

Figure. S1 The impact of *Trp53* genotype on AAI-induced gene expression *in vivo*. Hierarchical clustering and heat map of significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed (a) *Trp53(+/+)*, (b) *Trp53(+/-)* and (c) *Trp53(-/-)* mouse kidneys. The heat map colours are based on gene expression (ordered in a decreasing manner for the AAI group), with red being up-regulated and green being down-regulated. Batches #1 and #2 indicate grouping of samples during cDNA synthesis.

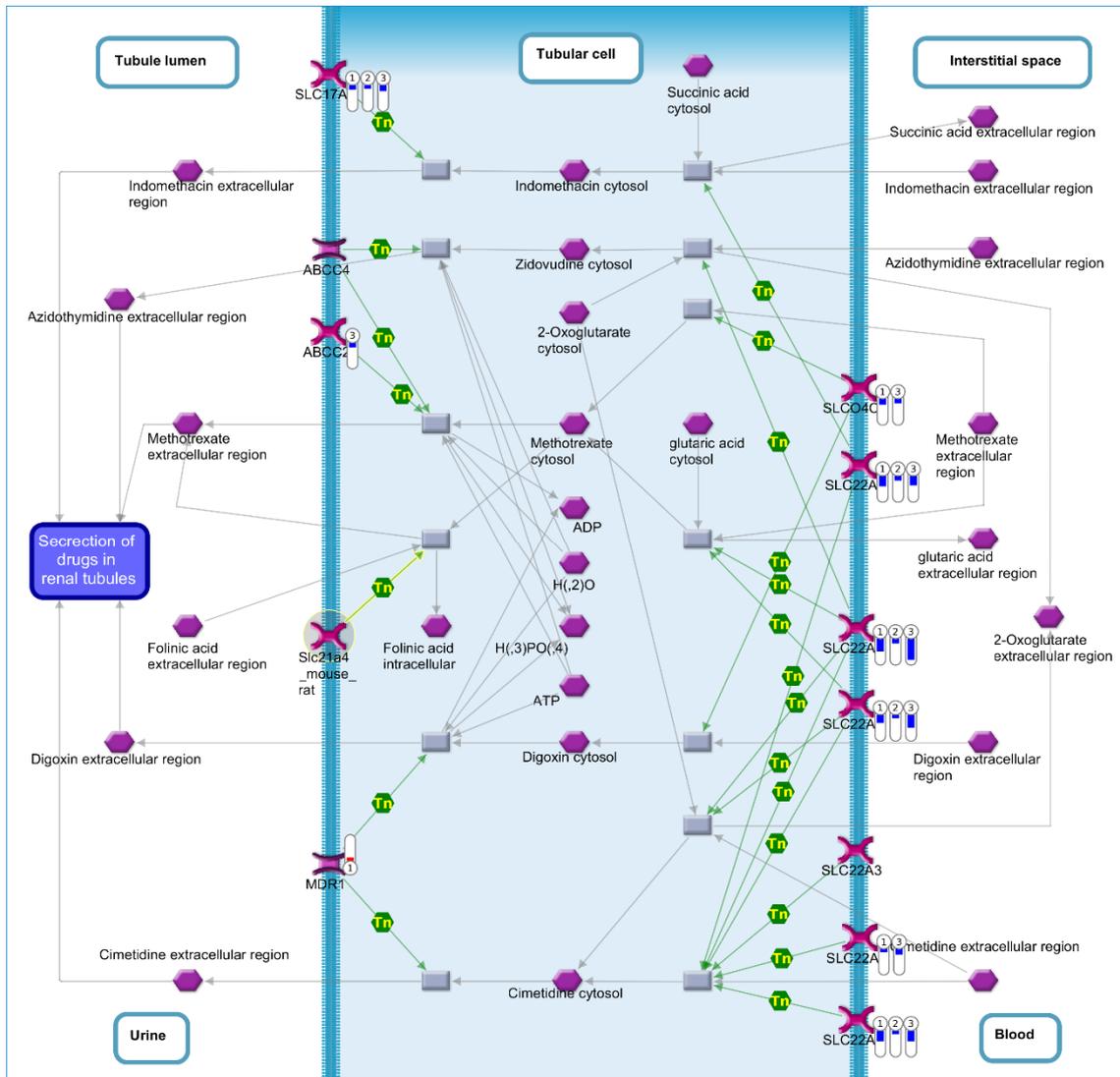


Figure. S2 Map of renal secretion of drugs in rodents. Significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed *Trp53*(+/+), *Trp53*(+/-) and *Trp53*(-/-) mouse kidneys were compared in MetaCore™. The enriched pathway (39th out of top 50; $p < 0.05$) shows up-regulated (thermometer-like symbols in red) and down-regulated (thermometer-like symbols in blue) genes. Numbers indicate genotype: 1) *Trp53*(+/+), 2) *Trp53*(+/-) and 3) *Trp53*(-/-). For detailed legend see **Figure. S22**.

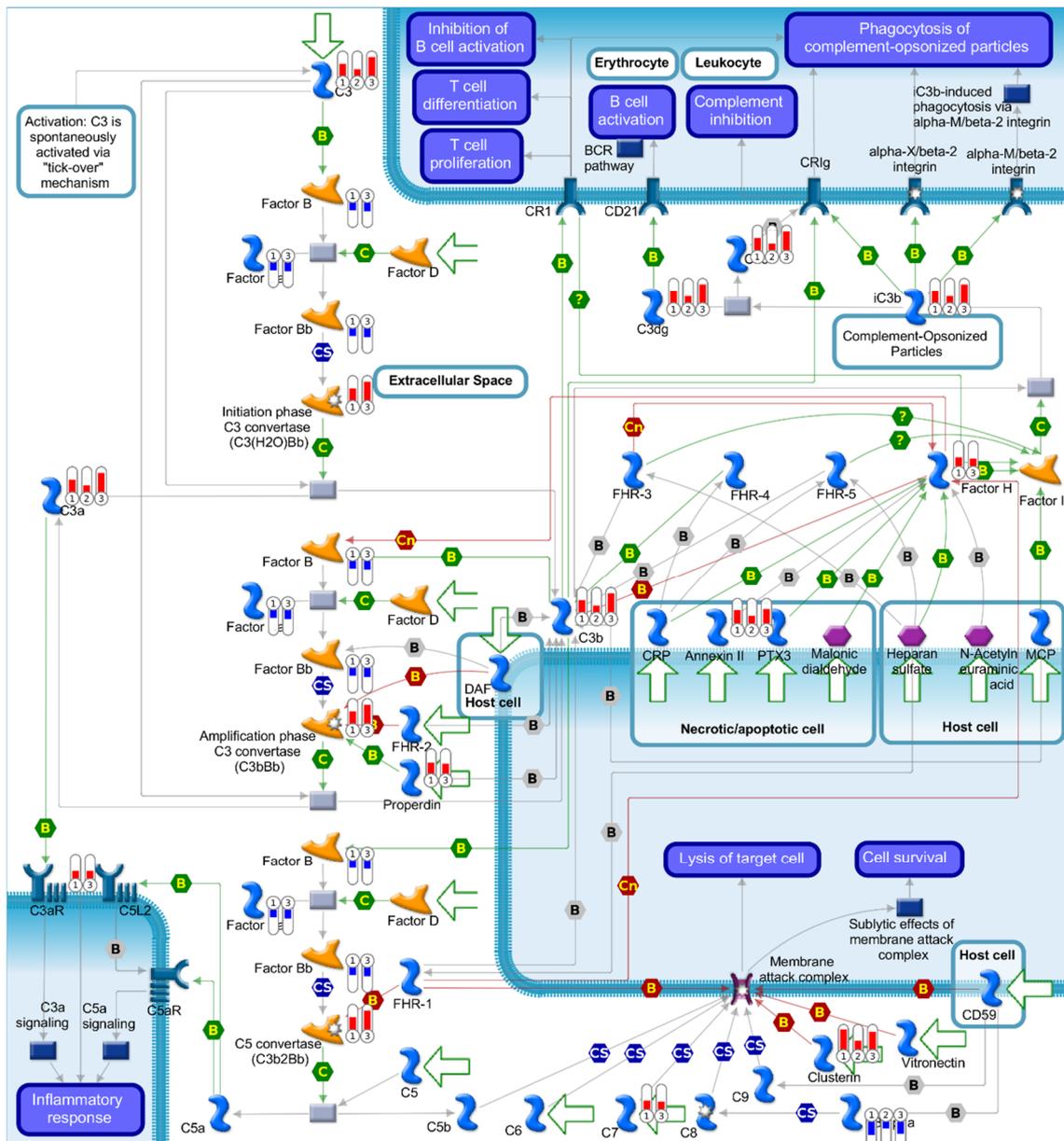


Figure. S3 Map of alternative complement pathway. Significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed *Trp53*(+/+), *Trp53*(+/-) and *Trp53*(-/-) mouse kidneys were compared in MetaCore™. The enriched pathway (3rd out of top 50; $p < 0.05$) shows up-regulated (thermometer-like symbols in red) and down-regulated (thermometer-like symbols in blue) genes. Numbers indicate genotype: 1) *Trp53*(+/+), 2) *Trp53*(+/-) and 3) *Trp53*(-/-). For detailed legend see **Figure. S22**.

