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Regulation of Epithelial Cell Proliferation by Transforming Growth Factors

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The autocrine hypothesis of neoplastic transformation originally stated that transformed cells escaped normal growth restraints by the production of and autostimulation by endogenous growth factors. This hypothesis followed the demonstration by DeLarco and Todaro [1] that murine sarcoma virus-transformed 3T3 cells produced a factor that was capable of reversibly inducing soft agar growth in anchorage-dependent target cells. The factor responsible for stimulating anchorage-independent growth was termed sarcoma growth factor (SGF); SGF preparations were later shown to consist of two separate molecules, transforming growth factors α and β (TGFα and TGFβ) [2]. The hypothesis, therefore, was that TGFs would be found only in malignant cells; however, recent evidence suggests that TGFα and TGFβ play important roles in normal growth and development. TGFα and TGFβ are unrelated molecules whose actions are quite distinct. TGFα is a potent mitogen, while TGFβ is inhibitory for most cells examined. A clear example of the normal growth regulatory roles of TGFα and TGFβ is seen in both human and murine keratinocytes.

TGFα

TGFα was originally purified by Marquardt et al. [3] and is a 5,600-dalton polypeptide that has sequence and significant structural homology to epidermal growth factor (EGF). Sequence data determined that TGFα is synthesized as a 160-amino acid precursor that is processed in a complex manner to yield the active molecule [4, 5]. TGFα binds to the EGF receptor and appears to mediate its biological activity through this interaction. When assayed in cell culture systems, the biological activities of TGFα and EGF are virtually identical. However, some in vivo and organ culture assays indicate quantitative, but not qualitative, differences between TGFα and EGF [6].

TGFα was originally isolated from conditioned medium of virally transformed 3T3 cells [1] and later from the conditioned medium of human carcinoma cells [7].

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TGFα was subsequentiy identified in embryonic tissue [8], suggesting that it might be an embryonic molecule inappropriately expressed in cancer cells. However, Coffey et al. [9] have recently shown that TGFα is present in secondary cultures of normal human keratinocytes that require EGF/TGFα for proliferation. Both neonatal and adult keratinocytes express TGFα mRNA and produce TGFα protein in culture. Interestingly, expression of TGFα mRNA is dependent on the presence of EGF; in fact, both TGFα and EGF induce significant levels of TGFα mRNA. EGF also increased the amount of TGFα protein released into the medium, as determined by an ELISA assay with antibodies specific for TGFα. In addition, evidence for TGFα mRNA and protein in vivo was obtained using in situ hybridization and immunocytochemistry, respectively. Therefore, TGFα production occurs in normal adult epithelial cells that are responsive to TGFα, suggesting the possibility of normal autocrine regulation of cell proliferation.

Results similar to these have been observed in a mouse keratinocyte cell line (BALB/MK), which also requires EGF for proliferation [10, 11]. BALB/MK cells also express TGFα mRNA. Furthermore, TGFα and EGF are equipotent in restimulating DNA synthesis in quiescent BALB/MK cells [12]. As in human keratinocytes, TGFα is induced following stimulation of the BALB/MK cells with either EGF or TGFα [12]. Thus both human and mouse keratinocytes require EGF/TGFα for proliferation, express TGFα message, and demonstrate autoinduction of TGFα mRNA. The results suggest that regulation of TGFα gene expression may be a mechanism of signal amplification for finer control of the proliferative response. Furthermore, if regulation of TGFα expression is lost, then one might expect to observe uncontrolled proliferation. Transfection of a TGFα construct into nontransformed rat fibroblast cells [13] and NIH 3T3 cells [14] did, in fact, result in increased proliferation. In the former case, the transfected cells were tumorigenic, and there was growth in soft agar, which was blocked by a TGFα antibody. The transfected NIH 3T3 cells did not, however, exhibit a transformed phenotype. The precise role of TGFα in neoplasia is uncertain.

TGFβ

TGFβ was identified by its ability to induce soft agar colony formation of mouse embryo-derived fibroblastic AKR-2B cells [15] and by its biological effects in combination with EGF on rat fibroblastic NRK cells [16]. Although TGFβ was originally described as being produced by transformed cells [15,16], it is now known that TGFβ is widely distributed in different tissues [17] and has been purified from cultured cells, placenta [18], bovine kidney [19], and platelets [20]. Platelets, which are the source of TGFβ found in serum [21], are the most abundant source for purification of TGFβ. The intact, active molecule from all sources has a molecular weight of 25 kD and is composed of two identical disulfide-linked subunits of 12.5 kD [22]. The gene for human TGFβ has been cloned and the amino acid sequence deduced from the cDNA sequence [22].

