**REVIEW**

*eph*, the largest known family of putative growth factor receptors

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Receptor tyrosine kinases (RTKs) and their ligands are involved in many different processes including cellular differentiation, proliferation, embryonic development and some cases of neoplastic growth (Ullrich & Schlessinger, 1990; Pawson & Bernstein, 1990). The RTKs all have a similar structure consisting of an extracellular ligand-binding domain, a hydrophobic transmembrane region and an intracellular domain that contains the tyrosine kinase catalytic activity (Yarden & Ullrich, 1988). Receptors of this type may be categorised according to their overall layout, their regions of sequence homology and on the similarity of their ligands. Several subclasses or families of RTKs can be defined using this approach. One such subclass is the recently discovered family of RTKs termed *eph*, which currently consists of seven distinct members, *eph*, *eck*, *elk*, *cek5*, *mek4*/*cek4*/*hek*, *sek* and *hek2*, all of whose cDNAs have been fully sequenced. The relationships between the Eph family members is illustrated in a phylogenetic tree (Figure 1) constructed using the amino acid sequence from the consensus sequence Gly-X-Gly-X-Gly, found towards the amino terminus of the catalytic region (Hanks et al., 1988), to the carboxy-terminal tail. The tree was constructed using the De Soete Tree Fit program (De Soete, 1983, 1984). There are at least another five *eph*-related putative receptors reported in the literature that have not yet been fully sequenced. Taken together, this appears to be the largest known family of RTKs. The pattern of expression of mRNA or protein of the full and partial length *eph*-like receptors is summarised in Table I.

*epp* family characteristics

The shared characteristics of the Eph family which allow it to be considered as a subclass of RTKs are depicted in Figure 2. The extracellular domain contains an immunoglobulin-like (Ig) loop (although this homology is very weak) and two fibronectin type III repeats. Ig loops are found in several RTK extracellular domains, notably in the fibroblast growth factor (FGF) receptor and platelet-derived growth factor receptor families. Fibronectin type III repeats are found in many proteins, including some RTKs and a number of neural cell adhesion molecules. The function of these motifs in growth factor receptors is unclear, however they may be involved in cell-cell interactions. There is also one cysteine-rich region, containing 13 cysteine residues, in the extracellular domain. The spacing of the cysteines is different to the cysteine-rich region found in the type I RTK family, which includes the epidermal growth factor (EGF) receptor, c-*erbB*-2, c-*erbB*-3 (Prigent & Lemoine, 1992) and c-*erbB*-4 receptors (Plowman et al., 1993), and the type II family, which consists of the insulin receptor, IGF-1 and the insulin receptor-related receptor.

So far no ligands for any of the Eph RTK family have been reported, and therefore they should be considered 'putative' growth factor receptors. Lack of known ligands severely restricts the studies that can be performed on their functions. However, several reports on the expression pattern of the mRNA and protein of the various members have been performed, and this may ultimately aid in the discovery of the ligands for this family and help unravel their normal cellular functions.

*epp*

*epp*, the first receptor to be discovered, was isolated from a human hepatocellular carcinoma cell line cDNA library (Hirai et al., 1987). The *eph* gene has been well conserved throughout evolution as the human *eph* cDNA probe detected specific bands on a Southern blot of DNA from mouse, chicken, rat and *Drosophila melanogaster*. The human *eph* gene has been mapped to chromosome 7 and codes for a 3.5 kb mRNA. *eph* has been found to be most highly expressed at the mRNA level in adult rat liver, lung and kidney and to a lesser extent in the testis (Table I). It was also noted that some human breast, lung, liver and colon carcinomas overexpress *eph* mRNA compared with normal tissues, but no gene amplification was seen (Maru et al., 1988). This observation of overexpression without gene amplification has been reported for several RTKs, e.g. c-*erbB*-3 in breast carcinomas (Lemoine et al., 1992). When the human breast cancer cell line MCF-7 was analysed for the expression of