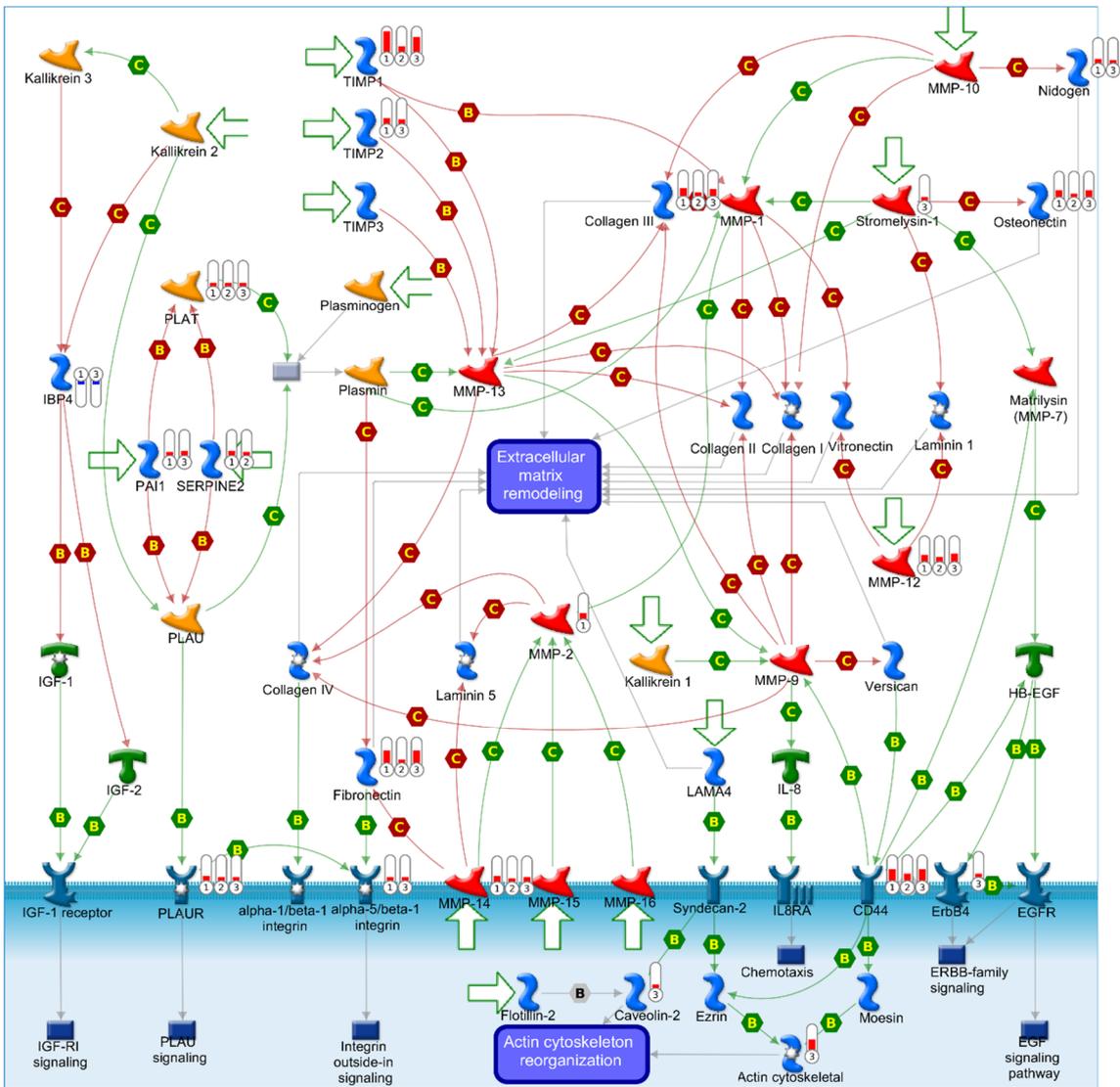


Figure. S4 Map of extracellular matrix remodelling. Significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed *Trp53(+/+)*, *Trp53(+/-)* and *Trp53(-/-)* mouse kidneys were compared in MetaCore™. The enriched pathway (4th out of top 50; $p < 0.05$) shows up-regulated (thermometer-like symbols in red) and down-regulated (thermometer-like symbols in blue) genes. Numbers indicate genotype: 1) *Trp53(+/+)*, 2) *Trp53(+/-)* and 3) *Trp53(-/-)*. For detailed legend see **Figure. S22**.

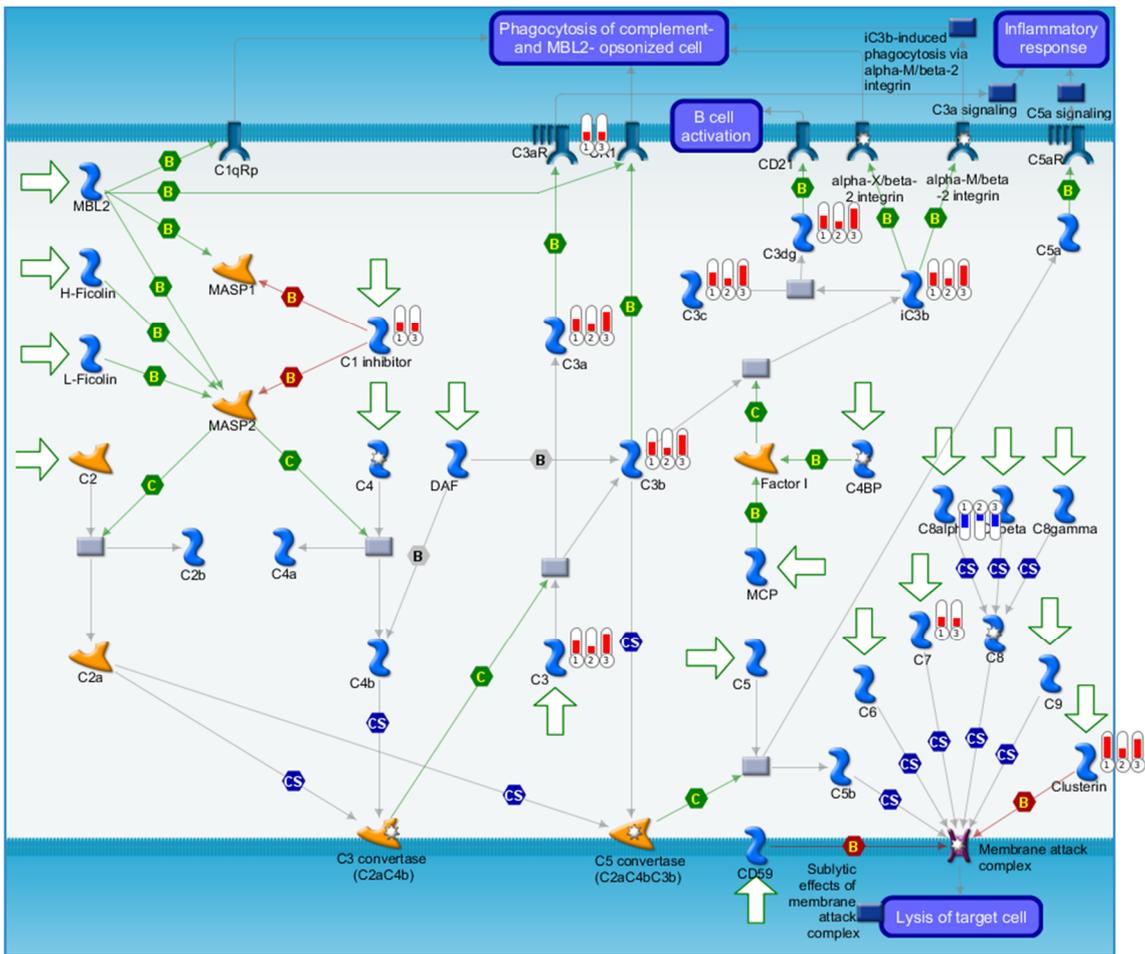


Figure. S5 Map of lectin-induced complement pathway. Significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed *Trp53*(+/+), *Trp53*(+/-) and *Trp53*(-/-) mouse kidneys were compared in MetaCore™. The enriched pathway (6th out of top 50; $p < 0.05$) shows up-regulated (thermometer-like symbols in red) genes. Numbers indicate genotype: 1) *Trp53*(+/+), 2) *Trp53*(+/-) and 3) *Trp53*(-/-). For detailed legend see **Figure. S22**.

