The insulin-like growth factor system as a therapeutic target in colorectal cancer

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Received 15 June 2001; revised 5 October 2001; accepted 23 October 2001

The purpose of this review is to examine recent evidence that investigates the role of the insulin-like growth factor (IGF) system in colorectal cancer. We concentrate on the evidence that makes the case for the investigation of strategies that might be used to disrupt the IGF system in prevention and treatment. Even though the weight of evidence suggests that components of the IGF system may be appropriate targets, there are a lack of studies that make a systematic characterisation of all the system components in human colorectal cancer. It is anticipated that this information, and the new therapeutic molecules which follow, will impact on the prevention and treatment of patients with this disease.

Key words: colorectal cancer, growth factors, insulin-like growth factor-I, insulin-like growth factor-II, insulin-like growth factor-I receptor, insulin-like growth factor-II receptor

Introduction

One of the important themes of cancer growth centres on the coordination of cell growth with the promotion of cell number, either by increasing cell division or by enhancing cell survival. Conventional chemotherapy agents appear to reverse some of these processes by inhibiting cell division and increasing cell death. The dose and delivery of these agents are chosen so that the therapeutic effect preferentially occurs in tumours rather than in normal tissues. A variety of experimental approaches have shown that promoters of tumour progression include molecular pathways that activate proliferation and survival signals. The complexity of the interactions between these signals, and the fact they are generally also important for the maintenance of normal tissues, means that a specific molecular intervention must also aim to be selective for the tumour. Examples of tumour growth promoters acting at the cell surface include growth factor pathways that are either activated by excess production of ligand or by mutation of a receptor that leads to continuous high level activation of these downstream pathways. Progress in the development of interventions to these cell surface targets are now reaching clinical application. For example, the tumour inhibitory activity of EGF receptor antibodies (e.g. C225, Her2-Neu) and small molecule inhibitors of the EGF (e.g. ZD1839), C-kit/BCR-ABL (e.g. STI571) and VEGF receptor tyrosine kinases (e.g. SU5416) have now been clearly demonstrated [1–3].

This review addresses the recent evidence in colorectal cancer in support of another growth factor pathway, the IGF system, that may also be a suitable target for the development of therapeutic molecules (see also [4, 5]). For the sake of brevity, we have concentrated on areas of interest that will have implications for colorectal cancer. The reader is directed to a recent review for a broader coverage of the IGF system and cancer [6].

The insulin-like growth factor system

The insulin-like growth factors (IGFs) are comprised of two ligands, IGF-I and IGF-II (Figure 1) [7]. Both are small, single chain polypeptides synthesised as pre-pro molecules in a manner similar to insulin. However, unlike insulin, IGF-I and IGF-II are expressed mainly from the liver during adult life and IGF-I mediates most of the growth effects of growth hormone, with high circulating IGF-I serum levels often detected in patients with acromegaly. Genetic knock-out studies of the gene coding for IGF-II in mice results in proportional growth retardation, suggesting that IGF-II is principally an embryonic growth promoter [8, 9]. Serum levels of total IGF-II are detectable in human adults but the situation is different in rodents, where serum levels are at the lower limit of detection. This may be accounted for by differences between species in basal and tissue specific mRNA expression and ligand bioavailability. Both ligands bind a group of at least six binding proteins, present in molar excess in the circulation and in tissues, which appear to control systemic and local bioavailability. IGFBP maintains IGF half-life in the circulation and extra-cellular space, and may have specific functions in...
the delivery of IGFs to signalling receptors at the cell surface. These proteins bind IGFs with high affinity (10^{-8} to 10^{-9} M), but are proteolytically labile, so that their cleavage alters the local bioavailability of IGFs [10, 11]. Both IGF-I and IGF-II can activate the heterotetrameric IGF1 receptor, and an isoform of the insulin receptor (A), leading to auto-phosphorylation and also to phosphorylation of downstream proteins including IRS1 [12–14]. This leads to activation of Akt, PI3 kinase, MAPK kinase, β catenin and other molecules that enhance proliferation, cell survival and cell migration [15–17].