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**Figure 1** Phylogenetic tree of the Eph family of receptor tyrosine kinases. The tree was constructed using the De Soete Tree Fit program. The amino acid sequence from the consensus sequence GXGXGG, of the catalytic region, to the carboxy-terminal tail was used. The predicted amino acid sequences of human Eph, Hek, Hek2, Erk and Eck, rat Eek and Elk, chicken Cek4, Cek5, Cek6, Cek7, Cek8, Cek9 and Cek10 and mouse Mek4 and Sek were used in the construction for the above tree. The following partially sequenced Eph-like receptors were of insufficient length to be included; rat Tyro 1, Tyro 4, Tyro 5, Tyro 6 and Tyro 11 and human Tk2.
Table 1 Summary of the expression of mRNA or protein of all fully and partially sequenced eph-like receptors

| Name | Species | Homologue(s) | mRNA (kb) | Normal distribution of mRNA or protein | Overexpression of mRNA in human cancers |
|------|---------|--------------|-----------|----------------------------------------|----------------------------------------|
| eph  | Human   | NI           | 3.5       | Highest in adult rat liver, lung and kidney. Lower in testes | Some lung, liver, breast and colon carcinomas |
| elk  | Rat     | cek6a        | 4.0       | Highest in adult rat brain and embryonic day 14–16 stomach. Lower in adult rat testes | 2/3 gastric carcinomas |
| eck  | Human   | NI           | 4.7       | Highest in rat lung, skin, small intestine and ovary. Lower in kidney, brain, spleen and submaxillary gland |  |
| cek5 | Chicken | erk*/tyro5*  | 4.4 and 10| Highest in chicken embryonic day 10 and adult brain. Lower in kidney, lung, thigh and intestine |  |
| sek  | Mouse   | cek8*/*yro1* | 7.0       | Highest in adult mouse brain. Lower in heart, lung and kidney. Expressed during embryonic brain development |  |
| cek4 | Chicken | mek4/hek/*yro4* | 7.5     | Highest in adult chicken brain and retina, but detectable in all adult tissue, except liver |  |
| mek4 | Mouse   | cek4/hek/*yro4* | 6.0 and 3.4 | Highest in adult mouse brain. Lower in testes (3.4 kb) |  |
|hek  | Human   | cek4/mek4/*yro4* | 5.5–6.0 | Undetectable at the protein level | 1/28 CLL and 2/39 AML |
|hek2 | Human   | cek10*/tyro6* | 4.6       | Highest in human pancreas, lung, placenta, brain and kidney. Lower in heart, skeletal muscle and liver |  |
| eek* | Rat     | NI           | ND        | Rat brain | 3/3 gastric carcinomas |
| erk* | Human   | cek5/*yro5*  | 4.0       | Highest in adult rat lung. Lower in placenta, brain and kidney. Expressed in 16 day rat embryo stomach |  |
|tyro1* | Rat     | sek/*cek8*   | ND        | Constant expression from rat embryonic day 12 to adulthood in CNS |  |
|tyro4* | Rat     | cek4/mek4/hek | ND        | Constant expression from rat embryonic day 12 to birth in CNS |  |
|tyro5* | Rat     | cek5/*erk*   | ND        | Constant expression from rat embryonic day 12 to birth in neural tissue |  |
|tyro6* | Rat     | hek2/*cek10* | ND        | Maximal in rat embryonic day 12 brain |  |
|tyro11* | Rat     | NI           | ND        | Highest in rat heart and kidney, lower in neural tissue |  |
|cek6* | Chicken | elk          | 4.4 and 6.5| Highest in chicken embryonic day 10 and adult brain, lung, heart and skeletal muscle. Low level of 6.5 kb adult brain |  |
|cek7* | Chicken | NI           | 4.4, 7.0  and 8.5 | Chicken embryonic day 10 brain. Low level of 8.5 kb transcript in adult brain |  |
|cek8* | Chicken | sek/*yro1*   | 6.0       | Highest in adult chicken brain and retina. Lower in adult kidney, lung, skeletal muscle and thymus |  |
|cek9* | Chicken | NI           | 4.4       | Highest in chicken adult thymus. Lower in brain, retina, kidney, lung and heart. Expressed in embryonic day 10 brain |  |
|cek10* | Chicken | hek2/*yro6* | 4.4 and 6.0 | Highest in adult chicken kidney. Lower in adult lung. Expressed in embryonic day 10 brain and body tissues |  |