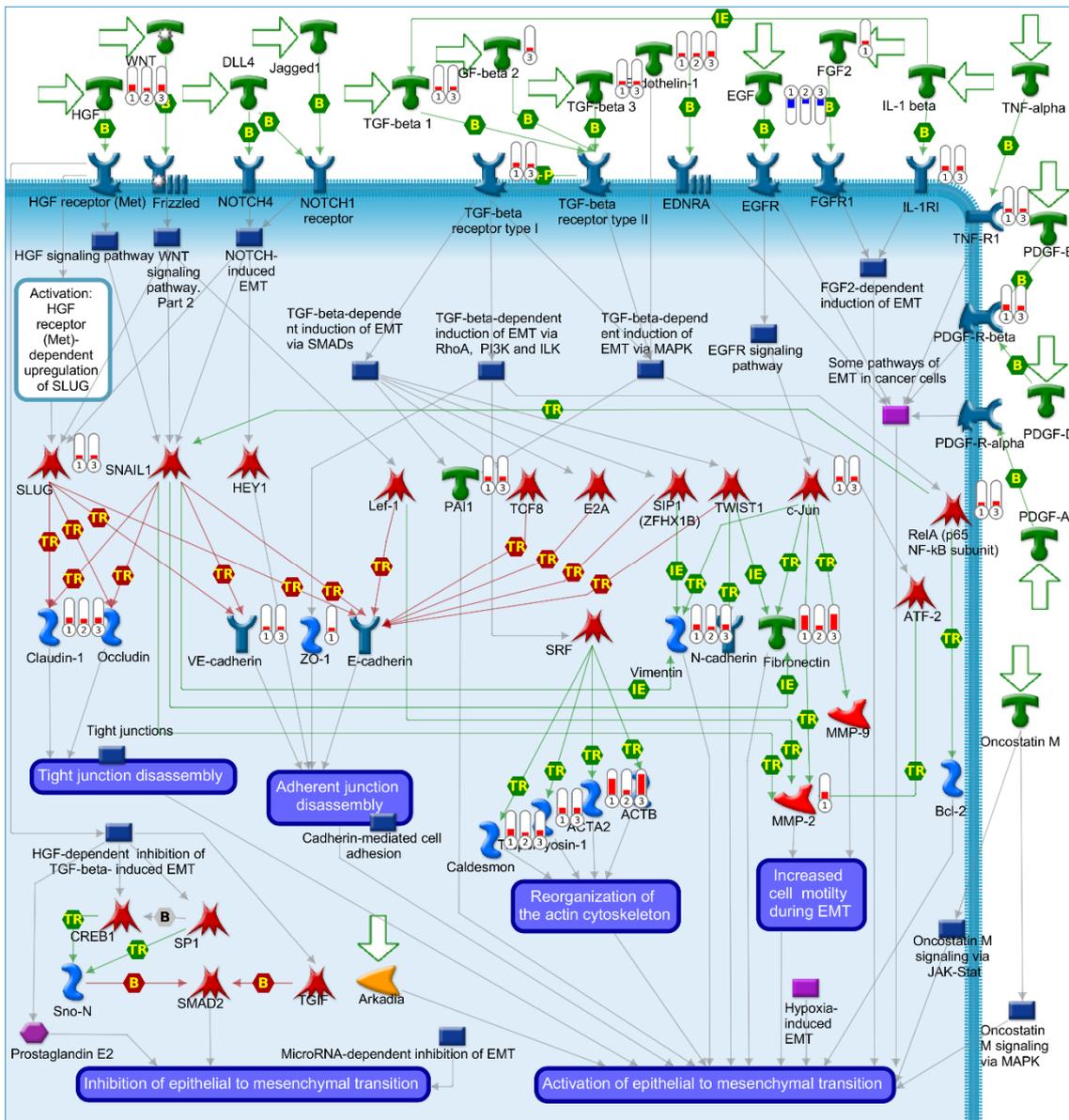


Figure. S7 Map of regulation of EMT. Significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed *Trp53*(+/+), *Trp53*(+/-) and *Trp53*(-/-) mouse kidneys were compared in MetaCore™. The enriched pathway (11th out of top 50; $p < 0.05$) shows up-regulated (thermometer-like symbols in red) and down-regulated (thermometer-like symbols in blue) genes. Numbers indicate genotype: 1) *Trp53*(+/+), 2) *Trp53*(+/-) and 3) *Trp53*(-/-). For detailed legend see **Figure. S22**. Abbreviation: epithelial-to-mesenchymal transition (EMT).

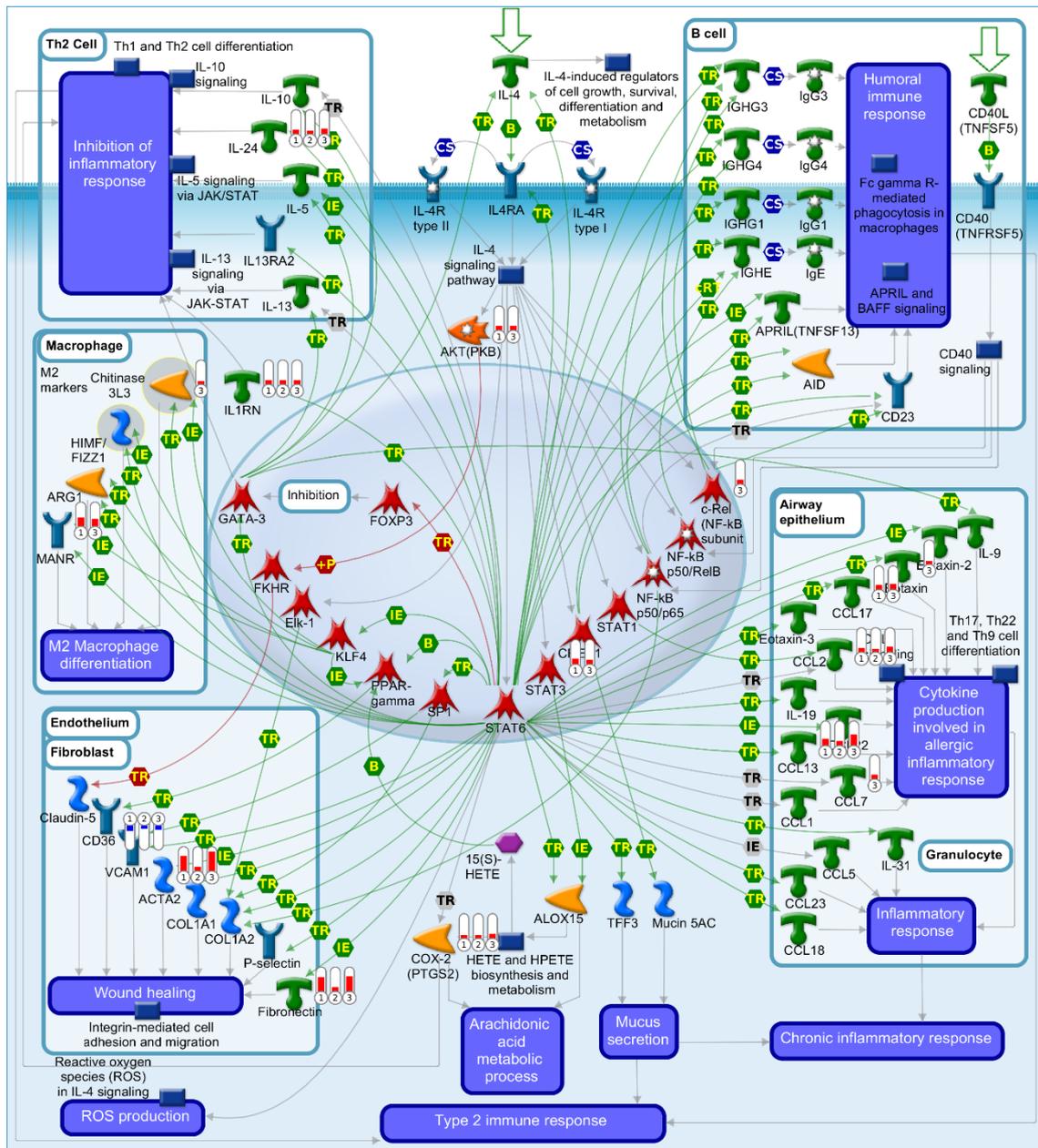


Figure. S8 Map of IL-4-responsive genes in type 2 immunity. Significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed *Trp53*(+/+), *Trp53*(+/-) and *Trp53*(-/-) mouse kidneys were compared in MetaCore™. The enriched pathway (13th out of top 50; $p < 0.05$) shows up-regulated (thermometer-like symbols in red) and down-regulated (thermometer-like symbols in blue) genes. Numbers indicate genotype: 1) *Trp53*(+/+), 2) *Trp53*(+/-) and 3) *Trp53*(-/-). For detailed legend see **Figure. S22**. Abbreviation: interleukin-4 (IL-4).