It has been known for some time that IGF signalling is a mechanism of chemotherapy resistance in cell culture, an effect related to the prevention of cell death following challenge by chemotherapeutic agents [18–20]. This effect extends to colorectal tumour cell lines treated with 5-fluorouracil [21]. In addition, recent experiments utilising anti-sense RNA to inhibit IGF1 receptor expression have shown that receptor down-regulation enhances tumour cell radio-sensitivity by blocking activation of ATM, a key protein involved in the initiation of cell cycle checkpoints and repair pathways after DNA damage [22].

There are structural and protein sequence similarities between the IGF1 receptor and the insulin receptors, such that hybrids between the two often form in some cell types. Such similarities present a technical hurdle in the development of IGF1 receptor specific inhibitors, particularly of the tyrosine kinase domain. However, other potential interventions require further investigation, such as inhibitory antibodies, peptides and anti-sense RNA constructs [23–25]. Finally, IGF-II binds a large receptor not directly involved in signal transduction, the IGF-II/M6P receptor (referred to as IGF2R) [26]. This receptor binds IGF-II with very high affinity (10^{-9} to 10^{-10} M), and acts to internalise the ligand for degradation in the endosomal compartment of the cell [26–28]. Thus, all cells have a mechanism for limiting the bioavailability of IGF-II at the cell surface. IGF2R also binds mannose 6-phosphate residues on proteins such as lysosomal hydrolases, latent TGFβ1 and granzyme B [26, 29]. The binding to these various different of ligands is because this receptor transports these proteins during their production using glycosylated mannose 6-phosphate residues added post-translationally. The mannose 6-phosphate modification targets protein delivery from the Golgi to the endosomal compartment and the cell surface. In some instances the binding of these proteins has functional consequences in terms of cell signalling, e.g. activation of latent TGFβ1 to active TGFβ1 and transport of granzyme B from cytotoxic T-cells into target cells.

Modification of the IGF system, growth and cancer

Models of growth control

There are two complementary sources of evidence that make a strong case for the IGF system as a therapeutic target in cancer
The gene coding for IGF2 is imprinted, with the paternal (inherited from father) allele expressed at high levels during embryonic growth and in tumours. The maternal allele expression is reduced at the level of transcription because of activation of the non-coding RNA, H19, by downstream enhancers. A boundary element close to H19 is differentially methylated. In the non-methylated state, CTCF proteins can bind and establish a boundary to prevent the enhancer activating IGF2. This is the situation with maternal allele in normal tissues. IGF2 transcription is reduced but expression of H19 continues. In tumours, methylation of the CTCF binding sites allows the enhancer to activate IGF2 on the maternal allele because the boundary becomes disrupted and CTCF cannot bind. In this circumstance, biallelic expression or relaxation of imprinting occurs and results in increased IGF2 mRNA levels.

The first are genetic experiments on growth in whole animals, feasible because mice have the great advantage of being amenable to genetic manipulation. This genetic approach has proved to be the most powerful experimental method to underpin a set of experimental observations. The second are observational and correlative studies in human cancer. These do not have the benefit of genetic manipulation in vivo (except when using genetically modified tumour-derived culture cells), but are obviously of great importance in the development of diagnostics prior to treatment with therapeutics.

The genetic evidence for the general growth effects of IGF-II have come from embryonic stem cell knock-out technology. The phenotype following disruption of the gene coding for IGF-II in mouse (Igf2) leads to symmetrical embryonic growth retardation [31, 32]. Two surprises followed the investigation of these animals. First, unlike the knock-outs of the other main members of the IGF system, these mice were viable and fertile. (The individual IGFBP knock-outs are also viable, but do not have gross growth defects, suggesting redundancy in their function). Secondly, the Igf2 knock-outs appeared to inherit the defect from their fathers only, an effect known as genomic imprinting. In this case this leads to silencing of gene expression from the allele of the gene inherited from mothers.

