IGFs and IGFBPs: surrogate markers for diagnosis and surveillance of tumour growth?

W Zumkeller

Abstract
Insulin-like growth factors (IGFs), IGF receptors, and IGF binding proteins (IGFBPs) constitute the IGF system. Comprehensive data indicate that these factors play a pivotal role in tumorigenesis. Epidemiological data indicate that cancer risk is associated with high serum IGF-I values. Because dysregulation of the IGF system is a frequent pattern in malignancy, IGFs/IGFBPs might represent novel tumour markers that could be useful both for diagnosis and surveillance.

Keywords: insulin-like growth factors; insulin-like growth factor binding proteins; tumour marker

The insulin-like growth factor (IGF) system plays a crucial role in normal cell proliferation and malignant transformation. It comprises IGF-I and IGF-II, the type I and type II receptors, and a family of IGF binding proteins (IGFBPs) that specifically bind IGFs. During the transition from the benign to the malignant state, qualitative and quantitative changes of the components of the IGF system are frequently observed. For example, increases in the type I IGF receptor are seen in human pancreatic cancer when compared with benign tissue. Furthermore, IGFBP dysregulation also occurs in neuroblastoma, nephroblastoma, and acute lymphoblastic leukaemia, among others. Thus, there is increasing evidence that IGFs and IGFBPs should be included in the panel of tumour markers used for histopathological diagnosis and serological surveillance procedures in various malignancies.

Paediatric tumours and syndromes (such as Beckwith-Wiedemann syndrome) associated with such tumours show increased IGF-II gene expression and transgenic mice overexpressing IGF-II have an enhanced risk of developing tumours. Immunocytochemistry showed IGF-II in chordee plexus papillomas but not in normal human chordee plexus, suggesting that IGF-II is a useful marker for the differential diagnosis of chordee plexus papilloma. IGF-II and H19, which is considered to be an oncifetal RNA and tumour suppressor gene, are both imprinted genes located at 11p15. The H19 gene is expressed in tumours originating from tissues that express this gene in fetal life. Thus, these factors show a tissue specific oncifetal pattern of expression. In rhabdomyosarcomas, strong IGF-II mRNA expression was observed, which was inversely correlated with the degree of tumour cell differentiation. Various other soft tissue sarcomas showed no IGF-II mRNA expression and it was concluded that IGF-II is a potential new marker for differential diagnosis of rhabdomyosarcoma. There is evidence indicating that IGF-II plays a pivotal role in rhabdomyosarcoma tumorigenesis. Coexpression of IGF-II mRNA with the Ki-67 proliferation marker in hepatocellular carcinoma suggests that IGF-II may play an important role in the development of this particular tumour. In addition, the expression of H19 is under the control of the same regulatory genes as α fetoprotein, which is a widely used tumour marker for hepatocellular carcinoma. H19 was present in 13 of 18 cases, whereas staining for α fetoprotein was positive in only nine of 18 cases. Earlier reports indicated that H19 gene expression in human bladder carcinomas was associated with a more malignant grade. It was suggested that H19 is an oncodevelopmental marker for bladder tumour progression and that this gene has oncogenic properties in this type of tumour. Raised serum IGFBP-1 values have been reported in patients with primary liver cancer and ovarian cancer. Whether these serum concentrations of IGFBP-1 are related to tumour cachexia or to production by the tumour itself is unclear. In the serum of patients with non-islet cell tumour hypoglycaemia, free IGF-I and IGF-II, in addition to IGFBP-1 and IGFBP-2 values, are raised. Consistently increased concentrations of IGFBP-2 have been described in serum and cyst fluids surrounding tumours of different histology, such as lung tumours, Wilms’s tumours, prostate cancer, colorectal tumours, ovarian cancer, acute lymphoblastic leukaemia, and brain tumours. Increased IGF-I and decreased IGFBP-3 concentrations are found in patients with lung cancer in comparison with control subjects, so that measuring those factors might be useful for the assessment of lung cancer risk. IGFBP-2 serum concentrations were significantly increased in patients with lung cancer compared with normal controls.

Prostate cancer
Plasma IGF-I is a predictor of prostate cancer risk. High IGF-I and low IGF-II serum values are independently associated with increased risk of prostate cancer. The IGF-I/prostate specific antigen (PSA) ratio significantly improved the detection of prostate cancer over the use of PSA alone. Statin et al found an association between raised plasma IGF-I and increased prostate risk, whereas Finne et al found no such association. Another study showed a significant association between low serum concentrations of IGF-I and prostate cancer. The biological importance of these
with a significant decrease in colorectal cancer
concentrations of IGFBP-1 were associated
significantly decreased in malignant cells.
but IGFBP-3 protein concentrations were sig-
IGFBP-2 and IGFBP-3 mRNA expression,
intraepithelial neoplasia showed enhanced
values, and that measurement of IGF-I and
being proposed to clarify whether measurement
Serum concentrations of IGF-II were in-
compared with normal controls, indicating that
maintained. There may be a possible role for
tumour suppressor genes altered in malign-
nancies leading to increased IGFBP-2 expres-
sion, thus increasing tumour invasiveness as a
result of enhanced mitogenic action of IGF-I.
Recently, a silencer domain of the rat IGFBP-2
gene that contains a target sequence for the
retinoblastoma gene product was identified. The
raised serum concentrations of IGFBP-2 in
in patients with prostate cancer were related to
the concentration of PSA, which is also an
IGFBP-3 protease and thus alters IGF-
IGFBP-3 interactions. Serum IGFBP-2
values were significantly higher in patients with
prostate carcinoma and high PSA than in those
with normal PSA. High grade prostate
intraepithelial neoplasia showed enhanced
IGFBP-2 and IGFBP-3 mRNA expression,
but IGFBP-3 protein concentrations were sign-
ificantly decreased in malignant cells. It
appears that as prostate tissue progresses from
the benign to the malignant state, IGFBP-2
immunoreactivity in the prostatic luminal
epithelial cells increases and that of IGFBP-3
decreases. IGFBP-5 immunoreactivity was
also significantly increased in malignant pro-
state epithelium compared with benign epithe-
lium. Expression of IGFBP-2 and IGFBP-5
was higher, whereas IGFBP-3 was lower, in
high versus low Gleason score prostate can-
cer. It was also suggested that increases in
IGF-I and intact IGFBP-3 values are positively
associated with the presence of prostate
adenocarcinoma in patients with rather low PSA
values, and that measurement of IGF-I and
intact IGFBP-3 may be helpful for discriminating
between prostate carcinoma and benign
prostatic hyperplasia. Clinical studies have
been proposed to clarify whether measurement
of IGF-I and IGFBP-3 in addition to PSA
could improve the identification of men at high
risk for prostate cancer.