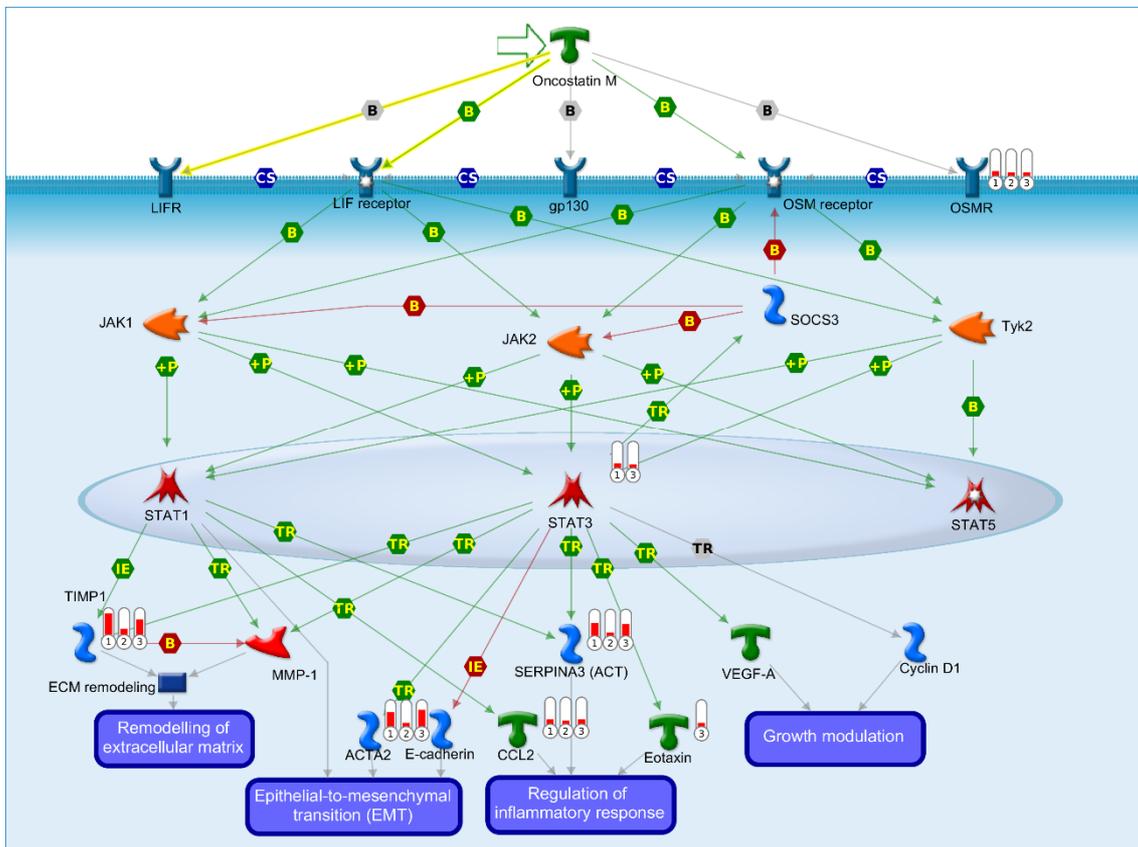


Figure. S9 Map of oncostatin M signalling via JAK-STAT. Significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed *Trp53*(+/+), *Trp53*(+/-) and *Trp53*(-/-) mouse kidneys were compared in MetaCore™. The enriched pathway (14th out of top 50; $p < 0.05$) shows up-regulated (thermometer-like symbols in red) genes. Numbers indicate genotype: 1) *Trp53*(+/+), 2) *Trp53*(+/-) and 3) *Trp53*(-/-). For detailed legend see **Figure. S22**. Abbreviations: Janus kinase (JAK); signal transducer and activator of transcription (STAT).

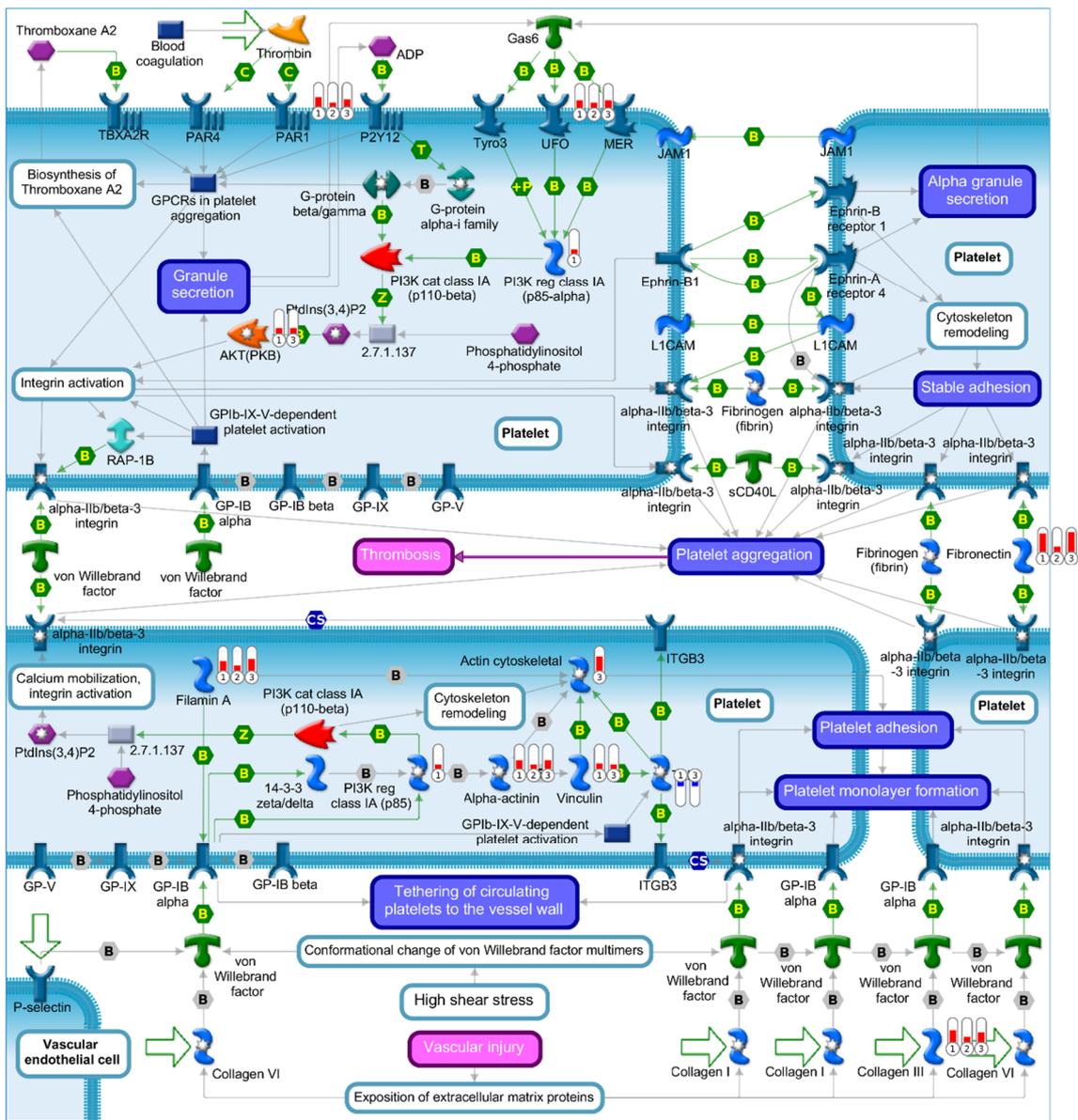


Figure. S10 Map of high shear stress-induced platelet activation. Significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed *Trp53*(+/+), *Trp53*(+/-) and *Trp53*(-/-) mouse kidneys were compared in MetaCore™. The enriched pathway (18th out of top 50; $p < 0.05$) shows up-regulated (thermometer-like symbols in red) and down-regulated (thermometer-like symbols in blue) genes. Numbers indicate genotype: 1) *Trp53*(+/+), 2) *Trp53*(+/-) and 3) *Trp53*(-/-). For detailed legend see **Figure. S22**.