Imprinting is one important mechanism where the expression of the IGF-II gene can be limited. Relaxation of imprinting appears to occur frequently in cancers and if it occurs during development, can result in similar human and mouse embryonic overgrowth syndromes (confirming the normal function of IGF-II as an embryonic growth promoter). One important theory of imprinting relates to the competition between a transcriptional enhancer located downstream of Igf2 and a non-coding RNA gene called H19 (Figure 2). If a boundary in the chromatin domain occurs, as in the maternal allele, H19 is preferentially expressed relative to Igf2. Conversely, if the domain boundary is not set up during gametogenesis, then the enhancer stimulates Igf2 expression from the paternal allele. The boundary is controlled by methylation of CpG nucleotides within the DNA sequence upstream of H19. Methylation reduces the affinity of the DNA sequence to proteins that set up the boundary, e.g. a protein called CTCF [33]. Thus, defects in DNA methylation (epigenetic modification) can modify imprinting, and consequently the expression of critical growth control. Imprinting of IGF2 occurs in humans [34] and Beckwith Weidemann is the overgrowth syndrome associated with increased IGF2 expression [35].

Models of cancer

Increased supply of IGF-II can also be generated in the mouse using transgenes. Over-expression of IGF-II using constitutive promoters results in embryonic lethality (as above), but over-expression of IGF-II using tissue specific promoters can result in overgrowth of the tissues that express the transgene and fairly normal development [36]. Following a latent period of at least 6–12 months, tumours in these tissues can occur, suggesting that increased local supply of this growth factor can lead to an increased susceptibility to cancer [37, 38]. Disruption of the IGF2 receptor in mouse can also increase the bioavailability of IGF-II, but in this case early neonatal lethality occurs in the enlarged embryos. With the advent of new gene knock-out technology (loxP/Cre), post-natal disruption of IGF2 receptor may be possible and will allow experimental investigation of the role of the IGF2 receptor as a potential tumour suppressor. Increased supply of IGF-I can also result in overgrowth and increased tumour susceptibility in animals, again supporting the genetic evidence using IGF-II. In all these circumstances of alteration in ligand supply alone, the development of tumours probably arises from progression of currently uncharacterised initiating mutations.

The specific role for IGF-II in cancer progression was initially supported by experiments using T-antigen expression in the pancreas, a way of genetically inducing tumours by molecular mechanisms that include binding of p53 and Rb. Using in situ hybridisation, Christofori et al. found that expression of T antigen in Islet cells led to early pancreatic
adenomas that also expressed IGF-II mRNA [39, 40]. This indicated that reactivation of embryonic expression patterns of this gene can occur during tumour growth. Smaller and fewer tumours arose when IGF-II was eliminated following crosses between these mice and mice with disruption of Igf2. These experiments also showed that the expression of Igf2 was often biallelic, due to relaxation of imprinting. Similar results have also been observed in mice with genetic susceptibility to tumours/adenoma arising in the liver and intestine [41–43].

Models of colorectal cancer

Relaxation of imprinting effects were seen in crosses between the Min mouse, a model for Familial adenomatous polyposis, and Igf2 knock-out mouse [43]. The Min mouse (ApcMut) has a single point mutation in the gene coding for APC, which is also commonly mutated in sporadic human colorectal cancer. This gene is regarded as one of the first to develop mutations and loss of heterozygosity in the development of colorectal cancer. As with the human syndrome, polyps in the mouse can develop into carcinomas. However, on the C57Bl6 genetic background, mice develop multiple intestinal adenoma by around 100 days of age and can become moribund due to anaemia and intestinal obstruction. This model is regarded as the closest mouse cancer susceptibility model to a human cancer. Using genetic crosses, increased IGF-II supply in the Min mouse results in increased growth of polyps and an increased progression from adenoma to carcinoma [43]. Furthermore, reduced IGF-II supply in Min crosses with Igf2 paternal allele knock-out mice resulted in reduced adenoma size and frequency. Importantly, Igf2 expression could be detected in adenoma that did form, suggesting that loss of imprinting occurs in these adenoma (LOI) [43]. The effects of IGF-II supply in other models of colorectal cancer, such as SMAD knockouts and defects in genes controlling mismatch repair is not known. In conclusion, evidence from murine models suggest that genetic manipulation of IGF supply (and the downstream signalling pathways) are a potent mechanism which can modify both normal and tumour tissue growth control. Recent evidence also suggests that the IGF system can modify colorectal tumour progression in a well defined mouse model of colorectal cancer, and which therefore provides a test bed for novel agents.

