REVIEW

The molecular pathogenetic role of cell adhesion in endocrine neoplasia

S Ezzat, S L Asa

J Clin Pathol 2005;58:1121–1125. doi: 10.1136/jcp.2004.024521

It is becoming increasingly evident that cell adhesion is an important determinant of organised growth and the maintenance of architectural integrity. Indeed, reduced adhesiveness between cells and with the extracellular matrix is a hallmark of neoplastic growth. In neuroendocrine tissues, neural cell adhesion molecule is implicated in modulating cell growth, migration, and differentiation. This review will focus on the molecular pathways involving key growth factor receptors that govern normal adhesive forces. The extent to which disruption of these adhesive forces contributes to the tumorigenic process in neuroendocrine tissues will be highlighted. Validation of the functional relevance of these adhesive pathways will be discussed in light of targeted pharmacotherapeutic studies that are unmasking novel approaches to the treatment of neuroendocrine tumours.

work is the morphological hallmark of the transition from hyperplasia to adenoma that is commonly used as a diagnostic feature for true neoplasia.⁷ For example, adenomatous pituitary cells are characterised by their ability to form solid nests or trabecula in the absence of a stromal support or framework.⁷ In this review, we will focus on the neoplastic consequences of dysregulated signalling between cell adhesion molecules and members of the fibroblast growth factor (FGF) family of tyrosine kinase receptors that are involved in modulating these functions.

NCAM AS A PIVOTAL CELL ADHESION FACTOR

Neural cell adhesion molecule (NCAM) is a well characterised cell membrane protein that modulates neuroendocrine cell growth, migration, and differentiation.⁸ NCAM is a member of a large family of calcium independent adhesion molecules that contain variable numbers of immunoglobulin (Ig)-like domains and fibronectin type III repeats.⁹ The alternatively spliced transcripts generate protein isoforms with five Ig-like domains and two fibronectin type III domains in the extracellular region (fig 1A). The structure of NCAM is further complicated by extensive post-translational modification with N-terminal polysialation.¹⁰ NCAM is a multi-valent adhesion molecule that mediates homotypic and heterotypic cell–cell adhesion through a homophilic binding mechanism.⁹ However, there is also evidence for heterophilic interactions with L1,¹¹ heparan sulfate proteoglycans, and collagens I–IV and IX.¹² Loss of NCAM signalling does not result in embryonic lethality but impairs the development of endocrine cells within pancreatic islets of Langerhans.¹³ In addition to its role in cell adhesion, NCAM has been implicated in signal transduction. NCAM induces neurite outgrowth in neurones by activating FGF receptor (FGFR) signalling. NCAM also associates with signal transducing molecules, including focal adhesion kinase and the src related tyrosine kinase, p59fyn.¹³ Interestingly, FGFs or a soluble NCAM peptide can replace NCAM in the induction of FGFR mediated neurite outgrowth.¹⁴ Two lines of study in endocrine tumours have recently underscored

Endocrine tumours, including those of the pituitary and pancreas, rarely harbour the mutations of oncogenes or tumour suppressor genes that are characteristic of other solid tissue malignancies.^{1–3} Interestingly, tumours of different endocrine glands occur spontaneously or as part of the familial multiple endocrine neoplasia (MEN) syndromes. For example, tumours of the pituitary and pancreas occur as part of the MEN-I syndrome, suggesting a common vulnerability.⁴ Increasing evidence suggests that disruption of common growth factor signals implicated in normal endocrine gland development are frequently involved in sporadic tumours of the pituitary and endocrine pancreas.¹

“Endocrine tumours, including those of the pituitary and pancreas, rarely harbour the mutations of oncogenes or tumour suppressor genes that are characteristic of other solid tissue malignancies”

Progression to neoplasia involves changes in the ability of cells to adhere to and interact with neighbouring cells and with their extracellular matrix environment.⁵ Correlative studies in human carcinomas and functional studies in vitro and in transgenic mouse models have suggested that loss of or impaired cell adhesion are important early determinants in epithelial neoplasia.⁶ Moreover, loss of the reticulin net-

