Review

Genetic, biochemical and evolutionary facets of Xmrk-induced melanoma formation in the fish Xiphophorus

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Abstract

Certain interspecific hybrids of the fish Xiphophorus spontaneously develop melanoma induced by the derepression of the Xmrk oncogene. Xmrk is a recent duplicate of an orthologue of the mammalian epidermal growth factor receptor gene Egfr. In addition to a specific overexpression in melanoma, amino-acid substitutions in the extracellular domain leading to ligand-independent dimerisation and constitutive autophosphorylation are responsible for the tumorigenic potential of Xmrk. The Xmrk receptor induces several signal transduction pathways mediating cell proliferation and resistance to apoptosis and initiating dedifferentiation. Moreover, Xmrk upregulates the expression of the secreted protein osteopontin, inducing an autocrine loop possibly allowing invasion and survival in the dermis as a first step in malignancy. Hence, Xmrk is able to induce pathways essential for a transformed phenotype. Some of these events are equivalent to those found downstream of the mammalian Egfr, but others have clearly evolved differently or are specific for pigment cells. Xmrk is potentially hazardous, nonessential and located in a very unstable genomic region. Nevertheless, Xmrk has been maintained under purifying selection in divergent Xiphophorus species. Hence, Xmrk has probably a beneficial function under certain conditions. The analysis of this function is a major challenge for future research in the Xiphophorus model.

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Keywords: Xiphophorus; Melanoma; Platyfish; Xmrk; Egfr; Osteopontin

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1. Introduction

Melanomas are among the most aggressive forms of human cancer. Both genetic and environmental risk factors can lead to the malignant transformation of melanocytes and result in the development of the disease. Among the 10% of familial melanoma cases, tumour suppressors like the cyclin-dependent kinase inhibitor 2 A (CDKN2A) and phosphatase and tensin homologue (PTEN), but also oncogenes like the serine/threonine kinase B-Raf, have been reported to play a role (for review, see Chin, 2003). Other so-called melanoma genes have been found as well, but their significance for the molecular processes of induction and progression of malignant melanoma is barely understood. It is, however, obvious that all those factors are members of the signalling network that regulates proliferation and growth in many cell types. It is therefore important to elucidate the components of this network in pigment cells and melanoma cells. An animal model for such a research is the melanoma system of the fish *Xiphophorus*.

2. The *Xiphophorus* melanoma model

In fish of the genus *Xiphophorus*, melanoma development can be induced by generating a developmental imbalance between a dominant tumour-inducing locus (*Tu*) and a *Tu*-repressing regulatory locus (*R*, aka Diff or *R*Diff), which are located on different chromosomes in *Xiphophorus maculatus* (platyfish). The receptor tyrosine kinase gene *Xmrk* (*Xiphophorus* melanoma receptor kinase) is the oncogenic determinant encoded by the *Tu* locus, which is found in the subtelomeric region of the *X. maculatus* sex chromosomes. The molecular nature of the autosomal regulatory locus *R* could not be identified up to now, but the *Xiphophorus* orthologue of the tumour suppressor CDKN2A belongs to the same linkage group as *R* and is a promising candidate gene (see Nairn et al., 1996; Kazianis et al., 1999).

Both *Tu* and *R* (or at least an allele of *R* able to suppress the oncogenic action of *Tu*) are absent in the swordtail *Xiphophorus hellerii*. This and the presence of *R* and *Tu* on different chromosomes allow for their separation through selective breeding. When *X. maculatus* individuals are crossed with *X. hellerii*, the F1 progeny is heterozygous for both *R* and *Tu*. Further crossing of these F1 animals with *X. hellerii* produces 25% offspring heterozygous for the *Tu* locus, but devoid of *R* (Fig. 1) (Gordon, 1927; Kosswig, 1928; Anders and Anders, 1978; Schartl, 1995). In this situation, *Tu* is out of control in the pigment cell lineage, where it is overexpressed and performs its oncogenic function. This results in the formation of highly malignant, invasive and exophytic melanomas that are fatal to the fish. In addition, siblings with the genotype [+/−; −/−], [+/−; *R*/−], and [*Tu*/−; *R*/−] are produced. While the former two do not exhibit any change in pigmentation pattern because of the absence of *Tu*, the latter due to the loss of one copy of *R*, such F1-fish may develop, like the F1-fish, noninvasive, superficially spreading neoplastic pigment cell lesions, which are obviously nonmalignant (so called “benign melanoma”) (Fig. 1).