*Partially sequenced. NI, none identified. ND, not determined.

tyrosine kinase mRNAs using the polymerase chain reaction (PCR), 17/76 tyrosine kinase clones isolated and sequenced coded for eph (Lehtola et al., 1992). It has also been observed that when the eph gene is artificially overexpressed in the mouse fibroblast cell line, NIH 3T3, it allows the transfected cells to grow in an anchorage-independent manner (determined by their ability to grow in soft agar) and to form tumours in nude mice (Maru et al., 1990). Taken together these data suggest that overexpression of the eph gene may have a role to play in certain human carcinomas. However only 50 tumours of different tissue types were examined and no clinical data were presented to allow the comparison of tumour characteristics with overexpression to be made. Larger studies must therefore be performed to allow the prevalence of overexpression of eph mRNA in human carcinomas to be more accurately determined.

**elk**

The second member of this family to be identified was termed elk for eph-like kinase and was isolated from a rat brain cDNA library (Letwin et al., 1988; Lhotak et al., 1991). This gene appears to have a different pattern of expression from eph. elk mRNA is 4.0 kb in size and can only be detected in adult rat brain and to a lesser degree in the testis. A partial elk cDNA clone was isolated by Iwase et al. (1993) and used to screen a Northern blot of mRNA isolated from the stomach of adult, newborn and embryonic rats. It was found that elk expression increased in the stomach between embryonic days 14 and 16 but was very low by embryonic day 18 and in newborn rats. No expression was seen in the stomach of adults. RNA was also prepared from three cases of human gastric cancer and it was found that elk...
mRNA levels were several times higher in 2/3 cases when compared with RNA prepared from normal gastric tissue (Table I). elk may therefore have a role to play in human gastric cancer; however, a larger study must be undertaken before any firm conclusions may be drawn.

eck

The third member, isolated from a human keratinocyte cDNA library, has been termed eck (epithelial cell kinase), and as the name suggests is expressed primarily in cells of epithelial origin (Lindberg & Hunter, 1990). The mRNA is 4.7 kb in size and was shown to be most highly expressed in rat lung, skin, small intestine and ovary, with lower levels seen in the kidney, brain, spleen and lymphoid tissue (Table I). Eck was the first member of this family to be shown to have intrinsic tyrosine kinase activity. This was demonstrated by immunoprecipitation of the 130 kDa Eck protein from A431 cells (a human vulva carcinoma-derived cell line) using an antibody raised against a TrpE fusion protein containing 101 amino acids from the C-terminal tail of Eck and then performing an in vitro kinase reaction on the immune complex. The phosphorylated protein was subjected to phosphoamino acid analysis, which confirmed that the majority of the phosphate was on tyrosine.

cék

cék (chicken embryo kinase) was isolated from a 10 day chicken embryo cDNA expression library probed with antiphosphotyrosine antibodies (Pasquale, 1991). Antibodies to the Cék protein were raised against a β-gal fusion protein consisting of 759 amino acid residues (including all of the intracellular domain) and a synthetic peptide consisting of the ten amino acids from the C-terminal tail. Using these antibodies the Cék protein was found to have an apparent molecular mass of 120 kDa and its pattern of expression in the 10 day chicken embryo, determined by Western blotting, was found to be highest in the brain, marginally lower in the kidney, lung, thigh, gizzard and intestine and lower still in the liver, heart and lens (Table I). In the adult chicken protein expression was found to be most abundant in the brain and detectable in most of the tissues seen in the embryo, but at a lower level. A more detailed study on the embryonic and newly hatched chicken brain revealed that expression decreases gradually during embryonic development and after hatching. Immunocytochemical staining showed that the Cék5 protein is expressed in regions that are rich in nerve cell processes especially in the submammillary and the cerebellum (Pasquale et al., 1992). Cék5 is specifically expressed in neurons and may play a role in neuronal maintenance in the chicken brain.