Murine TGFβ has been cloned and is highly homologous to the human sequence, suggesting a high degree of evolutionary conservation [23]. Furthermore, from the sequence data it appears that TGFβ is synthesized as a 390-amino acid inactive precursor that must be processed to yield the 112-amino acid subunit. Because TGFβ is secreted from cells in an inactive form, activation of latent TGFβ may play

a critical role in cellular responsiveness to TGFβ. The physiologic mechanism by which TGFβ is activated is unclear. However, several laboratories have demonstrated that extremes of pH or chaotropic agents activate TGFβ [24–26]. Lyons et al. [26] have recently demonstrated that certain proteases (plasmin and cathepsin D) will activate TGFβ, suggesting a more physiologic mechanism for TGFβ activation.

Related Molecules

Tucker et al. [27] have previously demonstrated that human platelet-derived TGFβ1 is similar to a growth inhibitor originally described by Holley et al. [28] from BSC-1 cells (now called polyergin or TGFβ2 [29]). TGFβ2 has also been purified from several other sources, including porcine platelets [30], human prostatic adenocarcinoma cells [31], and bovine demineralized bone [32]. In addition, a molecule similar to TGFβ2 has been implicated as an immunosuppressive agent produced by glioma cells [33]. TGFβ1 and TGFβ2 apparently have the same biological activities, although some differences between TGFβ1 and TGFβ2 have been observed in hematopoietic stem cells [34] and in mesodermal induction [35]. Furthermore, examination of TGFβ1 and TGFβ2 mRNA expression has suggested that there is generally no qualitative difference in tissue, cell strain, or cell line distribution between TGFβ1 and TGFβ2 mRNAs (unpublished observations). There are other molecules with structural and some sequence homology to TGFβ1 that have been purified or identified by gene cloning and DNA sequencing. These include Müllerian inhibiting substance (MIS) [36], inhibins (and their B chain dimers, activins) [37], the *Drosophila* decapentaplegic gene complex (DPP-C) [38], and the Xenopus Vg-1 gene [39].

TGFβ Receptors

TGFβ has its own specific cell surface receptors, which, like the TGFβ molecule itself, are ubiquitous. TGFβ receptors are present in both normal and transformed fibroblastic, epithelial, or lymphoid cells of human, rat, or mouse origin [40–42]. Generally, there are from 1×10^3 to 1×10^4 specific TGFβ receptors/cell with affinity constants within the 1–60 pM range. Three structurally distinct, glycoslyated cell surface TGFβ binding proteins presumed to be receptors have been identified by affinity crosslinking: these have been classified as type I (60–70 kD), type II (85–95 kD), and type III (280–330 kD) receptors [43]. Type III receptors, which form a disulfide-linked complex of 560–600 kD, are the predominant form of the receptor in most mammalian and avian fibroblasts and epithelial cells. However, there are cell lines, such as myoblasts, that do not contain type III receptors. Furthermore, the EGF/TGFα paradigm does not exist for TGFβ and related molecules; MIS and the activins/inhibins do not bind any of the three TGFβ receptor types [43]. In contrast, TGFβ2 apparently binds to the same receptors as TGFβ1 [27,30], although TGFβ2 has an apparently lower affinity for type I and type II receptors when compared with TGFβ1.

Type III receptors may mediate several TGFβ-regulated events, such as induction of matrix components and inhibition of epithelial proliferation and adipogenic differentiation [43]. Several compounds have been shown to alter the cellular responsiveness to TGFβ [40]; however, none of these agents affected TGFβ binding, and it was suggested that modulation of TGFβ receptors in these examples may not be an important control point in regulating TGFβ action. Further, TGFβ receptors differ

from other known growth factor receptors in that no tyrosine kinase or enzymatic activity has been detected. In addition, the signal transduction mechanism for the TGFβ receptor is not yet known [43].

Stimulatory Effects

The biological effects of TGFβ are highly diverse, depending both on cell type and culture conditions [44]. TGFβ stimulates morphologic transformation and induces latent stimulation of DNA synthesis in anchorage-dependent fibroblastic cells in culture [45]. The mitogenic effect of TGFβ on monolayer cultures of AKR-2B cells has been suggested to be the indirect result of induction of c-*sis* mRNA and autocrine stimulation by endogenous platelet-derived growth factor-like protein production [46]. Also, TGFβ may stimulate anchorage independent growth through secondary effects on induction of fibronectin synthesis and release [47]. TGFβ regulates extracellular matrix accumulation by inducing procollagen type I and fibronectin synthesis and by decreasing matrix degradation through simultaneously increasing synthesis of protease inhibitors and by decreasing protease activity [48, 49]. TGFβ is also a potent chemotactic agent for dermal fibroblasts [50]; all of these activities probably contribute to the ability of TGFβ to stimulate connective tissue formation in vivo and to enhance wound healing [51] and may contribute to stroma formation in tumors.