3. The melanoma-inducing *Xmrk* oncogene

*Xmrk*, the gene responsible for tumour development at the *Tu* locus, encodes a subclass I receptor tyrosine kinase belonging to the epidermal growth factor receptor (Egfr) family. In contrast to nematodes and flies, where only one egfr-like gene has been described, mammals and birds have four genes: *Egfr* (also called *HER1* or *erbB1*) as well as *HER2/neu* (*neu* or *erbB2*), *HER3* (*erbB3*) and *HER4* (*erbB4*). Probably due to an event of genome duplication having occurred early in the lineage leading to the modern-day ray-finned fishes, fish have generally at least seven egfr-like genes, including two egfr (*egfra* and *egfrb*), two *erbB3* and two *erbB4* genes (Vollff and Schartl, 2003; Gómez et al., 2003). Fish Egfra and Egfrb display an overall similarity of 69% at the amino-acid level (Gómez et al., 2003). The natural ligand of both receptors is hitherto unknown, but *egfra*-transfected mouse lymphocytes (Baf3 cells) respond with proliferation after stimulation with human EGF (Gómez et al., 2003).

The *Xmrk* oncogene was generated from *egfrb* (formerly called INV-*Xmrk*) early during the evolution of the genus *Xiphophorus* by a local event of gene duplication (Adam et al., 1993; Vollff and Schartl, 2003). With only 14 differences over about 1165 amino-acid residues, both proteins are almost identical, indicating that this duplication occurred relatively recently. Consistently, *Xmrk* is apparently restricted to the genus *Xiphophorus* (Weis and Schartl,
Egfrb and Xmrk are both located in the subtelomeric region of the sex chromosomes of *X. maculatus* where they are separated by about 1 Mb, suggesting that Xmrk was formed by intrachromosomal segmental duplication (Gutbrod and Schartl, 1999; Nanda et al., 2000; Froschauer et al., 2001 and cited references). Both genes are closely linked to the master sex-determining gene SD of the platyfish on the X and Y chromosomes (Kallman, 1984; Morizot et al., 1991; Kazianis et al., 1996; Volff and Schartl, 2001 and cited references). Other gene loci mapped in this region include the *RY* (Red/Yellow) locus, which is responsible for red, brown, orange and yellow pigmentation patterns in the iris, on the body and on the fins, and the *P* (puberty) locus, influencing the onset of sexual maturation of the fish (Kallman et al., 1973, 1989).

Another Xmrk-linked locus of great relevance for the formation of melanoma is *Mdl*, the macromelanophore-determining locus. Macromelanophores are large melanin-containing cells that produce highly polymorphic pigment patterns. They are the cellular progenitors of Xmrk-induced melanomas. *Mdl* determines not only the phenotype of macromelanophore patterns, but also, probably in combination with *Xmrk*, the location, onset and malignancy of melanoma. Therefore, *Mdl* can be defined as a tumour modifier. *Mdl* is intimately linked to but different from *Xmrk* (Weis and Schartl, 1998). The different gene loci linked to *Xmrk* and *egfrb* have not been identified so far at the molecular level, but their positional cloning has been initiated using a bacterial artificial chromosome (BAC) genomic library (Froschauer et al., 2002).

