Signaling by ERBB2 in Cancer

Bose, R., Kancha, RK., Krishna, A., Orlic-Milacic, M.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

28/03/2022
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 79

This document contains 7 pathways (see Table of Contents)
Gene amplification of the ERBB2 (HER2) oncogene is observed across various different cancer types. In addition to HER2 gene amplification, sequencing of tumour samples have revealed HER2 mutations, which fall within three major regions: the extracellular domain (ECD), transmembrane domain/juxtamembrane domain (TMD/JMD) and kinase domain (KD). Based on the functional studies of their catalytic activity, signaling and drug sensitivity, as well as their time of occurrence with respect to treatment, these mutations can be classified as primary mutations, that can be activating or silent, and may confer drug resistance, and secondary mutations, associated with development of drug resistance upon initial response to targeted therapy.

Overexpression of ERBB2 (HER2) protein, usually as a consequence of ERBB2 gene amplification, leads to formation of constitutively active, growth factor independent, ERBB2 homodimers, which are sensitive to the therapeutic antibody trastuzumab (herceptin) (Pickl and Ries 2009).

Co-overexpression of ERBB2 and its dimerization partner ERBB3 leads to formation of both ERBB2 homodimers and ERBB2:ERBB3 heterodimers and is associated with chemotherapy resistance and reduced relapse-free and overall survival (Spears et al. 2012).


Sensitivity to tyrosine kinase inhibitors (TKIs) and the therapeutic antibody trastuzumab (herceptin) differs between different ERBB2 KD mutants (Bose et al. 2013, Rexer et al. 2013, Nagano et al. 2018).
ERBB2 extracellular domain (ECD) mutants harbor missense mutations that lead to substitutions of amino acid residues in the heterodimerization arm contact surface, involved in formation of ERBB2 heterodimers (Greulich et al. 2012).

Recurrent missense mutations in regions encoding the transmembrane domain (TMD) and the juxtamembrane domain (JMD) are frequently reported in cancer. TMD and JMD mutations can activate ERBB2 signaling by improving the active dimer interface or by stabilizing the active conformation (Ou et al. 2017, Pahuja et al. 2018).

ERBB2 TMD/JMD mutants differ in their sensitivity to the therapeutic antibody pertuzumab, which blocks ligand-driven heterodimerization of ERBB2 (Pahuja et al. 2018).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019-07-31</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2019-09-16</td>
<td>Reviewed</td>
<td>Kancha, RK.</td>
</tr>
<tr>
<td>2019-11-01</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
Constitutive Signaling by Overexpressed ERBB2

Location: Signaling by ERBB2 in Cancer

Stable identifier: R-HSA-9634285

Diseases: cancer

Overexpression of ERBB2 (HER2), usually as a consequence of ERBB2 gene amplification, results in formation of ERBB2 homodimers. Under normal conditions, only ERBB2 heterodimers form, as ERBB2 is expressed at low levels.

ERBB2 homodimerization leads to activation of ERBB2 signaling in the absence of growth factors. Signaling by ERBB2 homodimers mainly activates the RAS/RAF/MAPK signaling cascade, while PI3K/AKT signaling is not significantly affected (Pickl and Ries 2009).

Trastuzumab (Herceptin), a recombinant antibody clinically approved as an anti-cancer therapeutic for ERBB2-overexpressing cancers, preferentially binds to ERBB2 homodimers (Pickl and Ries 2009).

Accurate functional analysis of ERBB2 signaling may require 3D instead of 2D cell culture (Pickl and Ries 2009).

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019-01-09</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2019-09-16</td>
<td>Reviewed</td>
<td>Kancha, RK.</td>
</tr>
<tr>
<td>2019-11-01</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
Mutations in the kinase domain (KD) of ERBB2 result in constitutive activation of ERBB2 signaling, facilitate heterodimerization of ERBB2 with other EGFR family members and increase the signaling intensity, leading to cellular transformation (Kancha et al. 2011).