See end of article for authors' affiliations

Correspondence to:
Dr S Ezzat, 600 University
Avenue 437, Toronto,
Ontario, Canada, M5G-
1X5; sezzat@mtsinai.on.
ca

Accepted for publication
9 May 2005

Abbreviations: AdsFlt, adenoviral soluble vascular endothelial growth factor receptor 1; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; Ig, immunoglobulin; MEN, multiple endocrine neoplasia; NCAM, neural cell adhesion molecule; ptd, pituitary tumour derived

Figure 1 The prototypic structures of neuroendocrine adhesion molecules. (A) Prototypic modular structures of the neural cell adhesion molecule (NCAM). Note the potential for N-terminal modification of NCAM including polysialylation (PSA). (B) Prototypic structure of the N-cadherin family as effectors of physical interaction with the β catenin/ α catenin network to maintain cytoskeletal architecture. (C) Prototypic modular structures of the fibroblast growth factor receptor family. Note alternative splicing generates receptor isoforms varying in N-terminal and C-terminal structures. Receptor isoforms generate a functionally diverse family of receptors during developmental and neoplastic transitions. (See text for further details on structural and functional interactions between members of these adhesive molecules.)

the crucial contribution of NCAM heterophilic interaction with FGFRs, as detailed below.

N-CADHERIN AND β CATENIN: NEUROENDOCRINE ADHESION MOLECULES

N-cadherin is a member of the classic cadherin family of cell-cell adhesion molecules of particular importance in neuroendocrine cell function. The type I classic cadherin family has five members—E-cadherin, P-cadherin, R-cadherin, M-cadherin, and N-cadherin.¹⁵ These transmembrane proteins contain five highly homologous extracellular cadherin domains and a conserved intracellular domain (fig 1B). N-cadherin is the predominant member expressed in the nervous system and interacts directly with β catenin and in turn with α catenin as the intermediate link to the actin cytoskeleton. This cytoskeleton linkage is crucial in stabilising cadherin clusters at the cell surface and strengthening cell-cell adhesion. Oestradiol, a recognised promoter of rodent pituitary cell growth, reduces membranous N-cadherin protein expression to barely detectable levels, whereas anti-oestrogen treatment reverses this effect.¹⁶

“Nuclear accumulation of β catenin in non-endocrine carcinomas is recognised as a feature of malignancy”

β Catenin is usually regarded as a transcription factor that targets genes with a lymphoid enhancer factor response element, including cyclin D1 and Myc.¹⁷ Typically, nuclear accumulation of β catenin in non-endocrine carcinomas is recognised as a feature of malignancy.¹⁷ However, in these solid tumours, nuclear catenin accumulation is the result of a defect in protein degradation. The normal function of β catenin is as a membrane protein that can associate with N-cadherin (fig 1B); this form is mainly dephosphorylated.¹⁸ NCAM is constitutively associated with N-cadherin, ensuring the integrity of cadherin mediated adhesion through β catenin. Conacci-Sorrell *et al* recently reviewed the pleiotropic signalling and functional properties of β catenin.¹⁵ Indeed, uncoupling of cadherins from the cytoskeleton may be an essential aspect of neuroendocrine cell migration. Moreover, N-cadherin mediated neurite outgrowth depends on inactivation of N-cadherin mediated adhesion at pathway boundaries.¹⁹ The regulation of β catenin stability is a means of effecting such changes. Several

tyrosine kinases, including members of the epidermal growth factor receptor²⁰ and hepatocyte growth factor receptor families,²¹ also target β catenin. Suppressing the association of epidermal growth factor receptor with β catenin increases the association of β catenin with cadherin²² and inhibits invasive gastric cancer growth through enhanced cadherin mediated adhesion.²³

INTEGRINS AS ENDOCRINE CELL SURFACE MEDIATORS OF ADHESION

Integrins are a family of structurally related heterodimeric cell surface receptors involved in adhesion to molecules in the extracellular matrix, including collagen.²⁴ Integrin receptors are expressed by many cell types, including those in the anterior pituitary,²⁵ where they mediate a variety of processes such as cell-matrix and cell-cell adhesion, cell migration, growth, and differentiation.