As a result of the duplication event, *Xmrk* has been fused to a new 5′ region, which is supposed to alter the transcriptional control of the oncogene (Adam et al., 1993; Volff et al., 2003). Sequence analysis in *X. maculatus* showed the presence of a large repetitive sequence called *D* (for “donor”) located directly upstream of the transcriptional start of *Xmrk* (Adam et al., 1993; Förmzler et al., 1996; Nanda et al., 1996). This suggested that *Xmrk* has been duplicated through ectopic recombination between *egfrb* and one copy of *D*, and that the *D* sequence might carry important regulatory elements significant for the abnormal transcriptional regulation of *Xmrk* in hybrids (Adam et al., 1993; Schartl, 1995). Nevertheless, subsequent comparative analysis of the 5′ region of *Xmrk* in two divergent *Xiphophorus* species (*X. maculatus* and *Xiphophorus montezumae*) and of the corresponding region from the *egfrb* proto-oncogene of *X. maculatus* minimized the role of the *D* sequence in both the formation and regulation of *Xmrk* (Volff et al., 2003; Fig. 2). In the 5′ region of *Xmrk* of *X. maculatus*, a 460-bp segment with more than 97% nucleotide identity to the promoter sequence of *egfrb* was detected upstream from *D*. This clearly demonstrated that *D* was not involved in the initial recombination event having generated *Xmrk*. The *D* sequence was rather integrated into the *Xmrk* region after duplication, and even after the divergence between *X. maculatus* and *X. montezumae*, since no *D* element was found 5′ from *Xmrk* in *X. montezumae* (Fig. 2). This also indicated that *D* does not carry any sequences important for the regulation of the transcription of *Xmrk* at least in *X. montezumae*.

Even if the *egfrb*-derived 5′ sequence of *Xmrk* was apparently more rearranged after duplication in *X. maculatus* than in *X. montezumae*, a common 500-bp large part of

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**Fig. 2.** Comparative structural analysis of the 5′ region of the *egfrb* and *Xmrk* genes in *Xiphophorus*. *D*, “Donor” sequence; *rep*, XIR sequence-containing clusters of repeats (see Volff et al., 2003). A piggyBac-like DNA transposon is integrated in the *D* sequence of the Y- but not of the X-chromosomal allele of *Xmrk* in the platyfish. A sequence with inverted repeats (IR), possibly a DNA transposable element, was inserted into the *egfrb*-related region before divergence between *X. maculatus* and *X. montezumae* (the question mark indicates that the intervening sequence between the repeats could not be completely determined). The *egfrb* sequence shown is the one located on the X chromosome of *X. maculatus* from Rio Janapa exhibiting the Spotted Dorsal macromelanophore and the Dorsal Red RY pattern.
the original promoter was maintained over millions of years in both species. This conservation suggests that this region might contain important regulatory sequences. In addition, the egfrb-derived 5′ sequence is flanked by clusters of repetitive sequences (rep) in both Xiphophorus species analyzed (Fig. 2). These clusters particularly carry putative promoters predicted as “excellent” as well as sequences related to the XIR repeat (Volf et al., 2003). XIR is able to activate the transcription of a reporter gene after UV-B irradiation (Roushdy et al., 1999). Hence, these observations suggest not only that XIR-containing repeat clusters might have been involved in the recombination event responsible for the formation of Xmrk, but also that these repeats might play a role in the regulation of the transcription of the oncogene.

The fact that Xmrk is exclusively overexpressed in malignant melanoma suggests the involvement of a pigment cell-specific transcription factor in tumour development. One obvious candidate is the Mitf-m protein (Altschmied et al., 2002; Delfgaauw et al., 2003). Accordingly, putative Mitf-m binding sites have been found in the rep clusters (unpublished observation), but their functionality has not been tested so far. Specific hypomethylation of sequences close to the transcriptional start site of the Xmrk oncogene has been reported, but the relevance of this is still unclear (Altschmied et al., 1997).