A variant of cék5 was isolated from the same 10 day chicken embryo cDNA library and is termed cék5* (Sajjadi & Pasquale, 1993). This partial length cDNA variant codes for an eph-like receptor with an insert of 16 amino acids in the juxtamembrane region, which may be the result of alternative splicing. A Northern blot of 10-day-old chicken embryo brain and body tissue was screened with a probe specific for cék5* and one that would recognise both cék5 and cék5*. Using the probe that recognises both cék5s a 4.4 kb transcript was detected in 10 day embryonic brain and body tissues, with a 10 kb transcript also being detected in the brain. The cék5* probe detected the 4.4 kb transcript only, and this was expressed exclusively in the CNS. cék5* therefore appears to be a neuronal-specific variant of cék5.

sek

Another eph family member, sek (segmentally expressed kinase), seems to be involved in the development of the mouse hindbrain. sek was isolated from an 8.5 day mouse embryo cDNA library and the gene has been mapped to mouse chromosome 1 and human chromosome 2 (Gilardi-Hebenstreit et al., 1992). Murine sek mRNA is 7.0 kb in size and was found to be most highly expressed in the adult mouse brain. However it was also detectable in the heart and lung, with a lower level of expression being seen in the kidney (Table I). A detailed study of the expression of mRNA in the developing mouse brain revealed sek is expressed initially in the forebrain and hindbrain but not in the midbrain, with expression becoming more restricted within the developing forebrain (Nieto et al., 1992). sek also appears to be expressed in the developing neural tube of the spinal cord and sek may therefore have a role to play in the initial steps of neuronal differentiation in the spinal cord of the mouse. Later on in development sek may play a role in neuronal maintenance as is suggested for cék5.

cék4/mek4/lek

Chicken cék4 (isolated at the same time as cék5) encodes a 7.5 kb mRNA which was detectable in brain, head structures and body tissues of an 8 day chicken embryo (Sajjadi et al., 1991). Expression of the 7.5 kb transcript was most pronounced in adult brain and retina, but was detectable in all other adult tissue except the liver (Sajjadi & Pasquale, 1993). cék4 was used to isolate the mouse homologue termed mek4 (mouse embryo kinase) (Sajjadi et al., 1991), not to be confused with MAP kinase/ERK kinase (MEK), which is responsible for phosphorylating the extracellular signal-regulated kinases (ERK) (Crews et al., 1992). A cDNA coding for a soluble form of mek4 was isolated at the same time as the usual membrane-spanning form. The soluble form consists of the extracellular domain only and possesses no transmembrane coding region. The mek4 gene that codes for the full-length and secreted form of the receptor possesses an internal exon which encodes a polyadenylation signal. Use of this exon would result in the secreted form of mek4 being transcribed. This phenomenon has been noted for various RTKs, including the EGF receptor, c-erbB-2 and some of the FGF receptors. There is evidence to suggest that expression of truncated receptor tyrosine kinases are developmentally regulated (Vu et al., 1993), however full-length secreted extracellular domains has not been determined. One suggestion is that they may help regulate the levels of growth factors surrounding the cell or alternatively they could bind to the full-length receptor and inhibit activation by preventing productive dimersisation (Petch et al., 1990).

The mek4 mRNA is 6.0 kb in length and expression is similar to elk in that the highest level is seen in the brain and a lower level is detected in the testis, but the mRNA found

Figure 2 Schematic representation of the eph subclass of putative receptor tyrosine kinases.
here is only 3.4 kb in length and may represent a third form of this receptor, which may again be the result of alternative splicing (Table 1). No mRNA of the soluble form of mek4 was detected, and it may be that this form is expressed in a tissue-specific and/or a stage-specific manner. Further studies are required to confirm this.