Colorectal cancer
Serum concentrations of IGF-II were in-
creased in patients with colorectal adenomas
compared with normal controls, indicating that
IGF-II may be a tumour marker for these
adenomas, which are known precursors of
colorectal carcinomas. IGFBP-2 was raised in
patients with colorectal cancer and, in com-
bination with carcinoembryonic antigen, showed
high sensitivity for colorectal cancer, and could
therefore be used for surveillance of cancer in
patients with colorectal cancer. IGFBP-2 mRNA
expression is increased in human colorectal
cancer cells, indicating that IGFBP-2 plays an autocrine role. Increasing
concentrations of IGFBP-1 were associated
with a significant decrease in colorectal cancer
risk. Therefore, high IGF-I and IGFBP-3
values may be markers for colorectal cancer
risk.

Breast cancer
The risk of breast cancer is reduced in women
who experienced pre-eclampsia during preg-
nancy or who were born to a mother with pre-
eclampsia. Pre-eclampsia is associated with
hormonal alterations, including a reduction in
IGF-I and an increase in IGFBP-1. Thus, IGF-I and IGFBP-1 values could in this
circumstance represent factors that determine a
lifelong risk for breast cancer. Epidemiologi-
cal studies have indicated an association
between serum IGF-I values and cancer risk
but have not established causality. Lower
serum concentrations of IGFBP-1, IGFBP-3,
and IGFB-6 were found in patients with breast
cancer, thus increasing the bioavailability of
IGF-I. The reduction of IGF-II after surgery
for breast cancer was more pronounced in
malignant tumours than in benign disease, and
this was directly related to the size of the
removed tumour. It remains to be elucidated
whether determination of IGF-II contributes
to early detection of tumour recurrence.

Other cancers
Not only do ovarian cancer tissues express
IGFBP-2 preferentially, but the increased
IGFBP-2 cyst fluid values mirror overproduc-
tion by the tumour itself, with IGFBP-2 mRNA expression being highest in invasive
tumours. IGFBP-2 concentrations correlated
positively with the highly sensitive serum
tumour marker, cancer antigen 125 (CA 125),
in patients with ovarian cancer.
Increased IGFBP-2 concentrations have also
been reported in patients with acute lympho-
blastic leukaemia and, in general, increased
serum IGFBP-2 concentrations coincide with
higher detection rates of IGF-II mRNA
transcripts in leukaemia cells. Previous investi-
gations had suggested that high serum concen-
trations of IGFBP-2 in patients with acute
lymphoblastic leukaemia may indicate an
increased risk of relapse.
 Patients with malignant brain tumours
showed increased IGFBP-2 concentrations in
cerebrospinal fluid and, furthermore, children
with various peripheral tumours were found to
have higher serum IGFBP-2 values, which
returned to normal during complete remis-
sion. In meningiomas, a high IGF-II/
IGFBP-2 mRNA ratio has been depicted as a
sign of biologically aggressive behaviour.
In gliomas, a highly significant correlation be-
tween IGFBP-2 cyst fluid values and immuno-
histochemistry and tumour grading was
found.
Patients with metastatic adrenocortical tu-
mours had significantly higher IGFBP-2
plasma concentrations than normal controls
and IGFBP-2 values in these patients were
inversely correlated with their survival.
Tumour cell growth appears to be modulated by
IGFBPs in different ways.
In carcinoma in situ (CIS) of the testis,
IGFBP-5 immunoreactivity was enhanced, so
that IGFBP-5 might be a novel tumour marker for CIS. It needs to be established whether patients with tumours of the testis also have increased IGFBP-5 values in their serum.

In conclusion, IGFs and IGFBPs are secreted by several tumours and modulate their malignant behaviour. The genes encoding IGF-II and IGFBP-2 are upregulated in human cancer, and these factors may therefore represent valuable tumour markers because they mirror the oncological pattern of expression. The consistent correlation between IGFBP overexpression and tumour grading or invasiveness could indicate their usefulness as a potential prognostic factor, which might predict outcome. Because of the pronounced expression of the IGF system seen during malignant transformation, these factors may also represent targets for therapeutic intervention.


