**Supplement**

**Signaling network building based on queries to Omnipath and literature**

Here we describe how each interaction in the PKN is found in Omnipath or in the literature.

1 - Retrieving interactions from Omnipath

[(Lescarbeau and Kaplan 2014)](https://paperpile.com/c/1fh5eq/pwMyL) provide a first sketch of an undirected map describing simplified views of the pathways containing the proteins measured or inhibited in their experiments: Erk1/2, AKT, RPS6, GSK3α/β, p38, JNK, HSP27, Stat3, PI3K, mTOR, MEK and IKKα/β. The ligands and treatments applied in the experiments are taken as inputs: EGF, IGF1, IL6, TNFα and DHT.

Additional proteins known to convey the signal between ligands and measured proteins are included in the map: IGF1-R, IL6R, Jak, EGFR, RAS, Rac, and TNFR. The map also features two downstream proteins with major roles in cancer: β-Catenin and NF-κB.

Starting from this map, we use the function list\_interactions (defined in pypath\_code.py) in *pypath* to retrieve the direction and sign of each interaction from *Omnipath*. This allows us to retrieve in *Omnipath* 16 interactions out of the 24 represented in [(Lescarbeau and Kaplan 2014)](https://paperpile.com/c/1fh5eq/pwMyL).

8 interactions are not found in *Omnipath*, likely because they are not direct interactions. To retrieve the paths of direct interactions that they represent, we use the function plot\_paths\_to\_listofnodes (defined in Supplement S2). This function finds all paths between two nodes with the shortest length. In addition to returning the detailed interactions involved, it plots the subgraph defined by the paths.

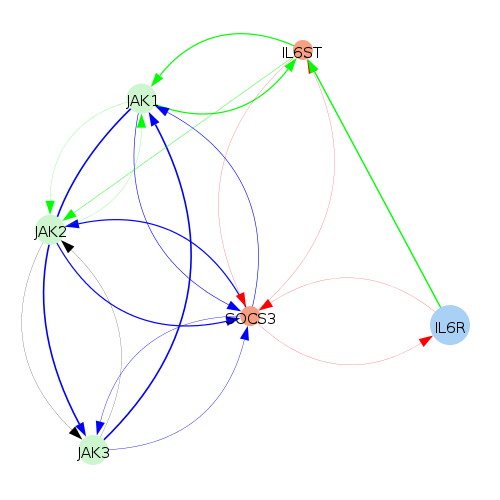
Example: No direct interaction between IL6R and JAK is found in *Omnipath*. However, the shortest paths between IL6R and JAK can be retrieved by using pypath and the function plot\_paths\_to\_listofnodes(pa,'IL6R',['JAK1', 'JAK2', 'JAK3']).

The function generates a subgraph showing all shortest paths (Figure S1). Edge widths are proportional to the number of Pubmed references associated with the interactions. From this figure, we can see that IL6R activates JAK via the signal transducer IL6ST:

IL6R =+=> IL6ST from SignaLink3, Signor

IL6ST =+=> JAK1 from SignaLink3, KEGG, Signor

IL6ST =+=> JAK2 from SignaLink3, Signor



**Fig S1.** Subgraph of all shortest paths between IL6R (in blue) and the list (JAK1, JAK2, JAK3) in green. Additional genes found by *pypath* are in orange. Edge widths are proportional to the number of Pubmed references associated with the interactions. Activations are in green, inhibitions are in red, and interactions associated with both signs are in blue.

We give at the end of this document the list of direct and indirect interactions represented in [(Lescarbeau and Kaplan 2014)](https://paperpile.com/c/1fh5eq/pwMyL) and retrieved from *Omnipath*, with their associated sources.

Some interactions were also confirmed with the literature or published models.

2 - Network extension: regulation of survival

In order to predict cell survival, the global influence of downstream components of the network on this phenotype is encoded in the network though the addition of pro-survival factors (MYC, Cell\_Cycle) and anti-survival factors (p53, Caspase 8, Caspase 9).

The caspase-dependent apoptosis pathway activated by TNF is taken into account in a simplified representation with a direct activation of the anti-survival factor Caspase 8 by TNFR.

Cancer cells often escape apoptosis with the activation of the transcription factor NF-κB with pro-survival effects. A simplified representation of the survival pathway is therefore included in the network, with a feedback loop composed of IKK, NF-κB and p53, that activates Caspase 9. A crosstalk with the Rac pathway is added, as the activation of p53 by Stress-induced p38 with anti-survival effect is widely known and represented in several published models (for example a logical model of MAPK pathways published in [(Grieco et al. 2013)](https://paperpile.com/c/1fh5eq/47qU)), such as the model in [(Flobak et al. 2015)](https://paperpile.com/c/1fh5eq/66jtE), and is also found in *Omnipath*.