FGF LIGANDS

The FGF family has 22 members (FGFs 1–14 and 16–23), each possessing a conserved 120 amino acid core domain.²⁶ Many FGF ligands display high affinity interactions with multiple FGFRs, whereas some activate unique receptors or receptor isoforms.²⁷ Most FGFs have mitogenic activity in a variety of systems. The proliferative capacity of an FGF is now recognised as a function of the FGFR(s) to which it binds and through which it signals.²⁷

FGFRS: A COMPLEX FAMILY OF BINDING PROTEINS AND RECEPTOR TYROSINE KINASES

Four mammalian FGFR genes encode a complex family of transmembrane receptor tyrosine kinases.¹⁴ Each prototypic receptor is composed of three Ig-like extracellular domains, two of which are involved in ligand binding, a single transmembrane domain, a split tyrosine kinase, and a C-terminal tail with multiple autophosphorylation sites (fig 1C).¹⁴ Multiple forms of cell bound or secreted forms of FGFR1, FGFR2, and FGFR3 are generated by alternative splicing, transcription initiation, or exon switching.^{28–29} Alternative splicing results in a secretable first Ig-like domain and a separate membrane bound two Ig-like domain form (fig 1C).³⁰ Soluble forms of the extracellular domain of FGFR1 may bind FGFs in blood.³¹ In FGFRs 1, 2, and 3, alternative RNA splicing of one of two exons results in two alternative forms of the second half of the third Ig-like

domain; exon 8 encodes the IIIb form and exon 9 encodes the IIIc form of a transmembrane tyrosine kinase. Whereas FGFRs 1–3 are known to have several isoforms, traditionally FGFR4 was not thought to have multiple isoforms. The FGFR4 gene has 18 exons instead of the 19 exons found in the other FGFRs.³² The additional exon in other FGFRs is located between exons 8 and 9 of FGFR4 and, by alternative splicing, encodes the isoforms of the third Ig-like domain.

NCAM-FGF-FGFR SIGNALLING IN ENDOCRINE TUMORIGENESIS

Pancreatic islet cell tumours: the role of NCAM

One of the better animal models of pancreatic endocrine tumorigenesis is transgenic mice that overexpress the SV40 virus oncoprotein under control of the insulin promoter. This so called Rip1Tag2 mouse model develops pancreatic endocrine tumours in a multistep pathway characterised by the appearance of distinctive hyperplastic islets, angiogenic dysplastic islets, solid nests of tumours with well defined margins and fibrous capsules, and eventually invasive lesions.³³ Moreover, loss of NCAM in this model was shown to promote the development of locoregional lymph node metastases.³³ Consistent with these observations, B cell tumours in NCAM deficient Rip1Tag2 transgenic mice show pronounced disaggregation of tissues.³³ More strikingly, cell lines established from these primary tumours exhibit reduced adhesion to various extracellular matrix components. Furthermore, NCAM deficient neoplastic B cells lack the ability to generate neurites. This combined loss of neurite formation and cell–matrix adhesion of tumour cells suggested a functional dependency on NCAM signalling interactions. Biochemical and pharmacological analyses of neoplastic B cells led to the development of a model that is similar but distinct from the current model of neurite outgrowth induced by NCAM. In contrast to neurones, where NCAM is able to induce neurite outgrowth only by being engaged in cell–cell adhesion, in tumour cells NCAM induces neurite outgrowth and matrix adhesion in single cells, in the absence of cell–cell contacts. In neurones, activation of FGFR mediated by NCAM, L1, and N-cadherin has been shown mainly by interfering with FGFR function. However, a direct association between NCAM and other adhesive and signalling proteins could not be excluded. Subsequently, there was evidence of unequivocal binding of NCAM to FGFR4. Inhibition of FGFR4 signalling repressed matrix adhesion induced by NCAM in pancreatic endocrine tumour cells.³³ Moreover, neurite outgrowth could not be reconstituted in the absence of both NCAM and FGFR4 signalling.³³

Pituitary adenomas: the role of NCAM

NCAM has been described as having tumour suppressor functions; however, NCAM polysialylation is a feature of progressive pituitary tumour development that also serves as a prognostic marker.³⁴ Tumour grafts of pituitary cells under the kidney capsule show an association between the expression of polysialylated NCAM and tumour growth rate and tissue invasiveness.³⁴