IGF system and human colorectal cancer

IGF system and established tumours and cell lines

In human tumours, several groups have observed mutations, mRNA and protein expression of IGF-II, IGF-I, IGFBP, IGF1 receptor and IGF2 receptor. Table 1 provides some examples of the data for colorectal cancer using mRNA and protein expression. There are several key points to note. First, most studies have been carried out on a relatively low number of samples with little correlation with patient data. Secondly, few studies have attempted a complete analysis of all members of the system. Thus, whilst an increase in IGF2 mRNA expression may have occurred in a tumour, this may be functionally redundant if either IGFBP3 or IGF2R are up-regulated, or if IGFR1 is down-regulated. Furthermore, the functional relationship between IGF-II and IGF2R means that supply of IGF-II may be significantly altered if there are mutations of this receptor. Recent evidence using expression profiling have advanced knowledge of the multiple differentially expressed genes between tumours and normal tissue. The first investigation to pave the way used serial analysis of gene expression (SAGE). Here, IGF-II was found to be the most abundant over-expressed RNA in colorectal tumour cell lines and primary tissue [44]. Recent information using gene chips arrays have failed to confirm over-exression of IGF-II, but have identified alterations in IGFBP expression and a relatively few genes (0.48%) that are over-expressed in colorectal adenoma and carcinoma compared with normal tissue [45]. Thus, as a whole, these data provide circumstantial evidence that members of this system can be altered in human colorectal cancer, particularly in the direction of increased IGF driven signalling. In particular, its also worth noting that expression can differ between stromal and tumour cells, suggesting paracrine as well as autocrine growth stimulation. Thus, the level of expression and distribution may have functional consequences in terms of the transition from adenoma to invasive carcinoma, rather than the total level of expression. However, a systematic study using both RNA, protein and histological analysis has not been carried out on a large number of patient samples. Finally, one further useful application of cell line experiments relates to the interaction of the IGF system with other cancer-related pathways. For example, recent evidence suggests that Cox2 mRNA levels are up-regulated by IGF1 receptor activation and may be one factor that contributes to the heterogeneity of response of colon adenomas to Cox2 inhibitors [46].

These studies also do not provide conclusive proof that increased IGF-mediated signalling allows essential alterations required for the maintenance of the established tumour in vivo. Whilst effective levels of cell proliferation and survival may have been important during the progression of tumours, these data do not constitute the evidence required to confirm that continued IGF signalling is required for tumour maintenance. This is partly related to the general problem of identifying the molecular players controlling differentiated tissue from more actively dividing progenitor cell types. Overall, this evidence again awaits the prospective evaluation of therapeutic modifiers of the IGF system on the growth of colorectal tumours and on patient benefit.

IGF system and colorectal cancer predisposition

Two recent studies provide important new information with regard to the prospective correlation of IGF supply and
tumour predisposition. The first concerns the systemic supply of IGF-I in humans. It is well known that an increase in colonic adenoma can occur in patients with acromegaly, with an increased supply of IGF-I [47]. Prospective case controlled studies in healthy adults have now observed an increased relative risk of developing colorectal cancer in patients with pre-morbid IGF-I levels in the highest quartile many years prior to diagnosis [48]. A total of 14 916 normal men were followed for 14 years in the Physician’s Health Study reported in 1999. Blood was taken for IGF-I, IGF-II and IGFBP3 levels at study entry when men were well. Only 193 cases of colorectal cancer developed during follow-up, and these were compared with age matched controls (n = 318). After adjusting for smoking, age, alcohol consumption and body mass, men with high IGF-I levels had a relative risk of developing colorectal cancer of 2.51 (95% CI 1.15 to 5.46; P = 0.02). Interestingly, the effect was reciprocal to the level of IGFBP3, the main binding protein that controls circulating levels, which was associated with a decreased relative risk (0.28, 95% CI 0.12 to 0.66; P = 0.005). The increased relative risk associated with high IGF-I levels equates to the average increased relative risk of colorectal cancer with a positive family history defined by the Amsterdam criteria [49]. The current hypothesis is that high IGF-I levels predispose to colorectal cancer and may identify