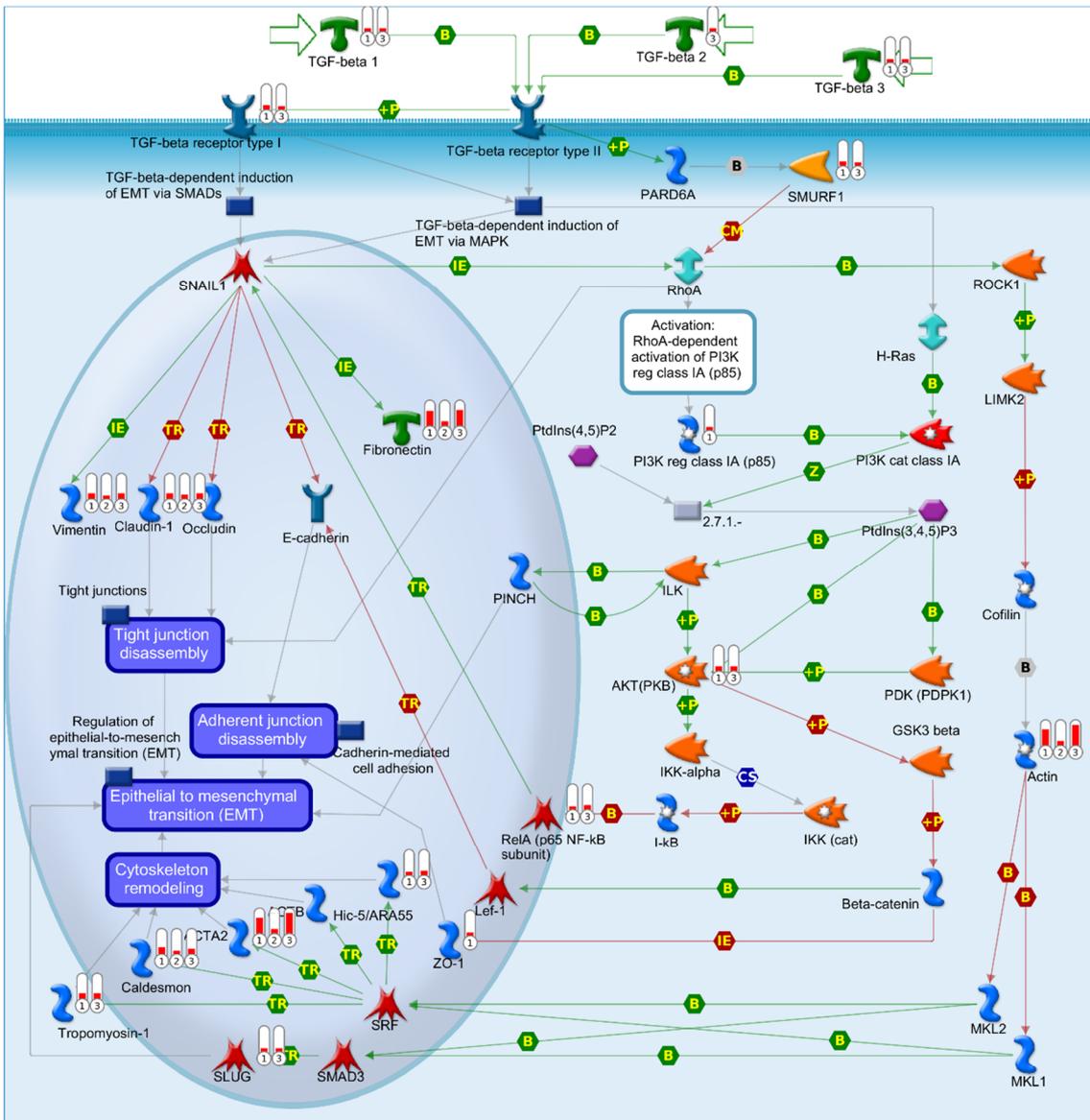


Figure. S11 Map of TGF- β -dependent induction of EMT via RhoA, PI3K and ILK. Significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed *Trp53*(+/+), *Trp53*(+/-) and *Trp53*(-/-) mouse kidneys were compared in MetaCore™. The enriched pathway (19th out of top 50; $p < 0.05$) shows up-regulated (thermometer-like symbols in red) genes. Numbers indicate genotype: 1) *Trp53*(+/+), 2) *Trp53*(+/-) and 3) *Trp53*(-/-). For detailed legend see **Figure. S22**. Abbreviations: epithelial-to-mesenchymal transition (EMT); integrin-linked protein kinase (ILK); phosphoinositide 3-kinase (PI3K); RAS homolog gene family, member A (RhoA); transforming growth factor β (TGF- β).

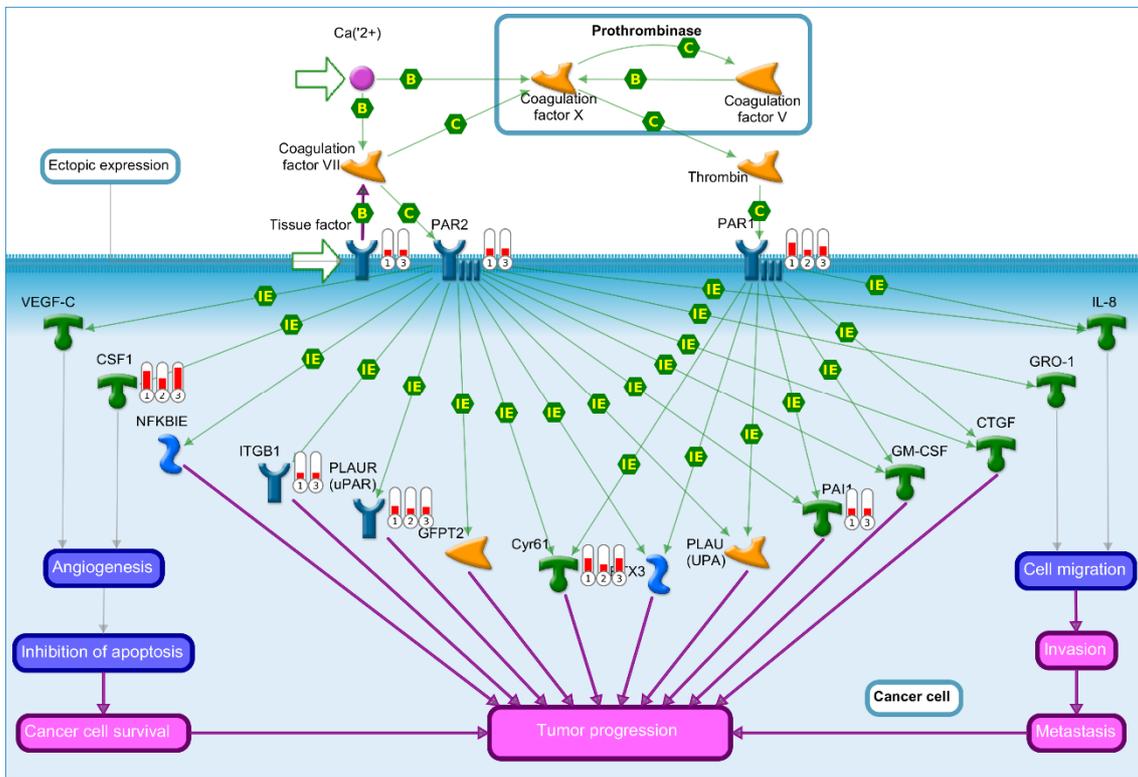


Figure. S12 Map of tissue factor signalling in cancer. Significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed *Trp53*(+/+), *Trp53*(+/-) and *Trp53*(-/-) mouse kidneys were compared in MetaCore™. The enriched pathway (26th out of top 50; $p < 0.05$) shows up-regulated (thermometer-like symbols in red) genes. Numbers indicate genotype: 1) *Trp53*(+/+), 2) *Trp53*(+/-) and 3) *Trp53*(-/-). For detailed legend see **Figure. S22**.

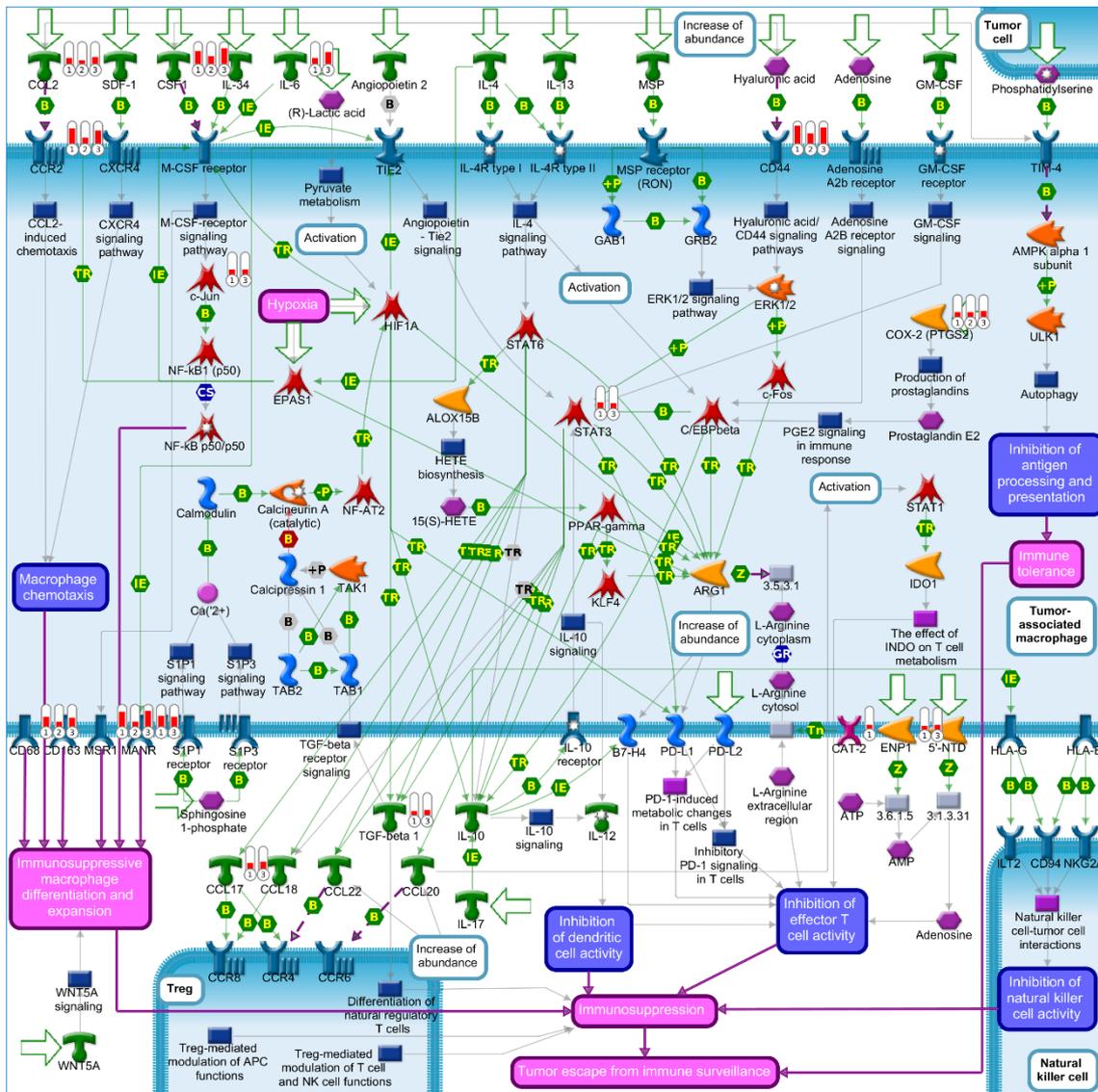


Figure. S13 Map of macrophage-induced immunosuppression in the tumour microenvironment. Significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed *Trp53*(+/+), *Trp53*(+/-) and *Trp53*(-/-) mouse kidneys were compared in MetaCore™. The enriched pathway (36th out of top 50; $p < 0.05$) shows up-regulated (thermometer-like symbols in red) genes. Numbers indicate genotype: 1) *Trp53*(+/+), 2) *Trp53*(+/-) and 3) *Trp53*(-/-). For detailed legend see **Figure. S22**.