Role in Development

TGFβs may play an important role in development. For example, TGFβ1 treatment of human bronchial epithelial cells [52], rabbit tracheal cells [53], rat intestinal crypt cells [54], and rat osteosarcoma cells [55] induces the differentiated phenotype. In addition, TGFβ-like activity has been demonstrated in 17-day mouse embryo extracts [56]. Furthermore, two TGFβ-like molecules, MIS and DPP-C, have been implicated in the embryologic development of the male reproductive system of mammals and in dorsal-ventral patterning in the *Drosophila* embryo, respectively [36,38]. In addition, Seyedin et al. and Ellingsworth and coworkers [57, 58] have shown that TGFβ1 is identical to cartilage-inducing factor-A, implicating a role for TGFβ in chondrogenesis. Homology between TGFβ1 and Vg1, a *Xenopus* vegetal pole mRNA thought to be involved in induction of mesoderm, has also been demonstrated [39]. Furthermore, while TGFβ1 synergizes with fibroblast growth factor in *Xenopus* mesodermal induction [59], Rosa et al. [35] have suggested that TGFβ2-like factors are important in mesodermal formation. Heine et al. [60] have recently demonstrated, utilizing immunohistochemical methods, that TGFβ1 is present in 8–18-day mouse embryos. TGFβ1 was further localized to tissues of mesenchymal origin or to regions where mesenchymal-epithelial interactions are important. In contrast, TGFβ has been demonstrated to inhibit myogenesis [61], adipogenesis [62], and IL-3-dependent hematopoiesis [34]. Although expression of TGFβ1 during development is intriguing, developmental regulation might also reside with expression of specific TGFβ receptors. For instance, Rizzino [63] has recently reported that TGFβ receptors appear in embryonal carcinomas following induction of differentiation by retinoic acid. The appearance of TGFβ receptors, however, may have been more important in regulating proliferation than differentiation.

Inhibitory Action

In several nontransformed cell systems including human keratinocytes [64], rat hepatocytes [65], myeloid cells [66], rat liver epithelial cells [67], human endothelial

cells [68], and T lymphocytes [69], TGFβ is a potent inhibitor of proliferation. In addition, several carcinoma cell lines are either sensitive [44, 70, 71] or refractory [64, 71] to the inhibitory effects of TGFβ1. As a model system to study the inhibitory role of TGFβ1 on epithelial cell proliferation, we have used the BALB/MK mouse keratinocyte cell line. BALB/MK cells are reversibly growth-arrested by picomolar concentrations of TGFβ1 [12]. In addition, TGFβ1 and TGFβ2 are equipotent in inhibiting BALB/MK DNA synthesis (Fig. 1), consistent with results of Tucker et al. [27] and Like and Massague [72], using CCL-64 mink lung epithelial cells. Furthermore, TGFβ production by human skin keratinocytes has been demonstrated [64], and TGFβ1 and TGFβ2 mRNA expression is observed in both human keratinocytes and BALB/MK cells (unpublished observations). Thus, TGFβ1 and/or TGFβ2 may function as an autocrine inhibitor of keratinocyte proliferation. TGFβ1 does not affect BALB/MK growth by altering EGF:EGF receptor interactions. In some systems, including BALB/MK cells, EGF receptor number and affinity (Fig. 2), internalization of the EGF receptor [12], or phosphorylation of the ribosomal protein S6 [72] are not affected by TGFβ1 treatment. In addition, neither total RNA nor total protein synthesis is affected by TGFβ1 [12], suggesting that inhibition of BALB/MK growth is not a reflection of general cytotoxicity. These data also suggest that selective changes occur in BALB/MK cells following TGFβ1 treatment that results in inhibition of DNA synthesis and cell growth. Coffey et al. [73] have shown that TGFβ1 selectively inhibits c-*myc* and KC gene expression in EGF-restimulated or rapidly growing BALB/MK cells. In contrast, c-*fos* mRNA expression is unaffected, while β-actin mRNA expression is slightiy increased. The inhibiton of c-*myc* by TGFβ1 appears to be at the post-transcriptional level and requires protein synthesis [73]. This mechanism of action appears to be quite different from other growth inhibitors. Tumor necrosis factor inhibits c-*myc* at the transcriptional level and is independent of protein synthesis [74], whereas inhibition of c-*myc* by interferons, depending on the cell system, yielded different results [75, 76]. In addition, TGFβ1 autoinduces expression