In addition to overexpression, amino-acid differences in the extracellular domain between Xmrk and its corresponding proto-oncogene egfrb are responsible for the tumorigenic potential. Two amino-acid substitutions (C578S and G359R) in the Xmrk protein interfere sterically with the formation of intramolecular disulfide bridges, leading to free cysteine residues in the extracellular part of the monomer. As a result, intermolecular disulfide bridges are formed. This leads to a permanent, ligand-independent dimerisation of the tyrosine kinase, constitutive autophosphorylation and deregulated signal transduction (Gómez et al., 2001). Comparable situations are seen in cells transformed with the retroviral oncogene v-ErbB and human EGFRvIII. Compared with EGFR, the extracellular (EC) part of EGFRvIII comprises a deletion of 269 amino acids, while in v-ErbB, only 70 amino acids of the EC domain are left (Graf and Beug, 1978; Roussel et al., 1979; Tang et al., 2000). Both oncogenic receptors are able to form constitutively active homo- or heterodimers which induce tumour development (Maihle et al., 1988; Adelsman et al., 1996; Moscatello et al., 1996). In Xiphophorus melanoma cells, the dimerisation occurs already in the endoplasmic reticulum and slows down the processing of the Xmrk receptor (Gómez et al., 2001). Only a fraction of newly synthesized Xmrk protein reaches the cell surface, but in analogy to a mutant of the cytokine receptor EPO-R and certain Ret receptor mutants, cell signalling may even occur from the endoplasmic reticulum-located receptor (Watowich et al., 1992; Bongarzone et al., 1999).

4. Xmrk-dependent signal transduction

As Xmrk is one fish orthologue of the well-studied mammalian EGFR, it is not surprising to find that it uses a number of pathways that have been established for EGFR signalling in other organisms from Caenorhabditis elegans to human. Like other receptor tyrosine kinases, it possesses a carboxy-terminus which contains specific substrate-binding sites. Certain phosphorylated tyrosine residues serve as docking sites for adapter proteins with src homology (SH) domains. In the cell line PSM, which is derived from malignant Xiphophorus melanoma, Xmrk is constitutively associated with the adapter GRB2 directly and via the SH2 and SH3 domains of Shc (Wellbrock and Schartl, 1999, 2000). Analogous to the situation of the stimulated EGF receptor, this association is followed by the induction of the ras/raf/MAPK pathway that mediates cell proliferation and resistance to apoptosis. Accordingly, PSM cells and Xiphophorus melanoma tissue exhibit a permanently elevated level of phosphorylated B-Raf (unpublished results), MEK and ERK (Wellbrock and Schartl, 1999; Wellbrock et al., 2002a). The src kinase fyn is also associated with the C-terminus of Xmrk and augments MAPK pathway signalling by inhibiting MAPK phosphatase 1 (MKP-1) (Wellbrock et al., 2002b).

This situation described for Xiphophorus melanoma is in perfect agreement with findings from many mammalian melanoma cell lines and tumour tissues, which show a high basal ERK activity. It is most likely that this is the result of mutations in upstream components of the MAPK pathway or autocrine growth factor loops (Smalley and Eisen, 2000, 2002; Ge et al., 2002; Smalley, 2003). For analyzing Xmrk signalling specifically in the pigment cell lineage, we use a model system where mouse melanocytes are stably transfected with a chimeric receptor that consists of the extracellular part of human EGFR and the cytoplasmic part of the fish receptor (HERmrk). This circumvents the problem of continuous stimulation of Xmrk-induced pathways due to its constitutive dimerisation and enables us to induce the signalling by providing EGF (which is readily available as a recombinant protein), while keeping the cytoplasmic kinase domain and docking sites of the fish receptor intact. In this system, we have observed the MAPK-dependent initiation of a dedifferentiation process, depicted by a loss of melanogenesis (Wellbrock et al., 2002b; Delfgaauw et al., 2003). Moreover, this pathway upregulates the RNA and protein expression of the secreted protein osteopontin (Opn), an arginine/glycine/aspartic acid (RGD) containing protein that binds to αvβ3 integrins on the cell surface (Geissinger et al., 2002; Fig. 3).