Pituitary adenomas: the role of FGFR4

Several FGF ligand family members have been identified in abundant amounts in the pituitary. FGF-2 was originally described in the non-hormone producing bovine pituitary folliculostellate cell, where it is known to regulate multiple pituitary hormones.³⁵ FGF-2 is also expressed by adenohypophyseal cells that comprise pituitary adenomas,³⁶ and oestrogen administration in rats results in pituitary tumorigenesis, which is accompanied by increased FGF-2 expression.³⁷ Increased circulating FGF-like immunoreactivity is

Figure 2 The balance between adhesion and proliferation in endocrine cells. The membrane location of neural cell adhesion molecule (NCAM), fibroblast growth factor (FGF) receptor 4 (FGFR4), and N-cadherin allows the formation of a pro-adhesive multiprotein complex. Wild-type FGFR4 resides predominantly in the cell membrane and interacts with NCAM to maintain intact N-cadherin and β catenin stability. In contrast, the pituitary tumour derived FGFR4 isoform (ptd-FGFR4) is cytoplasmic and displaces FGFR4 from NCAM, thereby disrupting N-cadherin and β catenin mediated cell–cell and cell–matrix adhesion. A similar interference with this multiprotein pro-adhesive complex is proposed for polysialylated NCAM.

found in patients with MEN-I and associated pituitary tumours,³⁸ and in patients with sporadic pituitary adenomas.³⁶ The product of the human homologue of the endogenous FGF antisense gene is expressed in the pituitary, with lower expression in tumorous than non-tumorous tissue, where it inhibits pituitary cell proliferation.³⁹

Our laboratory identified a difference in FGFR4 kinase expression between normal and neoplastic pituitary tissue.⁴⁰ In particular, human pituitary adenomas expressed an N-terminally deleted isoform identified as pituitary tumour derived (ptd-) FGFR4.⁴¹ This isoform is generated by alternative transcription initiation utilising a downstream cryptic promoter.^{42–43} This oncoprotein (ptd-FGFR4) lacks the signal peptide, and the first and second Ig-like domains of the extracellular part of the receptor. Wild-type FGFR4 is a 110 kDa protein that localises to the cell membrane; in contrast, ptd-FGFR4 is a 65 kDa cytoplasmic protein with transforming properties (fig 2).⁴¹ The tumorigenic role of ptd-FGFR4, but not wild-type FGFR4, was demonstrated by targeted pituitary expression in transgenic mice.⁴¹ The functional differences between FGFR4 isoforms formed the basis for the following interaction studies.

To explain the differences between the growth behaviour of the FGFR4 receptor isoforms identified *in vivo*, we examined their ability to modulate cell adhesiveness and assemble an NCAM multiprotein complex that contains N-cadherin and its downstream target β catenin. NIH 3T3 fibroblasts and GH4 pituitary cells were examined for their ability to adhere to distinct extracellular matrices. There was no appreciable difference in the adhesion to extracellular matrices such as fibronectin of control cells, cells overexpressing wild-type FGFR4, or those expressing ptd-FGFR4. In contrast, consistent and distinct differences in cell adhesiveness were noted when cells were grown on a collagen IV matrix.⁴⁴ Cells expressing ptd-FGFR4 adhered poorly to collagen IV. In contrast, FGFR4 overexpressing cells showed no significant loss of adhesiveness to the collagen IV extracellular matrix. Stimulation of wild-type FGFR4 transfected cells with either the non-FGFR selective FGF-1 or the

FGFR4 selective ligand FGF-19 could not recapitulate the effect of ptd-FGFR4 on cell adhesiveness. Moreover, pre-incubation with a neutralising antibody to activated β 1 integrin greatly inhibited FGFR4 mediated cell adhesiveness, but had no significant effect on the reduced adhesiveness of ptd-FGFR4 expressing cells.⁴⁴ These findings suggest that FGFR4 and ptd-FGFR4 recruit distinct adhesive complexes that cannot be explained on the basis of constitutive receptor activation alone.