Only a subset of potential heterodimerization partners has been tested for most ERBB2 KD mutant proteins, so our annotations here are correspondingly limited. ERBB2 L755S and ERBB2 V777L cancer variants were shown to heterodimerize with ERBB3 (HER3) at a higher rate than wild type ERBB2 (Croessmann et al. 2019). Increased activity of ERBB2 L755S, ERBB2 L755P, ERBB2 V777L, ERBB2 D769H, ERBB2 D769Y, ERBB2 V842I, ERBB2 R896C and ERBB2 P780_Y781insGSP in the presence of either EGFR (Kancha et al. 2011, Bose et al. 2013) or ERBB3 (Kancha et al. 2011, Bose et al. 2013, Collier et al. 2013) as a heterodimerization partner was also observed. The interplay of ERBB2 P780_Y781insGSP, ERBB2 I767M and ERBB2 R896C with ERBB3 has not been tested. ERBB2 L869R mutant shows increased activity in the presence of dimerization-facilitating ERBB3 E928G mutants (Hanker et al. 2017). The interplay of ERBB2 L869R with EGFR has not been tested. Heterodimerization of ERBB2 KD mutants with ERBB4 has not been tested and ERBB4 is a candidate heterodimerization partner for these KD variants.

ERBB2 H878Y mutant has ten times higher kinase activity than the wild type ERBB2 (Hu, Wan et al. 2015; Hu, Hu et al. 2015), but its heterodimerization properties have not been studied and it is therefore annotated as a candidate.

Ligand requirements have not been studied in the context of heterodimerization of ERBB2 KD mutants, but it is assumed that ligands are required.

(COSMIC database: Forbes et al. 2017) and they are annotated as candidates. ERBB2 T733I (Trowe et al. 2008), ERBB2 T798I (Trowe et al. 2008, Hanker et al. 2017) and ERBB2 T798M (Hanker et al. 2017) usually occur as secondary ERBB2 mutations and are responsible for treatment failure. On their own, ERBB2 T733I and ERBB2 T798I appear to be weakly transforming compared with the other ERBB2 KD mutants. As their signaling properties have been poorly studied, ERBB2 T733I, ERBB2 T798I and ERBB2 T798M are annotated as candidates.

The binding of ERBB2 KD mutants to ERBIN and the HSP90:CDC37 chaperone:co-chaperone complex has not been tested but is assumed to occur similarly to the wild type ERBB2.

Signaling by ERBB2 KD mutants has been organized into subpathways based on the current knowledge of biology of these mutants (heterodimerization, downstream signaling, drug interaction) and on the sequence similarity of their mutations.

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019-07-31</td>
<td>Authorized</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2019-09-16</td>
<td>Reviewed</td>
<td>Kancha, RK.</td>
</tr>
<tr>
<td>2019-11-01</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
Drug resistance in ERBB2 KD mutants

Location: Signaling by ERBB2 in Cancer

Stable identifier: R-HSA-9665230

Diseases: cancer

ERBB2 kinase domain (KD) mutants vary in their resistance to various tyrosine kinase inhibitors and therapeutic antibody trastuzumab (herceptin).

The following ERBB2 KD mutants are resistant to the therapeutic antibody trastuzumab (herceptin):

ERBB2 L755P (Nagano et al. 2018);
ERBB2 L755S (Nagano et al. 2018);
ERBB2 I767M (Bose et al. 2013);
ERBB2 D769Y (Nagano et al. 2018);
ERBB2 V777L (Nagano et al. 2018);
ERBB2 P780_Y781insGSP (Bose et al. 2013, Nagano et al. 2018);
ERBB2 T798M (Rexer et al. 2013);
ERBB2 V842I (Nagano et al. 2018);
ERBB2 T862A (Nagano et al. 2018);
ERBB2 L869R (Hanker et al. 2017);

For ERBB2 R896C, both resistance (Bose et al. 2013) and sensitivity (Nagano et al. 2018) to trastuzumab...
have been reported.

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Reviewed</th>
<th>Authored</th>
<th>Edited</th>
<th>Reviewed</th>
<th>Authored</th>
<th>Edited</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019-11-01</td>
<td>Orlic-Milacic, M.</td>
<td>Orlic-Milacic, M.</td>
<td>Orlic-Milacic, M.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ERBB2 extracellular domain (ECD) mutants harbor missense mutations that lead to substitutions of amino acid residues in the heterodimerization arm contact surface, involved in formation of ERBB2 heterodimers. The functionally studied ERBB2 ECD mutants, ERBB2 G309A (Bose et al. 2013), ERBB2 G309E (Greulich et al. 2012) and ERBB2 S310F (Greulich et al. 2012) seem to preferentially heterodimerize with EGFR. Heterodimerization of ERBB2 G309E involves formation of disulfide bonds (Greulich et al. 2012). ERBB2 S310F shows stronger activation of downstream signaling than ERBB2 G309A and ERBB2 G309E, and is hyperphosphorylated on tyrosine residues in the C-tail (Greulich et al. 2012), while the C-tail phosphorylation of ERBB2 G309A (Bose et al. 2013) and ERBB2 G309E (Greulich et al. 2012) is comparable to the wild type ERBB2.