<table>
<thead>
<tr>
<th>Source</th>
<th>Raised IGF2 RNA</th>
<th>Raised IGF-II</th>
<th>Raised IGF2R RNA</th>
<th>Raised IGF1R RNA</th>
<th>Raised IGF1-R protein</th>
<th>IGFBP</th>
<th>Note</th>
<th>References</th>
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<tbody>
<tr>
<td>Tumours (n = 2), Cell lines (n = 3)</td>
<td>×73</td>
<td>–</td>
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<td>–</td>
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<td>(Zhang et al., 1997) [44]</td>
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<tr>
<td>Tumour versus normal pair (n = 18)</td>
<td>NS</td>
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<td>NS</td>
<td>NS</td>
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<td>–</td>
<td>IGFBP3 and IGFBP4 P &lt;0.05</td>
<td>(Notterman et al., 2001) [45]</td>
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<td>Adenoma versus normal (n = 4)</td>
<td>NS</td>
<td>–</td>
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<td>NS</td>
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<tr>
<td>Tumours (n = 6)</td>
<td>×1-800 (n = 4)</td>
<td>×1.4–100 (n = 6)</td>
<td>–</td>
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<td>–</td>
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<td>(Winkler et al., 1999) [62]</td>
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<td>Tumours (n = 92)</td>
<td>–</td>
<td>68% versus 11%</td>
<td>–</td>
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<td>(Kawamoto et al., 1998) [63]</td>
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<td>Tumours (n = 6)</td>
<td>×40 (n = 6)</td>
<td>×2 (n = 10)</td>
<td>×5 (n = 6)</td>
<td>×2.5 (n = 6)</td>
<td>–</td>
<td>Equal (n = 10)</td>
<td>(Freier et al., 1999) [64]</td>
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<td>Cell lines (n = 6)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2 × 10³/cell</td>
<td>–</td>
<td>–</td>
<td>(Guo et al., 1992) [65]</td>
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<td>Tumours</td>
<td>×10–50 (n = 20)</td>
<td>–</td>
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<td>–</td>
<td>(Tricoli et al., 1986) [66]</td>
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<tr>
<td>Tumours (n = 21)</td>
<td>×2-800 in 6/21</td>
<td>–</td>
<td>–</td>
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<td>–</td>
<td>–</td>
<td>(Lambert et al., 1990) [67]</td>
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<tr>
<td>Cell line</td>
<td>×10</td>
<td>×20</td>
<td>–</td>
<td>–</td>
<td>8 × 10⁴/cell</td>
<td>–</td>
<td>–</td>
<td>(Zarrilli et al., 1994) [68]</td>
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<tr>
<td>Tumour/Cell line</td>
<td>3/10</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Decrease IGFBP2</td>
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<td>(Michell et al., 1997) [11]</td>
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<td>Tumours (n = 35)</td>
<td>–</td>
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<td>3/35 were mutant</td>
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<td>–</td>
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<td>(Souza et al., 1996) [69]</td>
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<td>Tumours (n = 75)</td>
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<td>–</td>
<td>–</td>
<td>34/36C 25/27M</td>
<td>–</td>
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<td>(Hakam et al., 1999) [70]</td>
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1Initial SAGE data suggested IGF-II as the most abundant overexpressed transcript in colorectal cancer. Subsequent examination of further tumour material confirmed over-expression, but not to such a great degree. See http://www.ncbi.nlm.nih.gov/SAGE/.

²Microarray analysis using Affymetrix gene chips (6600 mRNA sequences or tags).

³Structural modification of 3′ UTR of the IGF2 gene in highest mRNA tumours, use of promoter 3 and 4 of the IGF2 gene with loss of imprinting in 2/6.

⁴IGF-II positive tumours were more invasive and associated with worse prognosis. A later paper revealed IGF-II at invasive margins of hepatic metastasis [71].

Radio-immunoassay to quantify IGF-I and IGF-II.

Over-expression of IGF-II mainly in rectal, recto-sigmoid and Dukes’ C tumours.

Increased degradation of IGFBP-2 in tumours.

Microsatellite instability positive associated polyG tract modification (4089–4096).

Almost all carcinomas and metastatic tumours expressed high levels of IGF1 receptor.