β-Catenin, AR, JNK, RPS6KB1 and ERK1/2 are known factors which activate cell growth and proliferation. An important mechanism is the activation of the transcription factor MYC by β-Catenin and JNK (interactions found in *Omnipath*), as well as AR (see for example [(Ni et al. 2013)](https://paperpile.com/c/1fh5eq/wPNa)). But multiple alternative pathways are involved. For simplicity, we represent a second pathway with the generic node Cell\_cycle, regulated by ERK MAPK signaling and by the AKT/ mTOR pathway while bypassing the AR via RPS6. The two nodes MYC and Cell\_cycle activate the output Survival.

Direct interactions in Omnipath

**IFG-1 → IGF1-R**

IGF1 =+=> IGF1R from KEGG, Laudanna\_effects, SignaLink3, CA1, SPIKE, Signor

**IGF1-R → PI3K**

IGF1R =+=> PIK3CA from Laudanna\_effects, Wang, Signor

**PI3K → AKT**

PIK3CA =+=> AKT1 from SignaLink3, Laudanna\_effects, Wang, Signor

PIK3CA =-=> AKT1 from Laudanna\_effects

We select the activation which is associated to more sources. Moreover, the activation of AKT by PI3K is also present in the model of MAPK signalling pathways published in [(Grieco et al. 2013)](https://paperpile.com/c/1fh5eq/47qU) via PDK1.

**AKT → mTOR**

AKT1 =+=> MTOR from SignaLink3, Laudanna\_effects, Wang

MTOR =+=> AKT1 from SignaLink3, Laudanna\_effects, Signor, Wang, ARN

Although both directions are found for this interaction in *Omnipath*, the activation of mTOR by AKT is confirmed from the literature [(Rafalski and Brunet 2011)](https://paperpile.com/c/1fh5eq/FktV).

**AKT –| GSK3a/b**

AKT1 =+=> GSK3B from SignaLink3, Laudanna\_effects

GSK3B =+=> AKT1 from Laudanna\_effects, Wang

AKT1 =-=> GSK3B from Laudanna\_effects, Wang, Signor, SPIKE

AKT1 =-=> GSK3A from CA1, Laudanna\_effects, Wang, Signor

We select the inhibition of GSK3 by AKT, which is associated to more sources.

**GSK3a/b –| β-Catenin** (CTNNB1)

GSK3B =+=> CTNNB1 from Laudanna\_effects

GSK3B =-=> CTNNB1 from SignaLink3, KEGG, Signor, SPIKE

GSK3A =-=> CTNNB1 from CA1, Laudanna\_effects

We select the inhibition of β-Catenin by GSK3, which is associated to more sources.

**IL6 → IL6R**

IL6 =+=> IL6R from SignaLink3, KEGG, Laudanna\_effects, Signor

**Jak** (JAK1, JAK2, JAK3) **→ Stat3**

JAK1 =+=> STAT3 from SignaLink3, KEGG, Laudanna\_effects, Signor, SPIKE

JAK1 =-=> STAT3 from Laudanna\_effects, Wang

JAK2 =+=> STAT3 from KEGG, Laudanna\_effects, Wang, SignaLink3, SPIKE, Signor

**EGF → EGFR**

EGF =+=> EGFR from KEGG, Laudanna\_effects, Wang, SignaLink3, SPIKE, Signor

**MEK (**MAP2K1) **→ ERK1/2** (MAPK1, MAPK3)

MAP2K1 =+=> MAPK1 from KEGG, Laudanna\_effects, Wang, SignaLink3, SPIKE, Signor  
MAP2K1 =+=> MAPK3 from SignaLink3, Laudanna\_effects, Wang, Signor, SPIKE

MAPK1 =+=> MAP2K1 from Laudanna\_effects, Wang

MAPK1 =-=> MAP2K1 from SignaLink3, Signor

MAPK3 =+=> MAP2K1 from Laudanna\_effects, Wang

Although the reverse interaction is also found in *Omnipath*, we can reject it because it is associated with few databases. This interaction is also described in the model published in [(Grieco et al. 2013)](https://paperpile.com/c/1fh5eq/47qU).

**TNFa → TNFR**

TNF =+=> TNFRSF1A from SignaLink3, KEGG, Laudanna\_effects, Signor, SPIKE

TNFRSF1A =-=> TNF from Laudanna\_effects, Wang

We select the inhibition of TNFR by TNFa, which is associated to more sources.