RAS signaling and PLCgamma1 signaling are activated downstream of all three ERBB2 ECD mutants, ERBB2 G309A (Bose et al. 2013), ERBB2 G309E (Greulich et al. 2012) and ERBB2 S310F (Greulich et al. 2012), as evidenced by activating phosphorylation on ERKs (MAPK1 and MAPK3) and PLCG1, respectively. ERBB2 G309E and ERBB2 S310F also activate PI3K/AKT signaling, demonstrated by activating phosphorylation of AKT1 (Greulich et al. 2012). Activation of PI3K/AKT signaling downstream of ERBB2 G309A has not been tested. Signaling downstream of ERBB2 S310Y has been poorly characterized and it is annotated as a candidate. Many regulators of cell migration show increased phosphorylation in cells expressing ERBB2 G309E and ERBB2 S310F (Greulich et al. 2012).

Compared with the wild type ERBB2, ERBB2 G309E, ERBB2 S310F and ERBB2 S310Y are more sensitive to the ERBB2-directed therapeutic antibody trastuzumab (herceptin) and to tyrosine kinase inhibitors lapatinib, neratinib and afatinib (Greulich et al. 2012). ERBB2 G309A was also responsive to trastuzumab, lapatinib and neratinib (Bose et al. 2013).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019-10-25</td>
<td>Reviewed</td>
<td>Bose, R., Krishna, A.</td>
</tr>
<tr>
<td>2019-10-30</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2019-11-01</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2019-11-03</td>
<td>Reviewed</td>
<td>Kancha, RK.</td>
</tr>
</tbody>
</table>
Recurrent missense mutations in regions encoding the transmembrane domain (TMD) and the juxtamembrane domain (JMD) are frequently reported in cancer. The ERBB2 TMD mutants include ERBB2 V659E, ERBB2 V659K, ERBB2 G660D, ERBB2 G660R, ERBB2 S653C, ERBB2 R677L and ERBB2 R678Q. The ERBB2 JMD mutants include ERBB2 E693K and ERBB2 Q709L. ERBB2 TMD mutants ERBB2 V659E, ERBB2 G660D and S653C (de Martino et al. 2014) are known to be activating. ERBB2 TMD/JMD mutants ERBB2 R678Q, ERBB2 E693K, and ERBB2 Q709L mutations may be activating when co-expressed with a wild type ERBB2 receptor (Pahuja et al. 2018). TMD and JMD mutations can activate ERBB2 signaling by improving the active dimer interface or by stabilizing the active conformation. TMD/JMD mutants that are activating in the presence of wild type ERBB2, such as ERBB2 R678Q, may form homodimers with the wild type ERBB2 (Pahuja et al. 2018).

Based on trans-autophosphorylation of ERBB2 and its dimerization partners EGFR and ERBB3, the following ERBB2 TMD/JMD mutants are assumed to form heterodimers with EGFR and ERBB3:

ERBB2 S653C (de Martino et al. 2014)

ERBB2 R678Q (Bose et al. 2013, Pahuja et al. 2018).

Phosphorylation of tyrosine residues in the C-tail of ERBB2 was shown for the following ERBB2 TMD/JMD mutants:

ERBB2 V659E (Pahuja et al. 2018);

ERBB2 V659K (Pahuja et al. 2018);

ERBB2 G660D (Pahuja et al. 2018);

ERBB2 G660R (Pahuja et al. 2018);

ERBB2 S653C (de Martino et al. 2014 - phosphorylation at Y1248 demonstrated);

ERBB2 R677L (Pahuja et al. 2018);
ERBB2 R678Q (Bose et al. 2013; de Martino et al. 2014 - phosphorylation at Y1248 demonstrated; Pahuja et al. 2018); ERBB2 Q709L (Pahuja et al. 2018)

Phosphorylation of tyrosine residues in the C-tail of EGFR was demonstrated for ERBB2 S653C (de Martino et al. 2014 - phosphorylation at Y1068) and ERBB2 R678Q (Bose et al. 2013; de Martino et al. 2014 - phosphorylation at Y1068).