This kind of “inside-out”-signalling has been directly linked to neoplastic progression and tumorigenicity in melanoma, and αvβ3 integrins are often upregulated in metastasizing cells (Felding-Habermann et al., 1992; Seftor, 1998). In the HERmrk expressing mouse melanocytes, binding of Opn allows the cells to survive in 3D collagen matrices. It suppresses apoptosis, which is usually initiated.
by extracellular matrix (ECM) components like collagen or laminin. In normal melanocytes, cell death is quickly induced in such an environment, but melanoma cells are able to survive. Autocrine Opn loops may be the important factor that allows invasion and survival in the dermis as a first step in malignancy.

Phosphatidylinositol 3-kinase (PI3K) is another protein that binds to phosphorylated tyrosine residues of Xmrk and becomes activated (Wellbrock et al., 1999; Wellbrock and Schartl, 2000). The p85 subunit of the heterodimeric protein binds directly to residue Y983, which leads to activation of the catalytic subunit p110α and the induction of anti-apoptotic signals via the downstream effector Akt, also known as protein kinase B. As revealed by the formation of a ternary complex between Xmrk, fyn and PI3K in Xiphophorus melanoma, PI3K signalling is also triggered by receptor-bound fyn (Wellbrock and Schartl, 2000). In human dysplastic nevi and melanoma, an increased activity of Akt is frequently observed and correlates with the nuclear localisation of NF-κB (Dhawan et al., 2002). On the other hand, the tumour suppressor PTEN dephosphorylates the 3'-phosphate from the second messenger phosphatidylinositol-3,4,5-trisphosphate (PIP3) that is generated by PI3 kinase and thereby attenuates downstream effects. From 5% to 15% of analyzed human melanomas exhibit mutations or deletions of the PTEN gene, and growth factor-induced NF-κB activation can result in downregulation of PTEN mRNA (Guldberg et al., 1997; Teng et al., 1997; Vasudevan et al., 2004). Nevertheless, in the HERmrk expressing mouse melanocytes, the mRNA level of this tumour suppressor is not altered in response to receptor engagement, which suggests that increased levels of PIP3 are maintained only through high PI3K activity (data not shown).

A further contribution to the transformed phenotype of Xmrk expressing cells comes from the continuous binding and phosphorylation of the signal transducer and activator of transcription STAT5. STAT5 activation has important roles in cell differentiation, cell cycle control and development (Bowman et al., 2000; Levy and Gilliland, 2000). While other STAT proteins regularly bind to phosphorylated tyrosine residues of the intracellular part of receptor tyrosine kinases, an unusual, tyrosine-phosphate-independent type of binding of STAT5 to Xmrk was found (Morcinek et al., 2002). After this interaction, STAT5 is phosphorylated by the kinase domain of Xmrk and translocates to the nucleus where it activates specific target genes. In the Xiphophorus...
melanoma cell line PSM, the transcription factor is permanently found in the nucleus and induces proliferation signals and the expression of the antiapoptotic protein bcl-x (Morcinek et al., 2002). Accordingly, a positive correlation of STAT5 activation and the resulting SOCS2/3 inactivation with human melanoma development has recently been observed (Mirmohammadsadegh et al., unpublished results). In contrast, STAT1 and STAT3, which are involved in the development of several tumour types including melanoma, do not play a role in Xmrk-mediated signalling (Baudler et al., 1999; Morcinek et al., 2002). This highlights the specificity of STAT5 activation by Xmrk in Xiphophorus melanophore melanomas and attributes to this STAT protein an important role in pigment cell transformation.

In summary, Xmrk is able to induce several signal transduction pathways that are essential for the full neoplastic phenotype of the cell (Fig. 4). Some of these events are equivalent to the situation found in pathways downstream of mammalian Egfr; others have developed clearly differently or are specific for pigment cells.