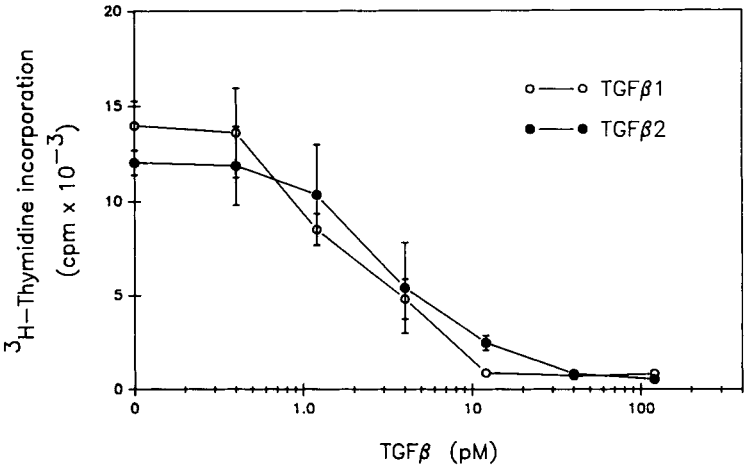

Fig. 1. Dose-dependent inhibition of BALB/MK DNA synthesis by TGFβ1 and TGFβ2. Rapidly growing BALB/MK cells were treated with various concentrations of TGFβ1 or TGFβ2 for 23 hours. At this time, 2.0 μCi/ml of ^{3}H-thymidine was added for 1 hour, and the acid-precipitable counts were determined as previously described [12].

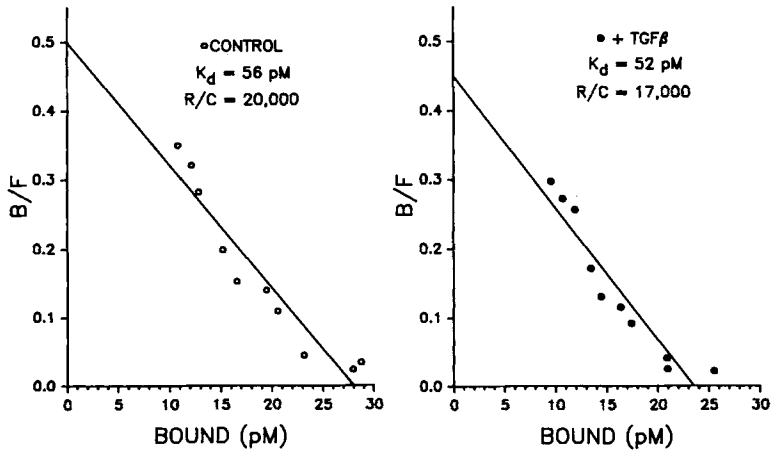

Fig. 2. Scatchard analysis of EGF binding to BALB/MK cells following TGFβ1 treatment. BALB/MK cells were placed in medium without EGF for 24 hours, treated with 10 ng/ml TGFβ1 for 18 hours at 4°C; binding of EGF was then performed as previously described [12].

of TGFβ1 mRNA in rapidly growing BALB/MK cells [77], possibly providing a mechanism for further downregulating the proliferative potential of BALB/MK cells. Therefore neoplastic transformation might be influenced by an inability to autoinduce TGFβl mRNA expression; preliminary results support this hypothesis.

CONCLUSIONS

The data summarized above clearly suggest that TGFα and TGFβs play integral roles in maintaining normal keratinocyte proliferation. Both human and murine keratinocytes produce the same peptides (TGFα and TGFβ), which stimulate or inhibit their growth. It is hypothesized that autocrine regulation of keratinocyte growth is a normal phenomenon involving both growth-stimulatory and growth-inhibitory molecules. The presence of opposing regulatory pathways, therefore allows for a more precise control of cell proliferation than merely having an on/off stimulatory pathway provided for by growth factors. However, TGFα and TGFβs might also play central roles in neoplasia; overexpression of TGFα or a lesion in the TGFβ autocrine inhibitory pathway (i.e., lack of expression, activation, or specific TGFβ receptors) could contribute to neoplastic transformation.

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