Rule-based Modeling of VEGF Signaling

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Introduction
- VEGF (Vascular Endothelial Growth Factor) is crucial for angiogenesis which has an important role in diseases such as cancer, arthritis and diabetic retinopathy.
- There are several published models for VEGF binding to their receptors but no model contains downstream events of receptor aggregation such as kinase activation or phosphorylation of receptor tyrosines. Development of such models may provide comprehensive understanding of the pathway dynamics and assist in developing new anti-tumor drugs and other therapies.
- We are developing a model of this VEGF pathway, including VEGFR sites that are known to couple directly to angiogenesis, vasculogenesis, and vascular permeability. This model is an extension of previously published models for the ligand-induced aggregation of VEGF receptors and co-receptors with the addition of kinase activation, receptor phosphorylation, and recruitment of downstream effectors. Its difference is having more clear structures and binding sites and rule-based reactions.
- Because of having large complexes and many number of phosphorylation sites, BioNetGen software platform is used for development. In this platform objects and their components represent signaling molecules and their functional elements, and rules describe biochemical interactions.

Background
- VEGF (Vascular Endothelial Growth Factor) is a crucial regulator of angiogenesis, the growth of new blood vessels from pre-existing microvessels.
- In this study, the used members of VEGF family is VEGF121 and VEGF165 isomers.
  - They bind to the RTK family members VEGFR1, VEGFR2 and co-receptor called Neuropilin-1. VEGF pathway receptors undergo receptor dimerization and activation of tyrosine kinase activity, resulting in cell migration, survival and proliferation.

Method

- BioNetGen software platform is used for developing model.

Results

- Identification of 3 cases of Neuropilin targeting, while developing model:
  1) Blocking Neuropilin expression
  2) Blocking VEGF165-Neuropilin binding
  3) Blocking of VEGFR2-Neuropilin Coupling

- How this BioNetGen language is used?

Future Research
- Since VEGF165 has an important role in pathological angiogenesis, new anti-tumor therapy strategies that aim for therapeutic effects by inhibiting VEGF signal-transduction pathways to prevent pathological angiogenesis are targeting this pathway in recent years. Thus such models will be required to develop a comprehensive understanding of the pathway dynamics and may be important in developing new anti-tumor drugs and other therapies.

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References