The gene encoding the putative fish homologue for the mouse tumour suppressor CDKN2A—namely, CDKN2X— is located on the same linkage group as R and has therefore been discussed as a candidate gene for the Tu-repressor (Kazianis et al., 1998). In contrast to the situation in human melanoma, CDKN2X is overexpressed in Xiphophorus melanomas, and analysis of the methylation state of CpG islands in the promoter region revealed no clear explanation for this phenomenon (Kazianis et al., 2000). At present, no biochemical data, which directly link the signal transduction initiated by Xmrk to cell cycle control, are available. It can only be speculated whether CDKN2X is potentially acting upstream or downstream of the receptor tyrosine kinase.

5. What is the “raison d’être” of Xmrk?

By plotting the presence/absence of Xmrk onto a molecular phylogeny of all known Xiphophorus species, it becomes apparent that its distribution is discontinuous (Weis and Schartl, 1998). Phylogenetic analysis of Xmrk and egfrb sequences from different species supports a unique origin of Xmrk before the divergence of the known Xiphophorus species a few million years ago (unpublished data). Xmrk has then been lost several times during the evolution of the genus Xiphophorus. It is completely absent from several species. Numerous species and populations are polymorphic for the presence of Xmrk, and the frequency of individuals with macromelanophores ranges from less than 1% to more than 50% of a given population (Gordon and Gordon, 1957). In addition, this gene has been found to become inactivated in laboratory strains by different mechanisms including deletion and disruption by retrotransposable elements (Schartl et al., 1999). Thus far, no differences with respect to viability, fertility or any other trait have been noted between Xmrk-carrying or Xmrk-deficient genotypes. Hence, Xmrk is generally dispensable under both natural and laboratory conditions.

The Xmrk oncogene is located like egfrb in the subtelomeric region of the sex chromosomes of the platyfish (Nanda et al., 2000). The genomic region around Xmrk is extremely unstable and undergoes genome rearrangements of different types very frequently. Particularly, like egfrb/Xmrk, many genes have been duplicated in this region (Volff et al., 2003 and unpublished). Generally, these duplicates are subsequently inactivated by deletion, disruption by transposable elements or other kinds of rearrangements, as occasionally observed for Xmrk. The Xmrk region looks like a “cemetery full of dead genes” (Volff et al., 2003).

In summary, Xmrk is apparently dispensable and located in a very unstable genomic region where genes are rapidly inactivated. In addition, this gene is potentially hazardous and can induce melanoma even in nonhybrid fishes (Schartl et al., 1995; Kazianis and Borowsky, 1995). One might therefore expect selection acting in favour of the elimination of Xmrk. However, a functional Xmrk with intact oncogenic potential has been maintained in several divergent Xiphophorus species over millions of years of evolution (Weis and Schartl, 1998). In the platyfish, Xmrk appears as an island of coding sequences properly encircled by multiple pseudogenes and repeats. For example, a DNA transposon, the D element, is integrated directly 5’ of the transcriptional start of Xmrk, and has been itself disrupted by a piggyBac-like DNA transposon on the Y- but not on the X-chromosome (Fig. 2). In addition, a copy of the retrotransponson Jule is inserted less than 60 nucleotides downstream of the polyadenylation signal (not shown). The functional persistence of the potentially hazardous, generally nonessential Xmrk over million years of evolution in such a very unstable genomic region suggests that this gene might fulfill a so far unknown beneficial function under certain conditions in Xiphophorus. This is supported by the fact that the ratio of substitutions is four times higher at synonymous than at nonsynonymous positions, indicating that Xmrk evolved under purifying selection acting in favour of the maintenance of its functionality (Volff and Schartl, 2003). New studies are now required to elucidate the function(s) of Xmrk and to understand how a cancer-promoting gene can be advantageous for its host under certain conditions.