The human homologue of cek4/mek4 is termed hek. This was cloned from a cDNA library prepared from mRNA obtained from a human pre-B-cell line LK63/C20* (a variant of the parental cell line, LK63) (Wicks et al., 1992). A monoclonal antibody, III.A4, which recognises the human Hek protein, was made by immunising Balb/c mice with the LK63 cell line. This was then used to perform biochemical analysis on the Hek protein. Immunoprecipitation of labelled Hek from LK63 cells showed the mature protein to have a molecular mass of 135 kDa, and 95 kDa when deglycosylated. When Hek was immunoprecipitated from LK63 cells labelled in vivo with 32P, a weak band of 135 kDa was detected, suggesting that Hek had been phosphorylated to a low level. However, in attempts to find a specific ligand, no increase in phosphorylation of Hek was observed when cells were treated with a variety of cytokines (Boyd et al., 1992).

Two approaches were taken to determine the distribution of the Hek protein in normal and tumour tissue. The first was using immunocytochemistry on frozen sections of solid human biopsy tissues and the second was immunofluorescence followed by flow cytometry on single-cell suspensions of human haematopoietic cells and solid tumours. These results showed that normal tissue (spleen, lymph node, bone marrow, tonsil, breast and brain) and some acute lymphoblastic leukaemia, breast, cervical, prostate, ovarian and renal carcinomas were negative for Hek protein expression, whereas 1/28 chronic lymphocytic leukaemias and 2/39 acute myeloid leukaemias were positive. These data suggest that Hek may play a role in some human haematopoietic cell tumours. Northern blot analysis was performed on DNA prepared from LK63 and LK63/C20*, which express higher levels of hek than LK63 cells, no amplification or rearrangement of the hek gene was detected. Further studies should be undertaken to determine whether the hek gene is overexpressed and/or amplified in human haematopoietic cell tumours and/or solid human tumours.

hek2

The hek2 gene was isolated using PCR technology. Human cDNAs from embryonic tissue were used as templates and the primers were designed to specifically recognise eph-like receptors. The predicted amino acid sequence on the hek2 gene is most similar to the partially sequenced eph-like receptor, cek10 (Figure 1), and the gene has been located to the distal end of human chromosome 3. Northern blot analysis of human tissue, using the hek2 probe, recognised a transcript of 4.6 kb. Expression was highest in pancreas, lung, placenta, brain and kidney, with lower expression being noted in heart, skeletal muscle and liver (Table 1). hek2 transcripts were also detected in tumour cell lines of squamous and breast origin but not from epithelial cells of the lung or HeLa cells. A hek2 transcript was detected in A431 cells and lysate from these cells was used in an in vitro kinase assay using polyclonal antibodies which were raised against a synthetic peptide to the C-terminal end of the predicted Hek2 protein sequence. The phosphorylated Hek2 protein was determined to be approximately 130 kDa (Bohme et al., 1993).

Partially sequenced eph family members

Many partial cDNA sequences of putative receptors belonging to the eph family have been reported. eek (eph-and elk-related kinase) was isolated from a rat brain cDNA library and was used to isolate human erk ( elk-related kinase) (Chan & Watt, 1991). This should not be confused with the ERK proteins, which are extracellular signal-regulated kinases which become phosphorylated by MEK (Crews et al., 1992). eek mRNA was only detectable in the rat brain, whereas erk mRNA was highest in lung and lower in rat placenta, brain and kidney. Recently a longer clone of erk was isolated from a human gastric cancer cDNA library and found to differ from the original clone in one predicted amino acid residue (Iwase et al., 1993). Northern blots of RNA prepared from the stomach of embryonic and adult human cDNA from Ehrlich ascites carcinoma were probed with this longer erk clone. It was found that erk was preferentially expressed in 16 day rat embryo stomach and weakly, if at all, in the adult forestomach and glandular stomach. erk expression was much higher in 3/3 human gastric cancers examined when compared with normal gastric tissue. erk may therefore play a role in human gastric cancer.