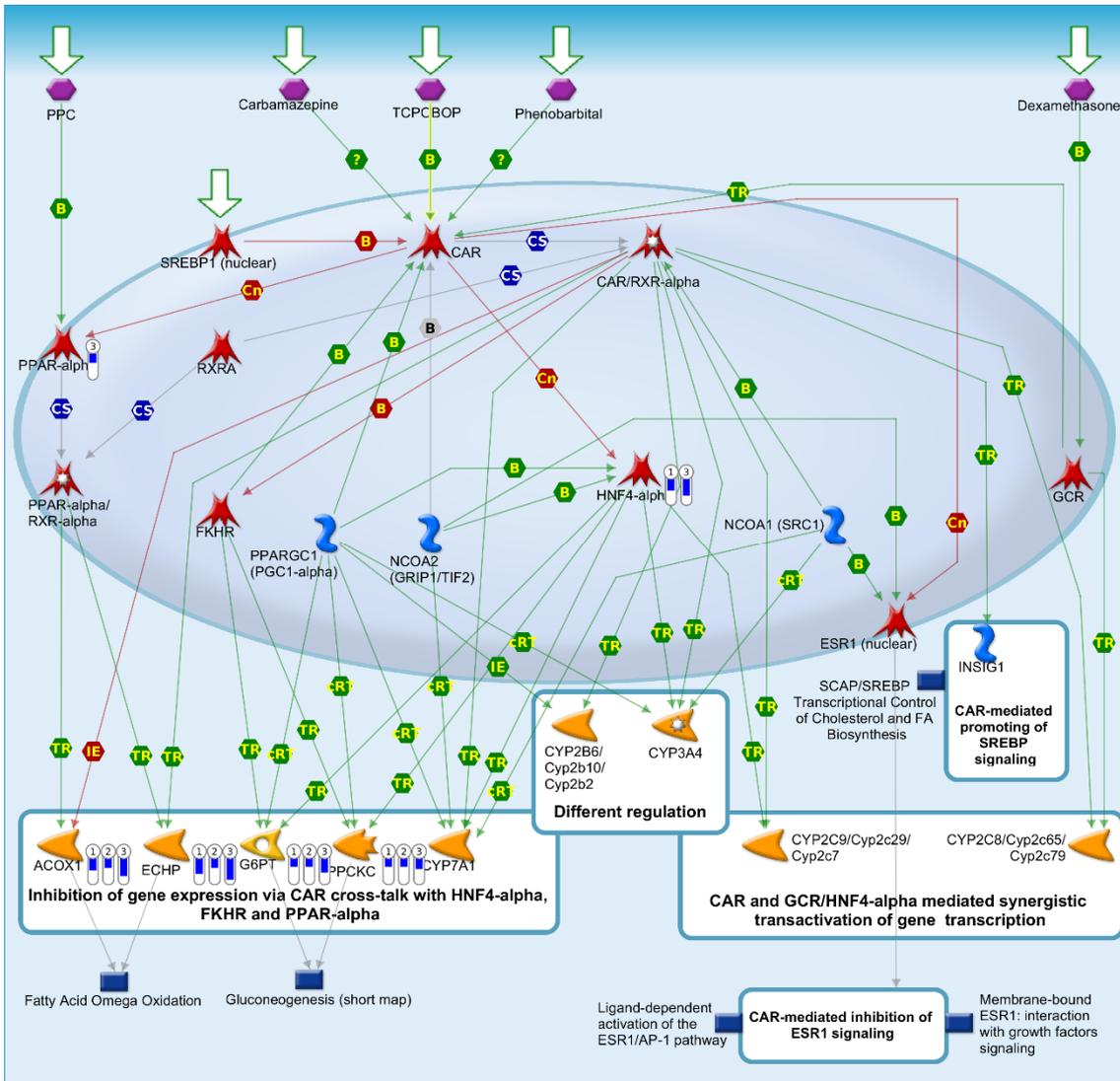


Figure. S15 Map of CAR signalling via cross-talk in rodents. Significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed *Trp53*(+/+), *Trp53*(+/-) and *Trp53*(-/-) mouse kidneys were compared in MetaCore™. The enriched pathway (38th out of top 50; $p < 0.05$) shows down-regulated (thermometer-like symbols in blue) genes. Numbers indicate genotype: 1) *Trp53*(+/+), 2) *Trp53*(+/-) and 3) *Trp53*(-/-). For detailed legend see **Figure. S22**. Abbreviation: constitutive androstane receptor (CAR).

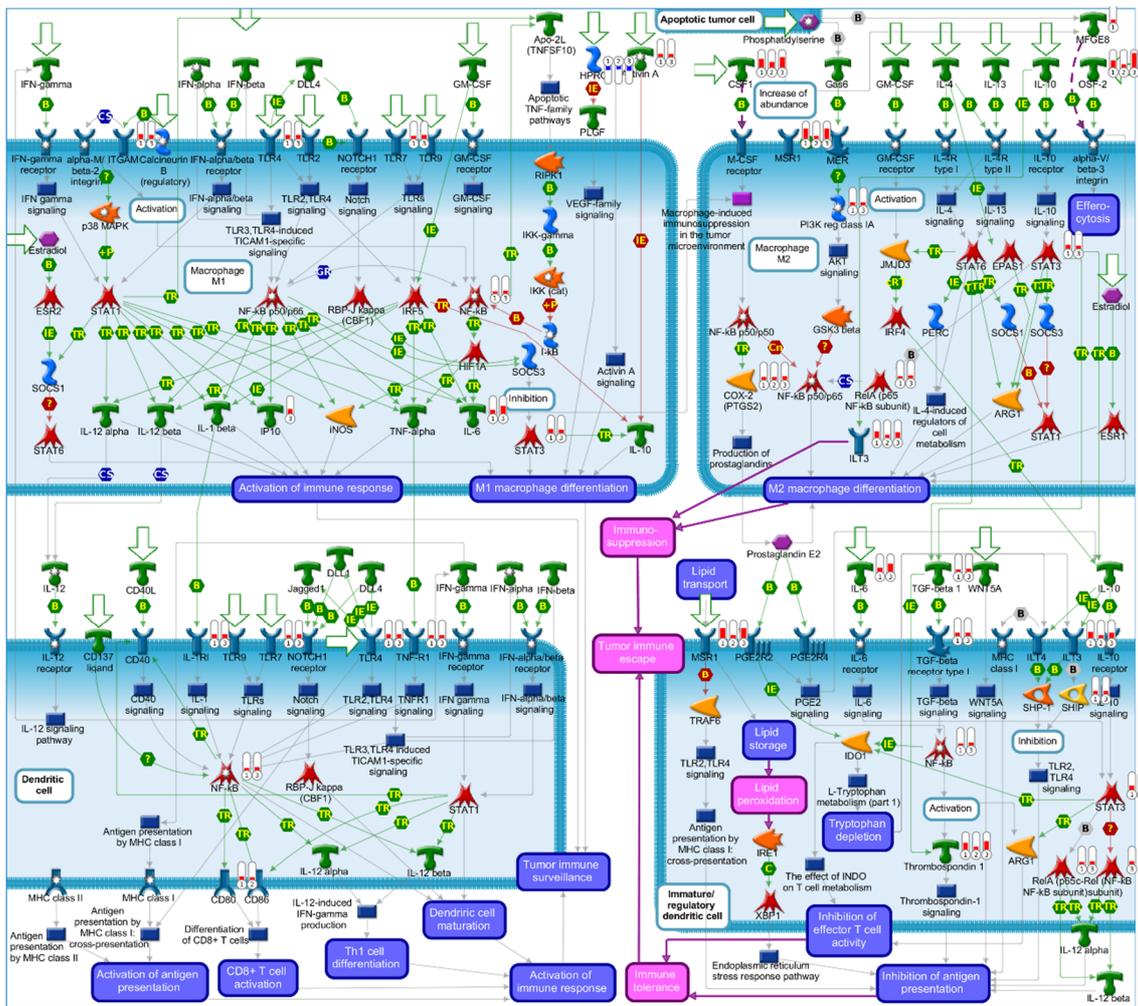


Figure. S16 Map of macrophage and dendritic cell phenotype shift in cancer. Significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed *Trp53*(+/+), *Trp53*(+/-) and *Trp53*(-/-) mouse kidneys were compared in MetaCore™. The enriched pathway (41st out of top 50; $p < 0.05$) shows up-regulated (thermometer-like symbols in red) and down-regulated (thermometer-like symbols in blue) genes. Numbers indicate genotype: 1) *Trp53*(+/+), 2) *Trp53*(+/-) and 3) *Trp53*(-/-). For detailed legend see **Figure. S22**.