We showed that an important function of FGFR4 is to orchestrate signalling events that are crucial for normal cell adhesiveness. Our data indicate that the transforming properties of the ptd-FGFR4 isoform are at least partially attributable to disruption of a pro-adhesive membrane complex, as depicted in fig 2.

"Pituitary tissue derived fibroblast growth factor receptor 4 expression, which is associated with reduced and ectopic cytoplasmic expression of N-cadherin, manifests invasive growth in vivo"

These differences were also associated with corresponding differences in invasive properties in vivo.⁴⁴ FGFR4 expressing pituitary cells display non-invasive growth associated with intact N-cadherin membranous expression.⁴⁴ In contrast, ptd-FGFR4 expression, which is associated with reduced and ectopic cytoplasmic expression of N-cadherin, manifests invasive growth in vivo.

Interestingly, ptd-FGFR4, but not FGFR4, in the absence or presence of FGF stimulation, was effective at destabilising β catenin from N-cadherin, with resultant reduced β catenin expression.⁴⁴ Reduced β catenin expression with only a modest degree of nuclear translocation is a feature of pituitary tumours that also correlates with tumour invasiveness.⁴⁵ Given that nuclear β catenin accumulation is a feature of rapidly proliferating and metastasising solid tumours, loss of β catenin is more consistent with the indolent non-metastasising but locally infiltrative nature of most pituitary adenomas.¹ These data are also in line with the importance of β catenin in maintaining adherens junctions.

Immunoneutralisation of β 1 integrin repressed cell adhesiveness in FGFR4 transfected cells³³ but did not significantly alter the reduced adhesiveness conferred by ptd-FGFR4.⁴⁴ Consistent with these data, ptd-FGFR4 failed to activate β 1 integrin and, when introduced in vivo, resulted in an increase in invasive growth into skin, nerves, and other local structures. These findings are reminiscent of the invasive behaviour noted in tumours of mice transgenic for ptd-FGFR4 that invade brain,⁴¹ and suggest that integrins are additional targets for the FGFR4–NCAM–N-cadherin adhesive complex.

FGFRS AS POTENTIAL THERAPEUTIC TARGETS IN NEUROENDOCRINE TUMOURS

The dramatic differences between FGFR4 isoforms in cell adhesiveness are attributed to distinct interactions with NCAM. These findings are consistent with the fact that wild-type FGFR4 associates strongly with NCAM, whereas ptd-FGFR4 has minimal direct interaction with NCAM. Therefore, disruption of NCAM–FGFR4 pro-adhesive complexes, as seen with ptd-FGFR4, may be an alternative mechanism of interrupting NCAM mediated cell adhesion.

A role for FGFR4 in cell adhesion has been suggested by an FGFR4 polymorphism in which arginine is substituted for glycine in the transmembrane domain, resulting in increased cell motility and acceleration in breast and colorectal cancer.⁴⁶ These changes are surprising because this polymorphism has no appreciable effect on receptor kinase activity. The

Take home messages

- Cell adhesion is an important determinant of organised growth and the maintenance of architectural integrity
- Reduced adhesiveness between cells and between cells and the extracellular matrix is a hallmark of neoplastic growth
- Neural cell adhesion molecule, N-cadherin, and fibroblast growth factor receptors are crucial mediators in the modulation of neuroendocrine growth
- Genetic or pharmacological interference with these components can modify the growth patterns of neuroendocrine tumours

functional differences between FGFR4 isoforms are also consistent with a C-terminally truncated breast cancer cell derived soluble FGFR4, which serves as a dominant negative isoform, by forming inactive heterodimers with wild-type FGFR4.⁴⁷ These data highlight the importance of FGFR interactions in mediating the distinct actions of FGFR isoforms.