**TNFR → JNK**

This interaction is represented in [(Lescarbeau and Kaplan 2014)](https://paperpile.com/c/1fh5eq/pwMyL).

**TNFR → IKKa/b** (CHUK, IKBKB)

TNFRSF1A =+=> IKBKB from KEGG, Laudanna\_effects, Wang

TNFRSF1A =+=> CHUK from Laudanna\_effects, Wang

**Rac → JNK**

RAC1 =+=> MAPK8 from SignaLink3, KEGG, Laudanna\_effects, Wang, Signor

**IKKa/b** (CHUK, IKBKB) **→ NF-kB** (NFKB1, NFKB2)

IKBKB =+=> NFKB1 from KEGG, Laudanna\_effects

NFKB1 =+=> IKBKB from Laudanna\_effects, Wang

IKBKB =-=> NFKB1 from SignaLink3, Laudanna\_effects, Wang, Signor, SPIKE

NFKB1 =+=> IKBKB associated from Laudanna\_effects, Wang

CHUK =+=> NFKB2 associated from SignaLink3, KEGG, SPIKE

The direction and sign of the interaction are confirmed in the literature.

**mTOR → RPS6KB1**

RPS6KB1 =+=> MTOR from SignaLink3, Signor

MTOR =+=> RPS6KB1 from KEGG, Laudanna\_effects, Wang, SignaLink3, CA1, Signor, SPIKE, ARN

We select the activation of RPS6KB1 by mTOR, which is associated to more sources.

Indirect interactions in *Omnipath*

**EGFR → RAS via SOS1**

EGFR =+=> SOS1 from KEGG, Laudanna\_effects, Wang

SOS1 =+=> NRAS from KEGG, Laudanna\_effects, Wang, SignaLink3, CA1, Signor

The activation of RAS by EGFR is also described in the model published in [(Grieco et al. 2013)](https://paperpile.com/c/1fh5eq/47qU) via EGFR → GRB2 → SOS → RAS.

**EGFR -> PI3K via PIK3R1**

EGFR =+=> PIK3R1 from Signor

PIK3R1 =+=> PIK3CA from Laudanna\_effects, Wang

The activation of PI3K by EGFR is also described in the model published in [(Grieco et al. 2013)](https://paperpile.com/c/1fh5eq/47qU) via EGFR → GRB2 → GAB1 → PI3K.

**RAS** (HRAS, KRAS) **→ MEK** (MAP2K1) **via ARAF or MAP3K1**

HRAS =+=> ARAF from SignaLink3, KEGG, Laudanna\_effects, Wang, Signor

ARAF =+=> MAP2K1 from KEGG, Laudanna\_effects, Wang, SignaLink3, SPIKE, Signor

KRAS =+=> MAP3K1 from SignaLink3, Signor

MAPK3 =+=> MAP2K1 from Laudanna\_effects, Wang

The activation of MEK by RAS is also described in the MAPK model published in [(Grieco et al. 2013)](https://paperpile.com/c/1fh5eq/47qU) via RAF.

**RAS → Rac**

It is not found in *Omnipath*, but looking for the shortest path between the two genes with *Pypath* shows two indirect interactions:

**IL6R → Jak** (JAK1, JAK2, JAK3) **via IL6ST**

IL6R =+=> IL6ST from SignaLink3, Signor

JAK2 <=+= IL6ST from SignaLink3, Signor

JAK1 <=+= IL6ST from SignaLink3, KEGG, Signor

**Jak** (JAK1, JAK2, JAK3) **→ RAS via SOCS3 and RASA1**

JAK1 =+=> SOCS3 from Laudanna\_effects, Wang

JAK3 =+=> SOCS3 from Laudanna\_effects, Wang

SOCS3 =+=> RASA1 from SignaLink3

RASA1 =+=> HRAS from SignaLink3

RASA1 =-=> HRAS from KEGG, Laudanna\_effects, Wang, Signor

Interactions confirmed from the literature

**Rac → p38δ** (MAPK13)

This interaction is not found in *Omnipath*. It is however present in the logical model published in [(Flobak et al. 2015)](https://paperpile.com/c/1fh5eq/66jtE), via MEKK4 and MKK4. A literature search also confirms that cyclic strain stress rapidly activates p38 MAPKs via activation of protein kinase C ras/rac signal pathways [(Li et al. 2000)](https://paperpile.com/c/1fh5eq/tIvd).

**p38δ** (MAPK13) **→ HSP27** (HSPB1)

This interaction is not found in *Omnipath*, but a published study shows that HSP27 is a downstream effectors of p38 MAP kinase [(Xu, Chen, and Bergan 2006)](https://paperpile.com/c/1fh5eq/O9fi).

**References**

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