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Comments and Critique

Growth Factors and Cell Movement

GROWTH FACTORS are cytokines that affect (and often enhance) the growth of target cells. There is extensive evidence, however, that many growth factors are multifunctional agents acting not solely on DNA synthesis and cell division but on a variety of functions ranging from enzyme levels and protein secretion to membrane receptor density [1]. In this article I wish to draw attention to their role in the regulation of cell movement.

The ability of most cells to migrate is essential in many embryogenetic events [2] and in adult life, in processes such as the inflammatory and repair reactions and tissue regeneration. Unscheduled locomotion, on the other hand, is perhaps the most distinctive and harmful feature of the malignant cancer cell as it leads to dissemination of the tumour. Yet, although the signals controlling the locomotion of free cells (such as blood leucocytes) have been known for several years [3], our understanding of the regulation of movement of fixed tissue cells (either fibroblasts or epithelial or endothelial) is very preliminary.

The classic studies of Abercrombie and his colleagues demonstrated that, when cultured *in vitro* in the presence of serum, the solitary fibroblast studied by time lapse videomicroscopy "crawls" on glass or plastic surfaces at a speed of 50–100 μm per hour. If two fibroblasts collide they come to a halt (a phenomenon known as contact inhibition of movement) and then depart away from each other [4]. On surfaces coated with certain substrate adhesion molecules (such as collagen, laminin or fibronectin) fibroblasts are capable of orientation and preferential migration on the surface paved with the extracellular matrix (haptotaxis) [5]. The locomotion of epithelial cells on glass or plastic surfaces is much slower than that of fibroblast cells but when epithelial cells collide they seldom separate again and their movement becomes highly restricted [6]. This is probably due to the formation of tight cell–cell interactions via cell junctional molecules (CJMs) and cell adhesion molecules (CAMs).

Although there are no direct observations of the movement of fixed mesenchymal or epithelial cells *in vivo* (except in embryos), it seems likely that their movement is highly restricted. Yet, both the cells of connective tissues and the epithelial cells of the basal layers are in direct contact with substrate adhesion molecules (SAMs) which promote movement *in vitro*.

The movement of fixed tissue cells may be controlled at two levels (Fig. 1). The first level consists of a signal which instructs the cell to move (or not to move) and converts its phenotype from stationary to motile. The second controls the direction of movement and is provided by the cell–substrate interactions which we have already mentioned. But what are the signals which convert the stationary cell to a motile one? Growth factors provide such signals.

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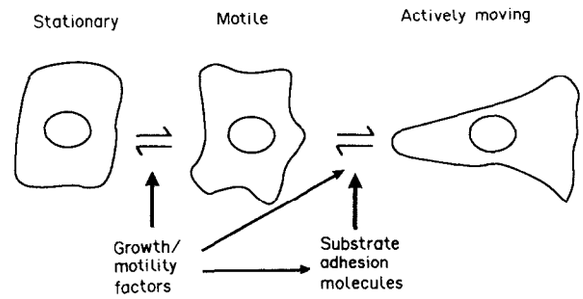

Fig. 1. Schematic view of the steps involved in the regulation of movement of tissue cells (either mesenchymal or epithelial). Growth/motility factors provide the signal which converts the cell from a stationary phenotype to a motile one. The motile cell can then be directed by the growth factor itself (in some instances) or by substrate adhesion molecules. Certain growth factors can also affect matrix synthesis.

In a recent review of the subject we concluded that the majority of the growth factors presently characterised have profound effects on cell motility (as well as growth) of target cells [7]. In most cases growth factors appear to stimulate both growth and movement (i.e. they act concurrently as mitogens and "motogens") [7] but in other cases they inhibit both or inhibit growth alone (Table 1). The interrelation between growth and movement is therefore a complex one and the growth and motility responses to the same factor appear to vary in different target cells. It is remarkable, nevertheless, that so many molecules can apparently initiate cell division and movement (Table 1).

The major morphological changes induced by motogenic cytokines are similar in different target cells and include the rapid appearance of extensive membrane lamellae and ruffles and pseudopodal extensions [7]. These changes are noticeable within minutes (in some cases within seconds) and mark the transition from the stationary to the motile phenotype (Fig. 1). Many growth factors, however, do not just signal the transition from the stationary to the motile phenotype; they also induce net cell movement, either random (chemokinesis) or directed toward the source of the factor (chemotaxis). Some of them—for example transforming growth factor β (TGF-β)—also affect the synthesis of SAMs and thus regulate directional cell movement too.