In another study using PCR technology five partial sequences coding for eph-like receptors, tyro1, 4, 5, 6 and 11, were identified using rat cDNA as the template (Lai & Lemke, 1991). When their predicted amino acid sequences are compared with all other Eph-like receptors it is noted that 100% identity exists between rat Tyro1 and mouse Sek/chicken Cek8 (see below). One hundred per cent identity is also shared between Tyro4 and human Hek, Tyro5 and human Elk and Hek2. Tyro11 is most closely related (93% identical) at the predicted amino acid level to human Hek2. These partial clones may therefore represent homologues of the full-length Eph-like receptors. The expression of the various tyro mRNAs in adult and neonatal rat tissues was examined. tyro1 and 4 are preferentially expressed in the cells of the CNS and the level is fairly constant from embryo day 12 to adulthood for tyro1, whereas tyro4 expression drops sharply at birth. The full-length mRNA is found exclusively in the neural tissue, and the level of expression falls shortly after birth. tyro6 mRNA is found in the brain, where expression is maximal at embryonic day 12, after which it gradually falls and by 10 days after birth is fairly constant. tyro11 has a different expression pattern and is found predominantly in the heart and kidney, with a lower level being detectable in neural tissue. Five partial length eek-like receptor cDNAs were isolated from the chicken embryo cDNA library, used to isolate cek4 and 5, and a 13 day chicken embryo brain cDNA library (Sajjadi & Pasquale, 1993). These have been termed cek6, cek7, cek8, cek9 and cek10. cek6 is thought to be the avian homologue of rat elk, while cek8 is considered to be the avian homologue of rat tyro1 and murine sek. cek9 is thought to be the avian homologue of human hek2, whereas cek7 and cek9 appear to be new eph-like receptors (see the phylogenetic tree in Figure 1). cek7 mRNAs were found to be mainly expressed in embryonic and adult brain. The highest level of cek8 mRNA expression is found in the adult chicken brain and retina. cek9 mRNA levels were highest in the adult chicken thymus, and lower in the brain, retina, kidney, lung and heart (Table 1).

A variant form of cek10, termed cek10*, was isolated. This variant possesses an insert of 15 amino acids in the juxtaplasmembrane domain, similar to that seen with the cek5 variant, cek5+. This variation may be the result of alternative splicing, but the significance of this is as yet unclear. A partial eph-like receptor sequence was isolated using PCR technology. mRNA from a human breast cancer cell line was used as the template and the primers were degenerate oligonucleotides based on a tyrosine kinase-coding PCR products was found to belong to the eph family and was termed tk2 (Cance et al., 1993). At the predicted amino acid level, 91% identity is shared between Tk2 and human Eck. The level of tk2 expression was beyond the limits of detection of a Northern blot of RNA prepared from various epithelial cell lines. However, tk2 expression could be detected in some of these cell lines
when PCR technology was used, but when nine human primary and metastatic breast cancers were examined using this technique tk2 was undetectable.

Conclusions

Owing to modern molecular biology techniques the eph family is rapidly expanding, and is presently the largest known family of RTKs. However, at present only very limited information as to their possible functions is available. It appears that sek, cek5, elk, eek and possibly tyro1, 4, 5 and 6 may have roles to play in the development of the brain and central and peripheral nervous systems. As to the functions of the remaining family members, further studies must be undertaken before any conclusions can be made. Although there is preliminary evidence to suggest that eph, hek, erk and elk may be involved in some forms of human cancers, larger studies are necessary to confirm this. Other family members should also be investigated for mutations, gene amplification and/or overexpression in human carcinomas.

There is evidence to suggest that cek5, cek10 and mek4 may exist as alternatively spliced variants. The significance of the resulting truncated receptor, in the case of mek4, or receptors possessing insertions in the juxtamembrane region, as is seen with cek5* and cek10*, is as yet unknown, however this warrants further investigation. The other eph-like receptors should also be examined for splice variants.

Once the ligands for the Eph-like receptors have been identified, biochemical studies will be possible and the true functions of this large family of ‘putative’ growth factor receptors will begin to be unravelled.

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