Transforming Growth Factor β
Prospects for Cancer Prevention and Treatment

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Summary

Transforming growth factor β (TGFβ) has emerged as a pre-eminently negative growth factor with inhibitory effects on a range of malignant epithelial cell types. There is increasing evidence that the malignant phenotype is associated with an imbalance of growth factors within the local microenvironment of tissues. Oncogenic events promoting neoplastic progression could involve either an excess of positive growth factors or a deficiency of negative ones such as TGFβ. Whether altered levels of TGFβ are directly implicated in processes of carcinogenesis remains unresolved, but local endogenous levels of TGFβ can be manipulated pharmacologically. This may be of relevance to the mode of action of some agents with proven therapeutic efficacy. Thus, boosting of endogenous TGFβ levels could correct any pre-existing or acquired deficiency, or compensate for overproduction of positive stimulatory growth factors resulting from activation of cellular proto-oncogenes. This article reviews the evidence for modulation of TGFβ synthesis and production by several commonly used pharmacological agents, and assesses the clinical potential of this strategy both for the treatment of established tumours and prevention of malignancy.

Many biological processes which involve cellular proliferation and differentiation are dependent on precise and coordinated networks of intercellular communication. A principal form of signalling between cells is via soluble factors, and polypeptide growth factors represent one group of regulatory molecules which have been isolated and characterised from serum and cell tissue extracts.[1] Some of these growth factors are stimulatory, whilst others are actually inhibitory to epithelial proliferation, and this has lead to a conceptual division into positive and negative growth factors.[2] These are produced and secreted locally by many cell types, and target cells possess specific transmembrane receptors to which these growth factors bind and subsequently activate intracellular signal transduction pathways. An extracellular stimulus is thus translated into an intracellular response.

Growth factors can function either in an autocrine capacity, whereby they act upon their cell of origin, or can interact with adjacent cells (of a similar or different type) in a paracrine action (fig. 1).[3] The local microenvironment of a cell contains a pool of positive and negative growth factors, which may be functioning in either an autocrine or paracrine manner. It is the balance of these which determines the polarity and intensity of the effective signal delivered to epithelial cells (fig. 2).[4]

The excessive proliferation of cells which characterises both preneoplastic states as well as established tumours could result from a breakdown of these autocrine and paracrine loops. There may be
Paracr ine Autocrine

Fig. 1. Autocrine and paracrine modes of action for growth factors. Cells produce and secrete soluble growth factors which enter the extracellular space, from where they can act via cognate membrane receptors upon either the same (autocrine) or adjacent (paracrine) cells.

an excess of stimulatory growth factors derived either from epithelial cells themselves or from stromal cells. Conversely, the production of negative growth factors which normally serve to keep cell proliferation in check may be deficient. Breakdown of these loops could also result from an abnormal response of target cells to normal levels of growth factors. There may be a failure of response to negative growth factors or enhanced sensitivity to positive ones, for which altered levels of cognate receptors or levels of nuclear oncogenes (e.g. c-myc) are a possible mechanism.\[5,6]\]

Whatever the mechanistic fault, aberrant function of these growth factor loops will lead to excessive epithelial proliferation and promote immortalisation of cells and in turn neoplastic development.

1. Transforming Growth Factor β (TGFβ)

TGFβ represents a family of multifunctional regulatory peptides which are involved in a range of processes including development, wound healing and carcinogenesis.\[7,8]\] TGFβ exists as 3 mammalian isoforms, each of which are homodimeric peptides composed of 2 peptide chains each of 112 amino acids in length, with a molecular weight of 25kD. TGFβ is synthesised as a latent precursor molecule, in which the mature moiety is noncovalently linked to a precursor pro-region which folds itself around the TGFβ molecule and renders it latent (fig. 3).\[9-11]\] Most TGFβ is secreted in the inactive form,\[10,12]\] and activation occurs followingprocessing and secretion into the extracellular space, where TGFβ may be bound and sequestered by the extracellular matrix.

TGFβ has a great diversity of functions, but in general it is inhibitory to a range of epithelial\[5,13,14]\]

Fig. 2. Cellular growth factors. The local microenvironment of a tumour contains a pool of positive and negative growth factors, both autocrine and paracrine. The balance of these determines the polarity and intensity of the net signal delivered to the epithelial cells.