But are there molecules capable of inducing a motility response in fixed tissue cells without an effect on growth, i.e. simple motogens? Molecules of this kind are known to be involved in the chemotactic response of the simple eukaryote *Dyctiostelium discoideum* (cAMP) or blood leucocytes (formyl-peptides or the complement component C5a) [3, 8]. In recent years at least three protein agents have been isolated and characterised as

Table 1. The complex interrelationship between the growth and motility responses to cytokines

Response	Cytokine	Target cell(s)
Motility stimulation and growth stimulation	PDGF-AA and BB	Mouse 3T3 fibroblasts Human haematopoietic cells Rat O-2A progenitor cells
	TGFβ	Human dermal fibroblasts
	EGF/TGFα	Human keratinocytes
	bFGF	Bovine capillary endothelium
	aFGF	Human skin and fetal bovine fibroblasts Rat astroglial cells Human umbilical vein endothelium Rat bladder carcinoma
	IGF-I	Human melanomas
	PD-ECGF	Bovine aortic endothelium
	G-CSF/GM-CSF	Human endothelium
	bombesin	Small lung carcinomas
Motility stimulation and growth inhibition	TGF-β	Human keratinocytes
	IL-6	Human breast carcinomas
	EGF	Rat intestinal epithelium
	TNF-α	Bovine capillary endothelium
Motility inhibition and growth inhibition	TGF-β	Bovine heart endothelium
	TNF-α	Bovine heart endothelium
	INF-γ	Human keratinocytes

EGF = epidermal growth factor, aFGF = acidic fibroblast growth factor, bFGF = basic fibroblast growth factor, G-CSF = granulocyte colony stimulating factor, GM-CSF = granulocyte–macrophage colony stimulating factor, IFG-I = insulin-like growth factor I, IFN-γ = interferon γ, IL-6 = interleukin 6, PD-ECGF = platelet-derived endothelial cell growth factor, PDGF = platelet-derived growth factor, TGF-β = transforming growth factor β, TNF-α = tumour necrosis factor α.

primary motility factors: scatter factor (a fibroblast-derived cytokine which affects the movement of certain epithelial and endothelial cells) [9–11], autocrine motility factor (AMF), a tumour derived cytokine which affects the movement of producer (as well as certain non-producer cells) [12] and migration stimulating factor (MSF), a cytokine produced by embryo and certain tumour-associated fibroblasts [13]. Whereas both AMF and MSF are capable of autocrine stimulation of movement, the principal mode of action of scatter factor appears to be paracrine, although there is evidence that certain epithelial variants may produce the factor [14]. On the target cells used for their isolation and characterisation, the effects of scatter factor, AMF and MSF are simply motogenic but scatter factor can be motogenic or mitogenic depending on the cell type [7]. Mitogenic activities of AMF and MSF have not yet been reported so it is possible that these two cytokines are simple motogens. Alternatively they may have yet undiscovered mitogenic activity for different target cells as it has appeared to be the case with scatter factor.

The fact that growth factors appear to play a major role in the initiation of cell movement has several implications. It strengthens the *rationale* for the therapeutic use of growth factors in wound repairs. Wound repair involves complex patterns of cell migration in addition to cell proliferation and matrix formation [15]. The ability of certain growth factors, like platelet derived growth factor PDGF, epidermal growth factor (EGF) and TGF-β to promote wound healing has already been reported in several model systems [16] and further developments in this area are likely to follow. For example, both the discovery of new factors and the sequential (or combined) use of factors with different cell specificity could enhance wound healing more effectively than individual growth factors.

The understanding of the role of growth factors in the initiation of cell movement also opens certain possibilities for the control of tumour metastasis. This is known to be a complex multistep process which, in the initial stages, requires tumour cells (i) to adhere to the extracellular matrix, (ii) to degrade the matrix and (iii) to migrate across the tissue [17]. It is conceivable that growth/motility factors may play a role in the third (migratory) stage as suggested by Liotta and colleagues [17] and this would seem even more likely with factors like scatter factor which are produced by stromal cells and are likely to be, at least partially, sequestered in the extracellular matrix. Indeed there is already some evidence that scatter factor may increase the invasiveness of certain carcinoma lines *in vitro* [17].

It is possible, however, that the role of growth-motility factors in the metastatic process is even more fundamental. The cytokine-induced transition from the stationary to the motile phenotype may, itself, induce the changes in the expression of cell adhesion molecules, surface receptors for matrix molecules (such as the laminin receptor), and enzymes involved in the degradation of the extracellular matrix which appear to accompany the metastatic process. To my knowledge there are no direct studies on this point or on the growth, adhesion and invasive properties of tumour lines in which expression of the motility factor had been inhibited (for example by antisense sequences) but this would seem an important area to explore.