Studies using recombinant adenovirus expressing soluble FGFR to interfere with FGF signalling repressed endothelial cell proliferation in vitro and inhibited tumour angiogenesis in an ex vivo bioassay. Moreover, this soluble FGFR repressed tumour angiogenesis and tumour growth in vivo in allograft transplantation experiments. Whereas adenoviral expression of a soluble form of the vascular endothelial growth factor receptor 1 (AdsFlt) predominantly affected the initiation of tumour angiogenesis, soluble FGFR appeared to impair the maintenance of tumour angiogenesis. The combination of soluble FGFR and AdsFlt had a synergistic effect on the repression of pancreatic endocrine tumour growth. Finally, intravenous injection of adenovirus expressed soluble FGFR resulted in a dramatic repression of tumour growth in the transgenic mouse model of pancreatic endocrine carcinogenesis. Similar to control infections with AdsFlt, tumour associated vessel density was decreased, indicating that the expression of soluble FGFR impaired tumour angiogenesis. These data indicate that FGFRs may also play a crucial role in the angiogenic phase of endocrine tumorigenesis.⁴⁸

CONCLUSIONS

The emerging theme identifies important differences in the ability of adhesion molecules, including NCAM and N-cadherin, to interact functionally and physically with receptor tyrosine kinase members of the FGFR family. These pivotal differences are associated with differences in β catenin stability and with activation of a β 1 integrin matrix network. Disruption of distinct NCAM–N-cadherin pro-adhesive complexes provides a novel tumorigenic mechanism that explains the pathobiology of proliferative and infiltrative but non-metastasising tumours, such as pituitary adenomas. This may result from alterations in FGFRs, as exemplified by the ptd-FGFR4 oncogene, or by polysialation of NCAM itself, which would interfere with multiprotein complex formation. More complete loss of NCAM provides a background that better explains the phenotype of invasiveness and metastasis in pancreatic islet cell carcinomas. The extent to which other adhesion molecules are involved in heterophilic interactions with other growth factor receptors or their signalling components will prove crucial to understanding their pathobiological contributions to other forms of endocrine tumour.

ACKNOWLEDGEMENTS

The work reviewed here was supported by the Canadian Institutes of Health Research (Grants MT-14404) and the Toronto Medical Laboratories.

Authors' affiliations

S Ezzat, Department of Medicine, University of Toronto, Endocrine Oncology Site Group, Mount Sinai and Princess Margaret Hospitals, Ontario Cancer Institute, University Health Network, Toronto, Ontario, Canada M5G-1X5