NS, not significantly different; C, carcinomas; M, metastatic tumours.
also occurs in the latter group of MSI positive, but mutation negative, tumours methylator phenotype whose origin is entirely epigenetic. The expression of IGF2 in normal mucosa is a predisposing factor to the development of colorectal cancer.

The second observation relates to the local supply of IGF-II in the normal colon and in colon tumours [52–55]. It appears that some individuals express both alleles of IGF2 (~12%) [52]. The inference is that these individuals may be producing twice as much IGF-II peptide and increased supply at the level of the IGF1 receptor. These patients also have biallelic expression in their colon tumours. However, in cases of microsatellite instability (MSI), assessed by the NCI panel of markers, almost all appeared bialleic expressers of IGF2 [52, 54, 56]. The catch is that these patients appeared not to have inherited mutations of MS2, MLH1 or PMS2, but have a methylator phenotype whose origin is entirely epigenetic. The latter group of MSI positive, but mutation negative, tumours accounts for 15% of colorectal cancers with MSI and is associated with methylation of the MLH1 promoter. Methylation also occurs in the IGF2/H19 imprinting domain, which modifies binding of the chromatin boundary protein CTCF. Methylation of this region on the maternal allele results in biallelic expression of IGF2 and explains this novel observation in microsatellite unstable tumours [54]. Further prospective studies are needed to determine whether local biallelic expression of IGF2 in normal mucosa is a predisposing factor to the development of colorectal cancer.

Future directions

It is difficult to predict what impact an inhibitor of the IGF system may have on human cancer in general and colorectal cancer specifically. There are several points to bear in mind. First, the evidence as a whole has almost conclusively shown that modification of IGF-driven growth, either at a particular time or cellular location, significantly enhances tumour cell growth. However, there are clear lines of experimental and clinical investigation that remain unanswered. The translation of this information directly to patients may be problematic. There are currently two main lines of approach. First, if increased IGF supply predicts for an increased relative risk of colorectal cancer, then we have to confirm this information and think carefully how this may be incorporated into prospective screening strategies. For example, it may be a combination of systemic IGF-I supply and local IGF-II supply that generates the highest predisposition. Blood samples, mucosa biopsies and colonoscopy may then provide more robust information compared with occult blood testing? If an inhibitor, such as silibinin, modifies the IGF system without inducing long-term toxicity, its effectiveness will need to be carefully monitored in conjunction with other preventative agents such as Cox2 inhibitors [57]. Secondly, a more thorough and systematic study of the IGF system in this disease is warranted. We believe this should now include defined patient subgroups (MSI, Site, Stage) and utilise a range of experimental methods. This information may help direct the most appropriate patients for further investigation and therapy.

Finally, in patients with cancer, an IGF system inhibitor may modify the growth of established tumours. It is not known what will be the best overall strategy, e.g. gene therapy, antisense therapy, small kinase inhibitor molecules, therapeutic receptors, therapeutic antibodies, etc. In particular, there are approaches that may either alter chemotherapy resistance if used in combination or may act via an unpredictable mechanism. For example, experiments first reported in glioblastoma, and more recently in murine colon cancer cells, suggest that cell death induced by blocking IGF-I signalling resulted in systemic anti-tumour immune responses [58, 59]. Importantly, the effect occurred following use of anti-sense agents and prevented tumour growth following re-challenge. A recent clinical study has been reported using this antisense approach in malignant astrocytoma derived cells transfected with antisense constructs to the IGF1 receptor and then encapsulated in diffusion chambers and placed in the abdominal wall [60]. It is thought that the apoptotic material generated may be antigenic and deliver an immune response to the primary tumour. However, the induction of class I restricted CTLs, the underlying basis for this immune type of effect, still remains unclear [61]. Overall, this type of experiment highlights the sometimes unpredictable interactions between different cell types and signalling systems within tumours.

Further high quality experimental studies and prospective trials will be required to understand fully the biology and pathology of the IGF system in colorectal cancer. In time, we hope this will ultimately accelerate the development of tailored therapeutic strategies in this common cancer.

Acknowledgements

We thank the Cancer Research Campaign, Medical Research Council, Chris Graham, David Kerr, Adrian Harris and Walter Bodmer for support, and members of our groups for discussion.

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