Phosphorylation of tyrosine residues in the C-tail of ERBB3 was demonstrated for ERBB2 S653C (de Martino et al. 2014 - phosphorylation at Y1197) and ERBB2 R678Q (Bose et al. 2013; de Martino et al. 2014 - phosphorylation at Y1197).

Activation of downstream RAS signaling was shown for ERBB2 S653C (de Martino et al. 2014) and ERBB2 R678Q (Bose et al. 2013, de Martino et al. 2014) through activating tyrosine phosphorylation on ERKs (MAPK1 and MAPK3) and SHC1.

Activation of downstream PLCG1 signaling was demonstrated for ERBB2 R678Q, through activating tyrosine phosphorylation on PLCG1 (Bose et al. 2013).

Activation of PI3K/AKT signaling by ERBB2 TMD/JMD mutants has not been tested.

Signaling by ERBB2 V659K, ERBB2 G660D, ERBB2 G660R, ERBB2 R677L, ERBB2 E693K and ERBB2 Q709L has not been sufficiently studied and they are annotated as candidates.

The following ERBB2 TMD/JMD mutants are sensitive to the therapeutic antibody trastuzumab (herceptin):

ERBB2 V659E (Pahuja et al. 2018);
ERBB2 G660D (Pahuja et al. 2018);
ERBB2 G660R (Pahuja et al. 2018);
ERBB2 R678Q (Bose et al. 2013, Pahuja et al. 2018);
ERBB2 Q709L (Pahuja et al. 2018);

With respect to pertuzumab, a therapeutic antibody that block ligand-driven heterodimerization of ERBB2, ERBB2 R678Q is sensitive to pertuzumab, while ERBB2 V659E, ERBB2 G660D, ERBB2 G660R and probably ERBB2 Q709L are resistant (Pahuja et al. 2018).

The following ERBB2 TMD/JMD mutants are sensitive to lapatinib:

ERBB2 S653C (de Martino et al. 2014);
ERBB2 R678Q (Bose et al. 2013);

The following ERBB2 TMD/JMD mutants are sensitive to neratinib:

ERBB2 V659E (Pahuja et al. 2018);
ERBB2 G660D (Pahuja et al. 2018);
ERBB2 G660R (Pahuja et al. 2018);
ERBB2 R678Q (Bose et al. 2013, Pahuja et al. 2018);
ERBB2 Q709L (Pahuja et al. 2018);

The following ERBB2 TMD/JMD mutants are sensitive to afatinib:
ERBB2 G660D (Pahuja et al. 2018);
ERBB2 G660R (Pahuja et al. 2018);
ERBB2 S653C (de Martino et al. 2014);
ERBB2 R678Q (Pahuja et al. 2018);
ERBB2 Q709L (Pahuja et al. 2018).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019-10-25</td>
<td>Reviewed</td>
<td>Bose, R., Krishna, A.</td>
</tr>
<tr>
<td>2019-10-31</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2019-11-01</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2019-11-03</td>
<td>Reviewed</td>
<td>Kancha, RK.</td>
</tr>
</tbody>
</table>
With respect to pertuzumab, a therapeutic antibody that block ligand-driven heterodimerization of ERBB2, ERBB2 R678Q is sensitive to pertuzumab, while ERBB2 V659E, ERBB2 G660D, ERBB2 G660R and probably ERBB2 Q709L are resistant (Pahuja et al. 2018).

**Literature references**

Table of Contents

Introduction 1

- Signaling by ERBB2 in Cancer 2
  - Constitutive Signaling by Overexpressed ERBB2 4
  - Signaling by ERBB2 KD Mutants 5
  - Drug resistance in ERBB2 KD mutants 7
  - Signaling by ERBB2 ECD mutants 9
  - Signaling by ERBB2 TMD/JMD mutants 11
  - Drug resistance in ERBB2 TMD/JMD mutants 14

Table of Contents 15