S L Asa, Department of Pathology and Laboratory Medicine, University of Toronto

REFERENCES

- Asa SL, Ezzat S. The cytogenesis and pathogenesis of pituitary adenomas. *Endocr Rev* 1998;**19**:798-827.
- Alexander JM. Tumor suppressor loss in pituitary tumors. *Brain Pathol* 2001;**11**:342-55.
- Asa SL, Ezzat S. The pathogenesis of pituitary tumours. *Nat Rev Cancer* 2002;**2**:836-49.
- Ezzat S, Asa SL. Molecular genetics of endocrine neoplasia. In: Kovacs K, Asa SL, eds. *Functional endocrine pathology*. Boston: Blackwell, 1998.
- Hirohashi S, Kanai Y. Cell adhesion system and human cancer morphogenesis. *Cancer Sci* 2003;**94**:575-81.
- Cavallaro U, Schaffhauser B, Christofori G. Cadherins and the tumour progression: is it all in a switch? *Cancer Lett* 2002;**176**:123-8.
- Asa SL. Tumors of the pituitary gland. *Atlas of tumor pathology*, 3rd Series, Fascicle 22. 1998. Washington, DC: Armed Forces Institute of Pathology.
- Christofori G. Changing neighbours, changing behaviour: cell adhesion molecule-mediated signalling during tumour progression. *EMBO J* 2003;**22**:2318-23.
- Crossin KL, Krushel LA. Cellular signaling by neural cell adhesion molecules of the immunoglobulin superfamily. *Dev Dyn* 2000;**218**:260-79.
- Tang J, Rutishauser U, Landmesser L. Polysialic acid regulates growth cone behavior during sorting of motor axons in the plexus region. *Neuron* 1994;**13**:405-14.
- Horsikorte R, Schachner M, Magyar JP, et al. The fourth immunoglobulin-like domain of NCAM contains a carbohydrate recognition domain for oligomannosidic glycans implicated in association with L1 and neurite outgrowth. *J Cell Biol* 1993;**121**:1409-21.
- Probstmeier R, Kuhn K, Schachner M. Binding properties of the neural cell adhesion molecule to different components of the extracellular matrix. *J Neurochem* 1989;**53**:1794-801.
- Esni F, Taljedal IB, Perl AK, et al. Neural cell adhesion molecule (N-CAM) is required for cell type segregation and normal ultrastructure in pancreatic islets. *J Cell Biol* 1999;**144**:325-37.
- Givol D, Yayon A. Complexity of FGF receptors: genetic basis for structural diversity and functional specificity. *FASEB J* 1992;**6**:3362-9.
- Conacci-Sorrell M, Zhurinsky J, Ben Ze'ev A. The cadherin-catenin adhesion system in signaling and cancer. *J Clin Invest* 2002;**109**:987-91.
- Heinrich CA, Lail-Trecker MR, Peluso JJ, et al. Negative regulation of N-cadherin-mediated cell-cell adhesion by the estrogen receptor signaling pathway in rat pituitary GH3 cells. *Endocrine* 1999;**10**:67-76.
- Yap AS, Kovacs EM. Direct cadherin-activated cell signaling: a view from the plasma membrane. *J Cell Biol* 2003;**160**:11-16.
- Xu G, Arregui C, Lilien J, et al. PTP1B modulates the association of beta-catenin with N-cadherin through binding to an adjacent and partially overlapping target site. *J Biol Chem* 2002;**277**:49989-97.
- Lilien J, Arregui C, Li H, et al. The juxtamembrane domain of cadherin regulates integrin-mediated adhesion and neurite outgrowth. *J Neurosci Res* 1994;**58**:727-34.
- Hoschuetzky H, Aberle H, Kemler R. Beta-catenin mediates the interaction of the cadherin-catenin complex with epidermal growth factor receptor. *J Cell Biol* 1994;**127**:1375-80.
- Shibamoto S, Hayakawa M, Takeuchi K, et al. Tyrosine phosphorylation of beta-catenin and plakoglobin enhanced by hepatocyte growth factor and epidermal growth factor in human carcinoma cells. *Cell Adhes Commun* 1994;**1**:295-305.
- Bonvini P, An WG, Rosolen A, et al. Geldanamycin abrogates ErbB2 association with proteasome-resistant beta-catenin in melanoma cells, increases beta-catenin-E-cadherin association, and decreases beta-catenin-sensitive transcription. *Cancer Res* 2001;**61**:1671-7.
- Shibata T, Ochiai A, Kanai Y, et al. Dominant negative inhibition of the association between beta-catenin and c-erbB-2 by N-terminally deleted beta-catenin suppresses the invasion and metastasis of cancer cells. *Oncogene* 1996;**13**:883-9.
- Hood JD, Cheresch DA. Role of integrins in cell invasion and migration. *Nat Rev Cancer* 2002;**2**:91-100.
- Horacek MJ, Kawaguchi T, Terracio L. Adult adenohypophyseal cells express beta 1 integrins and prefer laminin during cell-substratum adhesion. *In Vitro Cell Dev Biol Anim* 1994;**30A**:35-40.