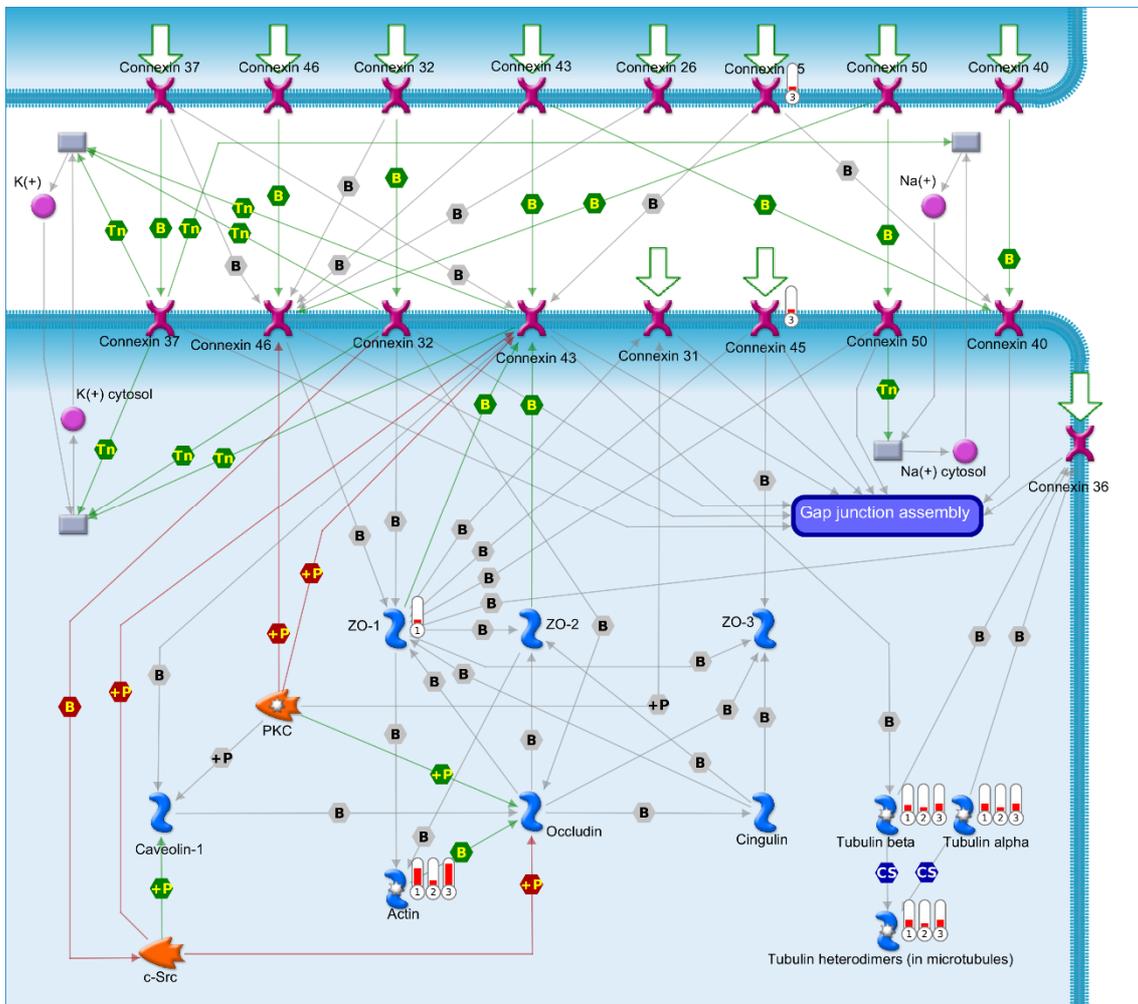


Figure. S17 Map of gap junctions. Significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed *Trp53*(+/+), *Trp53*(+/-) and *Trp53*(-/-) mouse kidneys were compared in MetaCore™. The enriched pathway (44th out of top 50; $p < 0.05$) shows up-regulated (thermometer-like symbols in red) genes. Numbers indicate genotype: 1) *Trp53*(+/+), 2) *Trp53*(+/-) and 3) *Trp53*(-/-). For detailed legend see **Figure. S22**.

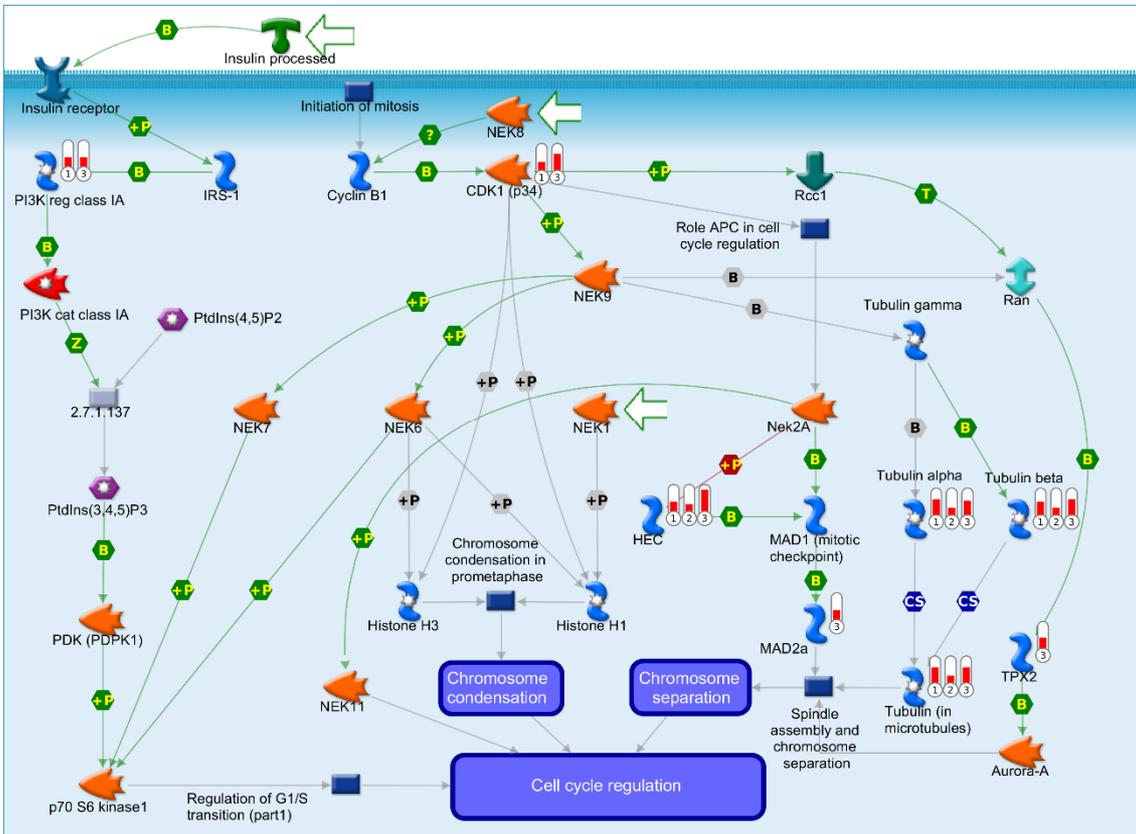


Figure. S18 Map of role of NEK in cell cycle regulation. Significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed *Trp53*(+/+), *Trp53*(+/-) and *Trp53*(-/-) mouse kidneys were compared in MetaCore™. The enriched pathway (47th out of top 50; $p < 0.05$) shows up-regulated (thermometer-like symbols in red) genes. Numbers indicate genotype: 1) *Trp53*(+/+), 2) *Trp53*(+/-) and 3) *Trp53*(-/-). For detailed legend see **Figure. S22**. Abbreviation: never in mitosis, gene A-related kinase (NEK).