If a role for growth-motility factors in tumour metastasis could be clearly demonstrated *in vitro* and *in vivo*, attempts to interfere with their aberrant expression (for example with therapeutic antibodies directed to the factors or their receptors) would be worth investigating and could become a useful step in the control of cancer.

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Possible Applications of Biotechnology to Radiotherapy

INTRODUCTION

MUCH OF the research emphasis in radiation oncology in the USA and Europe has focussed on improving the technical precision of radiotherapy delivery, understanding the effects of fractionation on tumours and normal tissues and strategies to overcome hypoxia as a therapeutic limitation. Detailed mathematical modelling of *in vitro* human tumour cell survival curves and *in vivo* normal tissue effects has been undertaken by some radiobiologists and radiotherapists without sufficient emphasis on potentially important advances in the molecular aspects of radiotherapy. The evolution of this relatively narrow focus is paradoxical since in the previous 20 years radiotherapists/radiobiologists have made seminal discoveries in biology, such as the application of a colony forming assay to study lethality induced by cytotoxins in mammalian cells, the cell cycle specificity of radiation killing, and the repair of sublethal and potentially lethal X-ray damage, to name just a few accomplishments. Thus it seems appropriate to look forward toward the potential applications of molecular biology to radiotherapy.

MOLECULAR BIOLOGY OF RADIORESISTANCE

A fundamental understanding of the molecular basis of radioresistance may be important in identifying genetic and biochemical targets to enhance the lethal effects of X-rays on tumours or reversing these effects in normal tissues. Studies in humans of DNA repair deficient syndromes such as ataxia telangiectasia and xeroderma pigmentosum strongly suggest that the response to physical agents in human cells has a genetic basis [1]. There is an interest in cloning genes that repair DNA damage; however, to date most of the mammalian repair genes cloned and characterised repair alkylating agent or ultraviolet light induced DNA damage [1–3]. Genes likely to be involved in the repair of lethal X-ray damage will probably encode for products that repair DNA double strand breaks. Thompson has pointed out that regulation of radiation repair genes may only explain radioresistance (greater than wild type survival), if the gene products are rate limiting in the biochemical steps of DNA repair [3]. Nonetheless identification of genes important in the repair of lethal X-ray damage presents exciting possibilities such as prediction of radiocurability or potentially manipulation of the radiation response in the clinic. Activation of the oncogenes *ras*, c-*raf* and c-*mos* have been shown in a variety of laboratory settings to confer radioresistance on cells [4–7]. Recently, this effect has been suggested to be the result of abnormal intracellular signal transduction with cell cycle alteration by aberrant oncogene products [8]. Hartwell and Weinert suggest that genetic control mechanisms in the cell cycle called "checkpoints" result in a cessation of cell cycle progression following X-ray and alkylating agent treatment in cells and that this growth arrest allows for repair of mutagen induced DNA damage [9]. These mutagen induced checkpoints may also be responsible for normal distribution of chromosomes or other organelles in a viable mitosis following DNA damage. Thus, combination of checkpoints followed by DNA repair (reminiscent of the potentially lethal damage repair) may be important in the survival of tumours and normal tissues following ionising radiation or other cytotoxic agents. Yeast genetics might be a good starting point to identify genes that control the cell cycle and subsequent survival after X-rays and thus have potential relevance for radiotherapy. The identification of the human homologs of the highly conserved *cdc*-2 and *cdc*-25 genes provide ample evidence of the feasibility and potential importance of this approach [10,11].

GENETIC SUSCEPTIBILITY TO CANCER

Families with a genetic predisposition to malignant tumours may provide important clues as to the genetic events involved in the various stages of carcinogenesis. Hereditary mutations at tumour suppressor loci may confer a highly penetrant predisposition to cancer. For example, patients with hereditary retinoblastoma have a high incidence of radiation induced osteosarcomas as well as spontaneous osteosarcomas distant from the irradiated site. This clinical observation suggested that inactivation of the retinoblastoma tumour suppressor gene may be involved in the aetiology of some osteo- and soft-tissue sarcomas [12, 13]. Recent findings suggest that inheritance of variant p53 alleles is associated with the Li–Fraumeni syndrome. This is a rare familial cancer syndrome characterised by a predisposition to breast carcinoma, soft tissue sarcomas, brain tumours, leukaemia and adrenal cortical carcinoma. Other possible components of the Li–Fraumeni syndrome are: melanoma, gonadal germ cell tumours and carcinoma of the lungs, pancreas and

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