- Itoh N, Ornitz DM. Evolution of the Fgf and Fgfr gene families. *Trends Genet* 2004;**20**:563-9.
- Ornitz DM, Zu J, Colvin JS, et al. Receptor specificity of the fibroblast growth factor family. *J Biol Chem* 1996;**271**:15292-7.
- Yan G, Wang F, Fukabori Y, et al. Expression and transformation of a variant of the heparin-binding fibroblast growth factor receptor (fgf) gene resulting from splicing of the exon at alternate 3'-acceptor site. *Biochem Biophys Res Commun* 1992;**183**:423-30.
- Peters KG, Werner S, Chen G, et al. Two FGF receptor genes are differentially expressed in epithelial and mesenchymal tissues during limb formation and organogenesis in the mouse. *Development* 1992;**114**:233-43.
- Crumley G, Bellot F, Kaplow JM, et al. High-affinity binding and activation of a truncated FGF receptor by both aFGF and bFGF. *Oncogene* 1991;**6**:2255-62.
- Hanneken A, Ying W, Ling N, et al. Identification of soluble forms of the fibroblast growth factor receptor in blood. *Proc Natl Acad Sci U S A* 1994;**91**:9170-4.
- Kostrzewa M, Muller U. Genomic structure and complete sequence of the human FGFR4 gene. *Mamm Genome* 1998;**9**:131-5.
- Cavallaro U, Niedermeyer J, Fuxa M, et al. N-CAM modulates tumour-cell adhesion to matrix by inducing FGF-receptor signalling. *Nat Cell Biol* 2001;**3**:650-7.
- Daniel L, Trouillas J, Renaud W, et al. Polysialylated-neural cell adhesion molecule expression in rat pituitary transplantable tumors (spontaneous mammatropic transplantable tumor in Wistar-Furth rats) is related to growth rate and malignancy. *Cancer Res* 2000;**60**:80-85.
- Gospodarowicz D, Abraham JA, Schilling J. Isolation and characterization of a vascular endothelial cell mitogen produced by pituitary-derived folliculo stellate cells. *Proc Natl Acad Sci U S A* 1989;**86**:7311-15.
- Ezzat S, Smyth HS, Ramyar L, et al. Heterogeneous in vivo and in vitro expression of basic fibroblast growth factor by human pituitary adenomas. *J Clin Endocrinol Metab* 1995;**80**:878-84.
- Heaney AP, Horwitz GA, Wang Z, et al. Early involvement of estrogen-induced pituitary tumor transforming gene and fibroblast growth factor expression in prolactinoma pathogenesis. *Nat Med* 1999;**5**:1317-21.
- Zimering MB, Katsumata N, Sato Y, et al. Increased basic fibroblast growth factor in plasma from multiple endocrine neoplasia type 1: relation to pituitary tumor. *J Clin Endocrinol Metab* 1993;**76**:1182-7.
- Asa SL, Ramyar L, Murphy PR, et al. The endogenous fibroblast growth factor-2 antisense gene product regulates pituitary cell growth and hormone production. *Mol Endocrinol* 2001;**15**:589-99.
- Abbass SAA, Asa SL, Ezzat S. Altered expression of fibroblast growth factor receptors in human pituitary adenomas. *J Clin Endocrinol Metab* 1997;**82**:1160-6.
- Ezzat S, Zheng L, Zhu XF, et al. Targeted expression of a human pituitary tumor-derived isoform of FGF receptor-4 recapitulates pituitary tumorigenesis. *J Clin Invest* 2002;**109**:69-78.
- Ezzat S, Yu S, Asa SL. Ikaros isoforms in human pituitary tumors: distinct localization, histone acetylation, and activation of the 5' fibroblast growth factor receptor-4 promoter. *Am J Pathol* 2003;**163**:1177-84.
- Yu SJ, Asa SL, Weigel RJ, et al. Pituitary tumor AP-2 recognizes a cryptic promoter in intron 4 of fibroblast growth factor receptor 4. *J Biol Chem* 2003;**278**:19597-602.
- Ezzat S, Zheng L, Asa SL. Pituitary tumor-derived fibroblast growth factor receptor 4 isoform disrupts neural cell-adhesion molecule/N-cadherin signaling to diminish cell adhesiveness: a mechanism underlying pituitary neoplasia. *Mol Endocrinol* 2004;**18**:2543-52.
- Qian ZR, Li CC, Yamasaki H, et al. Role of E-cadherin, alpha-, beta-, and gamma-catenins, and p120 (cell adhesion molecules) in prolactinoma behavior. *Mod Pathol* 2002;**15**:1357-65.
- Bange J, Prechtel D, Cheburkin Y, et al. Cancer progression and tumor cell motility are associated with the FGFR4 Arg(388) allele. *Cancer Res* 2002;**62**:840-7.
- Ezzat S, Zheng L, Yu S, et al. A soluble dominant negative fibroblast growth factor receptor 4 isoform in human mcf-7 breast cancer cells. *Biochem Biophys Res Commun* 2001;**287**:60-5.
- Compagni A, Wilgenbus P, Impagnatiello MA, et al. Fibroblast growth factors are required for efficient tumor angiogenesis. *Cancer Res* 2000;**60**:7163-9.