Acronyms and abbreviations

<table>
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<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>Akt</td>
<td>V-Akt murine thymona viral oncopgene homologue, aka protein kinase B (PKB)</td>
</tr>
<tr>
<td>BAC</td>
<td>Bacterial artificial chromosome</td>
</tr>
<tr>
<td>Baf3</td>
<td>Murine lymphoid cell line dependent on interleukin-3</td>
</tr>
<tr>
<td>Bcl-x</td>
<td>Bcl2-related regulator of programmed cell death</td>
</tr>
<tr>
<td>B-Raf</td>
<td>v-Raf murine sarcoma viral oncogene homologue B1, serine/threonine kinase</td>
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<tr>
<td>CDKN2A</td>
<td>Cyclin-dependent kinase inhibitor 2A</td>
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CDKN2X \(^{Xiphophorus}\) homologue of CDKN2A, candidate for R

\(D\) \(^{Xiphophorus}\) “donor” repetitive sequence integrated 5′ from the transcription start of \(Xmrk\)

EC Extracellular

ECM Extracellular matrix

EGF Epidermal growth factor

Egfr Epidermal growth factor receptor (aka HER1 or ErB1)

Egfra One of the two orthologues of Egfr in fish

Egfr b One of the two orthologues of Egfr in fish, protooncogenic counterpart of Xmrk (aka INV-Xmrk)

EPO-R Erythropoietin receptor EPO-R

ErbB2 v-ErbB2 avian erythroblastic leukemia viral oncogene homologue 2 (aka HER2, Neu), member of the Egfr family

ErbB3 v-ErbB2 avian erythroblastic leukemia viral oncogene homologue 3 (aka HER3), member of the Egfr family

ErbB4 v-ErbB2 avian erythroblastic leukemia viral oncogene homologue 4 (aka HER4), member of the Egfr family

Erb Extracellular signal regulated protein kinase

Erk Extracellular signal regulated protein kinase

Fyn Tyrosine kinase related to SRC, FGR, YES

GRB2 Growth factor receptor-bound 2

HERmrk Chimeric HER1/Xmrk receptor

IR Inverted repeat (not related to \(XIR\))

INV-Xmrk Protooncogenic counterpart of Xmrk (aka Egfrb)

MAPK Mitogen-activated protein kinase

Mdl \(^{Xiphophorus}\) macromelanophore-determining locus

MEK Map/Erk kinase

Mitf-m Microphthalmia-associated transcription factor (melanocyte-specific isoform)

MKP-1 Mitogen-activated protein kinase phosphatase 1

NF-\(\kappa\)B Nuclear factor kappa-B

Osn Osteopontin

\(P\) \(^{Xiphophorus}\) puberty locus

PIP3 Phosphatidylinositol-3,4,5-trisphosphate

P13K Phosphatidylinositol-3-kinase

PKB Protein kinase B, aka V-Akt murine thymoma viral oncogene homologue (Akt)

PSM \(^{Xiphophorus}\) melanoma cell line

PTEN Phosphatase and tensin homologue

\(R\) \(^{Xiphophorus}\) Tu-repressing regulatory locus (aka Diff or \(R_{Diff}\))

Ras Harvey rat sarcoma viral oncogene homologue, small G-protein

rep Cluster of repetitive sequences in the \(Xmrk\) region of \(Xiphophorus\)

Ret Rearranged during transfection protooncogene, receptor tyrosine kinase

\(RY\) \(^{Xiphophorus}\) Red–Yellow pigmentation locus

\(SD\) \(^{Xiphophorus}\) sex-determining locus

SH2/3 Src homology domains

SHC SH2/SH3-containing signalling and transforming molecule

SOCS Suppressor of cytokine signalling

SOS Son of sevenless homologue, guanine nucleotide exchange factor

Src v-src avian sarcoma (Schmidt–Ruppin A-2) viral oncogene homologue, tyrosine kinase

STAT Signal transducer and activator of transcription

\(Tu\) \(^{Xiphophorus}\) tumour-inducing locus

\(XIR\) \(^{Xiphophorus}\) retrotransposon-like repetitive sequence (not related to IR)

Xmrk \(^{Xiphophorus}\) melanoma receptor kinase (aka ONC-Xmrk)

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References


