results have been presented that raise the possibility that peptide growth factors (or polyfunctional regulating factors) are involved in uterine cell biology.

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Numerous growth factors and their receptors have been reported in mammalian uterine tissue. Their functions in uterine cell biology are largely speculative at present; the same can be said for their relationship to estrogen action. The purpose of this short report is to examine selectively some of the evidence currently available and to describe a framework in which to evaluate it.

Epidermal growth factor (EGF) and its receptor have been reported in uterine tissue and is described in more detail below. Transforming growth factor α (TGFα) has been described in the decidual portion of the rat uterus, but not in the intervening undecidualized tissue (1); moreover, in the same study TGFα mRNA was not found either by Northern analysis or in situ hybridization in uterine tissue before implantation. Both of these peptide factors, EGF and TGFα, are reported mitogens for various cells in culture and apparently share the same receptor (2).

Insulin-like growth factor I (IGF-I) is a polypeptide that shares sequence homology with insulin; it is only weakly mitogenic for cells in culture, although it potentiates the mitogenic effects of EGF (3). IGF-I protein and mRNA have been demonstrated in the rat uterus; IGF-I levels are increased in the uterus following treatment with estradiol, while no change in expression was seen in liver or kidney (4–5). Moreover, receptors for IGF-I were found in the uterus and were also shown to be under estrogen control (6). A function for uterine IGF-I has not yet been described, but the presence of both ligand and receptor raises the possibility for biologic function. This possibility is further supported by the observation that an IGF-I-binding protein is a major secretory product of the decidualized human endometrium (7).

A uterine growth factor for which a function has been proposed is colony-stimulating factor I (CSF-I). The postimplantation murine uterus expresses CSF-I mRNA (8), and the pregnant mouse uterus at term has CSF-I protein concentrations 1000-fold higher than the nonpregnant uterus (9). The fact that, among other considerations, the CSF-I receptor mRNA was first detected in the uterine decidua and, subsequently, in the mature placental trophoblast has led Pollard (10) to suggest that CSF-I plays a role in murine placentation and accumulation of uterine macrophages.

The transforming growth factor βs (TGFβs) are a family of polypeptides with both stimulatory and inhibitory actions on cell division in culture (11). TGFβ1, a member of this family, was localized immunocytochemically in the periglandular connective tissue of the mouse uterus (12). Recently, the localization and timing of TGFβ1 expression in the mouse uterus during the preimplantation stages of pregnancy were determined by immunocytochemistry and in situ and Northern blot hybridization analysis (13). These workers report that the TGFβ1 message was localized in uterine epithelial cells prior to implantation, while at least one form of the peptide was highly localized to the extracellular space around the stroma (especially during early decidualization). The authors conclude that in the early pregnant mouse uterus, TGFβ is a product of the epithelial cell that signals stromal differentiation. This attractive hypothesis awaits further experimental confirmation.