# The ligand shedding module

The reactions in current ligand shedding module:

NB: some of the reactions and kinetics can be changed (i.e. combined, expanded, replaced with better ones) in order to fit to the data and experimental results.

1. Shedding module:
   1. Activated ERK (pERK) binds to iRhom-TACE complex and phosphorylate iRhom
      1. pErk + iRhomTace -> pErkiRhomTace; kfErkiRhom \* pErk \* iRhomTace - kbErkiRhom \* pErkiRhomTace
      2. pErkiRhomTace -> pErk + iRhompTace; kpErkiRhom \* pErkiRhomTace
   2. Phosphorylated iRhom binds to 14-3-3 then TACE dissociate from iRhom
      1. iRhompTace + Pro1433 -> iRhompPro1433Tace; kfiRhomp1433 \* iRhompTace \* Pro1433 - kbiRhomp1433 \* iRhompPro1433Tace
      2. iRhompPro1433Tace -> iRhompPro1433 + Tace; kDisTace \* iRhompPro1433Tace
   3. TACE catalyze the ligands at membrane into soluble ligands
      1. Tace + mTgfa -> Tace + Tgfa; kShedTace \* Tace \* mTgfa
   4. Expression, internalization and degradation of iRhom-TACE complex, TACE, iRhomP-14-3-3 complex, 14-3-3 proteins
      1. -> iRhomTace; kExpiRhomTace
      2. -> Pro1433; kExp1433
      3. Pro1433 -> ; kDeg1433 \* Pro1433
      4. iRhompPro1433 -> ; kIniRhomp1433 \* iRhompPro1433
      5. Tgfa -> ; kDegTgfa \* Tgfa
      6. Tace -> ; kInTace \* Tace
      7. iRhomTace -> ; kIniRhomTace \* iRhomTace
      8. iRhompTace -> ; kIniRhompTace \* iRhompTace
   5. Phosphorylation of iRhom by Lpa
      1. Lpa + iRhomTace -> Lpa + iRhompTace; kpLpaiRhom \* Lpa \* iRhomTace
2. ERK activation module:
   1. ERK activation based on the available extracellular ligands
      1. Tgfa + Erk -> Tgfa + pErk; (basal + kAct \* (Tgfa / KD)^n / (1 + (Tgfa / KD)^n) ) \* Erk
      2. pErk -> Erk; kDephoErk \* pErk
3. Ligand expression module:
   1. TGFa transcription with activated ERK
      1. pERK -> pERK + mRna\_Tgfa; basal + kTrc \* (mRna\_Tgfa / KD)^n / (1 + (mRna\_Tgfa / KD)^n)
      2. mRna\_Tgfa -> ; kDegRna \* mRna\_Tgfa
   2. TGFa translation
      1. mRna\_Tgfa -> mRna\_Tgfa + mTgfa; kTrl \* mRna\_Tgfa
   3. mTGFa transportation
      1. mTgfa -> mTgfaIn; kInmTgfa \* mTgfa
      2. mTgfaIn -> mTgfa; kRecyc \* mTgfaIn
      3. mTgfaIn -> ; kDegmTgfa \* mTgfaIn

Species:

1. Shedding module:

pErk: phosphorylated ERK

iRhomTace: protein complex of iRhom and TACE (Adam17)

pErkiRhomTace: protein complex of phosphorylated ERK, iRhom and TACE

iRhompTace: protein complex of phosphorylated iRhom and TACE

Pro1433: 14-3-3 protein

iRhompPro1433Tace: protein complex of phosphorylated iRhom, 14-3-3 and TACE

iRhompPro1433: protein complex of phosphorylated iRhom and 14-3-3

Tace: TACE protein

mTgfa: TGFalpha precursor at membrane

Tgfa: soluble TGFalpha

Lpa: LPA

1. ERK activation module:

Erk: ERK

1. Ligand expression module:

mRna\_Tgfa: mRNA of TGFalpha

mTgfaIn: internalized TGFalpha precursor

Parameters:

1. Shedding module:

kfErkiRhom: forward binding rate constant of phosphorylated ERK and iRhom

kbErkiRhom: dissociation rate constant of ERK and iRhom complex

kpErkiRhom: phosphorylation rate constant of iRhom by phosphorylated ERK

kfiRhomp1433: forward binding rate constant of phosphorylated iRhom and 14-3-3

kbiRhomp1433: dissociation rate constant of phosphorylated iRhom and 14-3-3 complex

kDisTace: dissociation rate constant of TACE from phosphorylated iRhom

kShedTace: rate constant of proteolysis by TACE

kExpiRhomTace: expression rate of iRhom and TACE complex

kExp1433: expression rate constant of protein 14-3-3

kDeg1433: degradation rate constant of protein 14-3-3

kIniRhomp1433: Internalization rate constant of phosphorylated iRhom and 14-3-3 complex

kDegTgfa: degradation rate constant of soluable TGFalpha

kInTace: internalization rate constant of TACE

kIniRhomTace: internalization rate constant of iRhom and TACE complex

kIniRhompTace: internalization rate constant of phosphorylated iRhom and TACE complex

kpLpaiRhom: rate constant of LPA activating iRhom (since no clear and detail mechanism, the rate can be a hill equation if needed)

1. ERK activation module:

basal: basal activation of the Hill equation describing ERK activation by TGFalpha

kAct: activation rate constant of ERK by TGFapha

KD: threshold parameter in Hill equation

n: exponent parameter in Hill equation

kDephoErk: ERK dephosphorylation rate constant

1. Ligand expression module:

basal: basal activation of the Hill equation describing ERK activating TGFalpha expression

kAct: activation rate constant of phosphorylated ERK on TGFapha mRNA expression

KD: threshold parameter in Hill equation

n: exponent parameter in Hill equation

kDegRna: TGFalpha mRNA degradation

kTrl: TGFalpha translation rate constant

kInmTgfa: internalization rate constant of TGFalpha precursor

kRecyc: recycling rate constant of TGFalpha precursor

kDegmTgfa: degradation rate constant of TGFalpha precursor