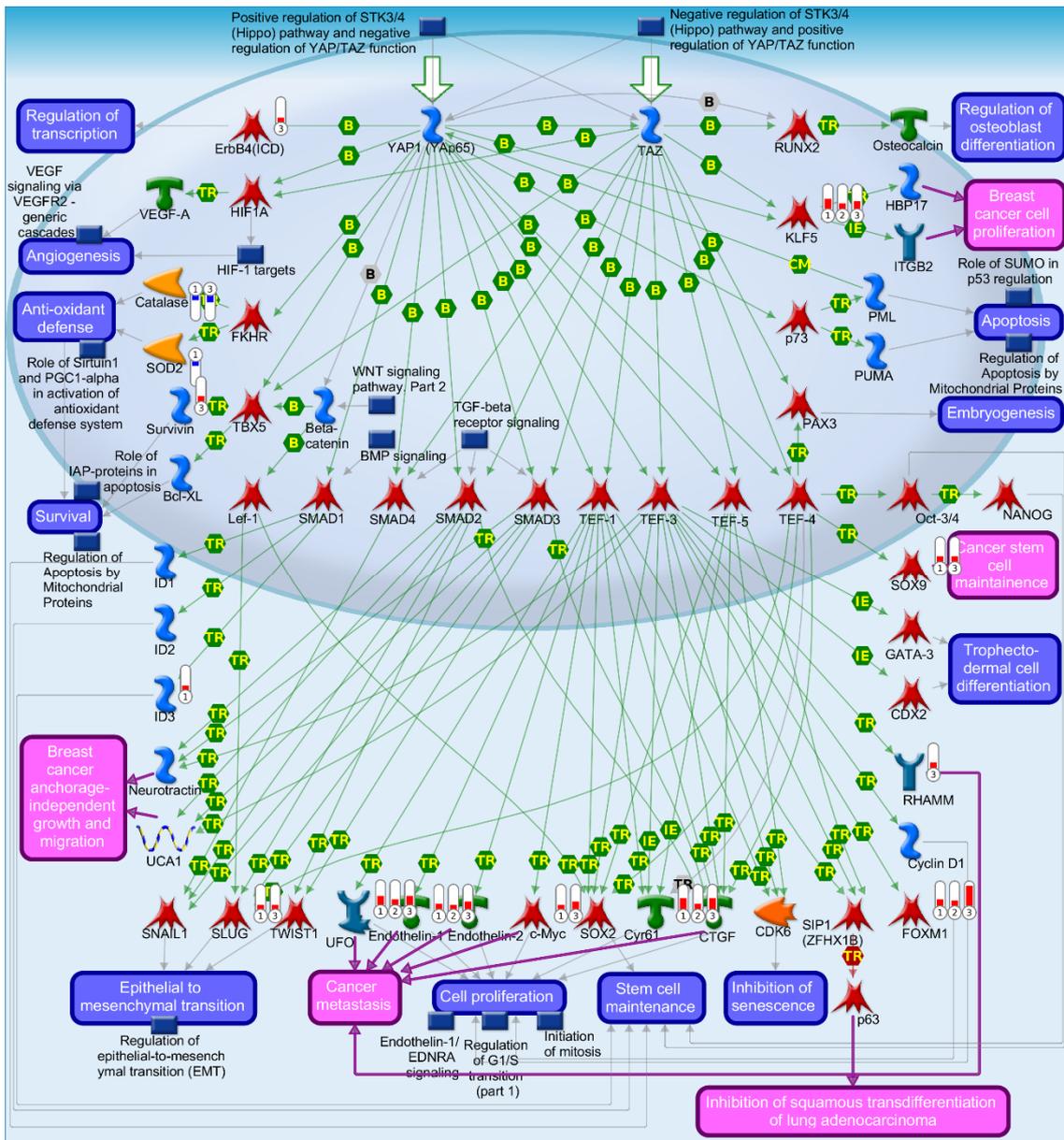


Figure. S19 Map of YAP/TAZ-mediated co-regulation of transcription. Significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed *Trp53*(+/+), *Trp53*(+/-) and *Trp53*(-/-) mouse kidneys were compared in MetaCore™. The enriched pathway (49th out of top 50; $p < 0.05$) shows up-regulated (thermometer-like symbols in red) and down-regulated (thermometer-like symbols in blue) genes. Numbers indicate genotype: 1) *Trp53*(+/+), 2) *Trp53*(+/-) and 3) *Trp53*(-/-). For detailed legend see **Figure. S22**. Abbreviations: Tafazzin (TAZ); yes-associated protein (YAP).

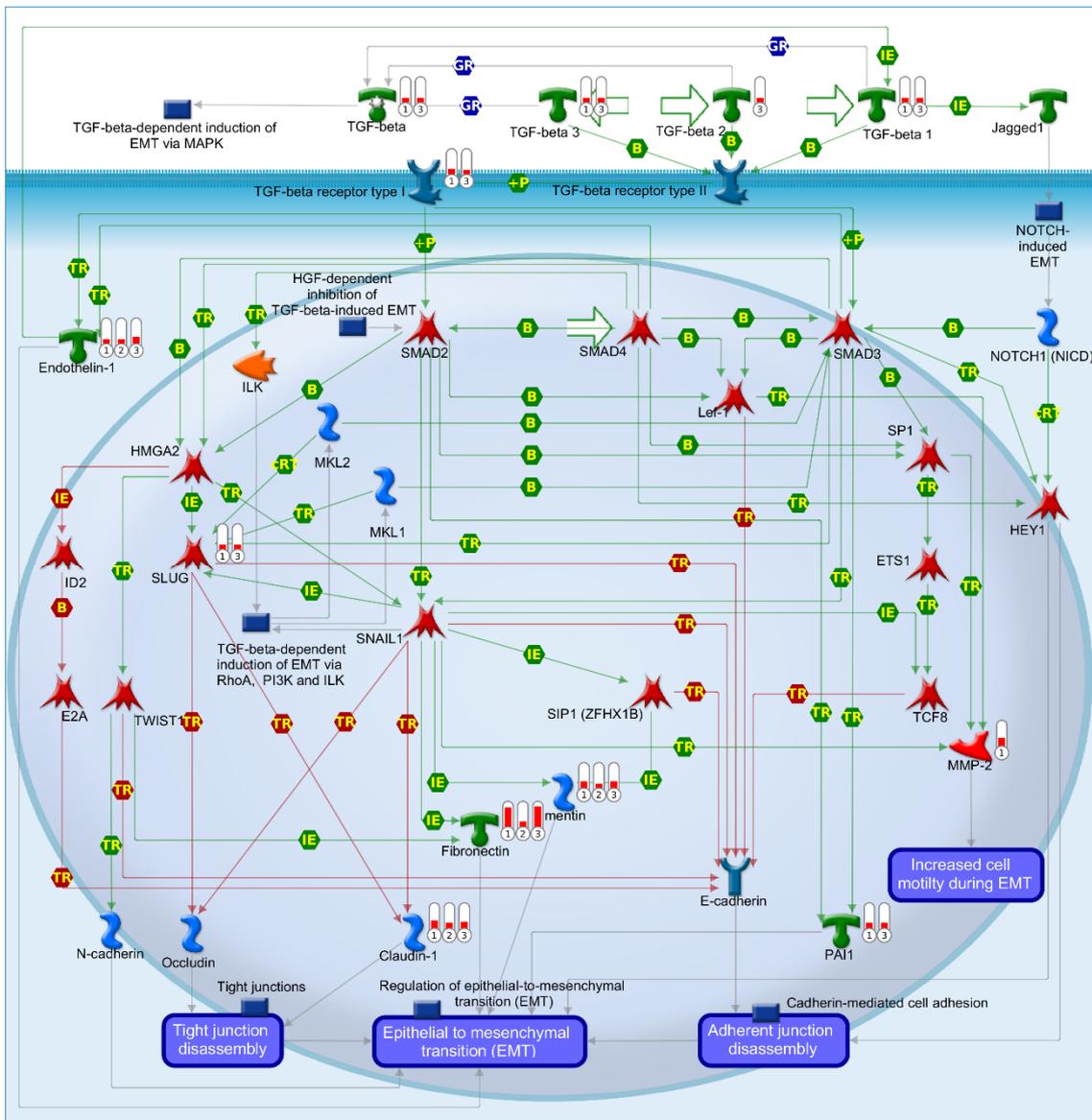


Figure. S20 Map of TGF- β -dependent induction of EMT via SMADs. Significantly altered ($p < 0.05$; fold change ± 2) genes for AAI-exposed *Trp53*(+/+), *Trp53*(+/-) and *Trp53*(-/-) mouse kidneys were compared in MetaCore™. The enriched pathway (50th out of top 50; $p < 0.05$) shows up-regulated (thermometer-like symbols in red) genes. Numbers indicate genotype: 1) *Trp53*(+/+), 2) *Trp53*(+/-) and 3) *Trp53*(-/-). For detailed legend see **Figure. S22**. Abbreviations: epithelial-to-mesenchymal transition (EMT); *Sma* mothers against DPP homology (SMAD); transforming growth factor β (TGF- β).

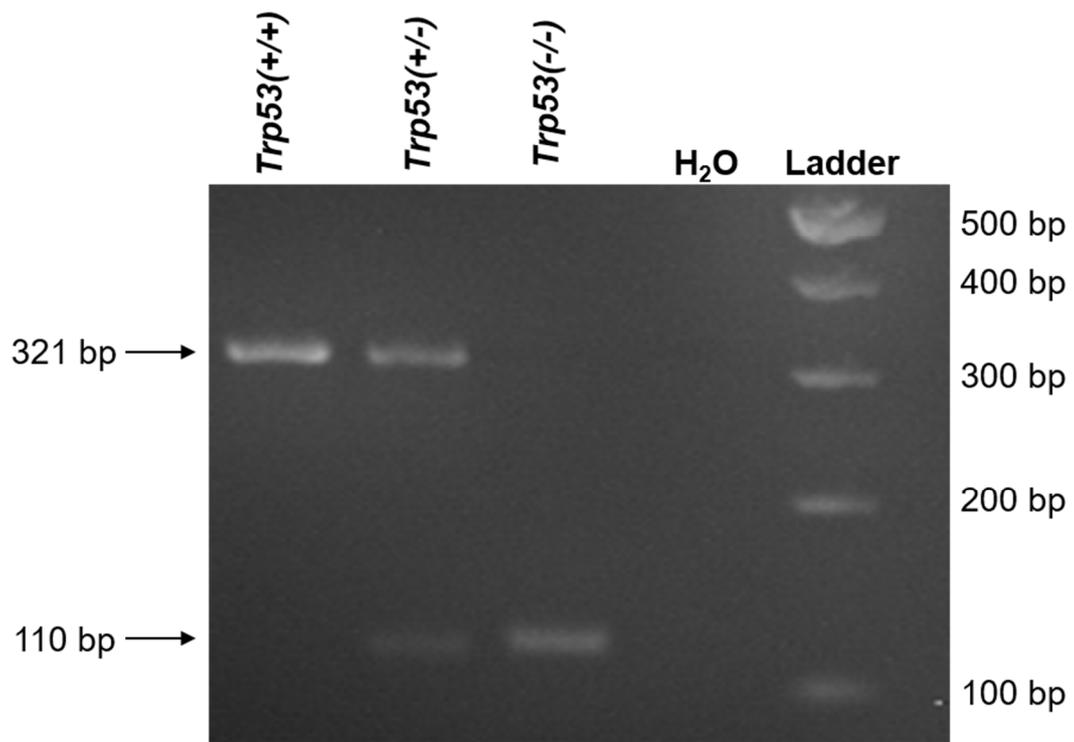


Figure. S21 Example of a *Trp53(+/+)*, *Trp53(+/-)* and *Trp53(-/-)* mouse genotyping PCR. H_2O indicates the negative control. bp, base pairs.

MetaCore Quick reference guide

User Data

NETWORKS	MAPS
	Up-regulated (+) Object has user data with positive value
	Down-regulated (-) Object has user data with negative value
	Mixed-signal (+/-) Object has user data with both positive and negative values
	Gene variants Object has user data with gene variants
	Mixed data Object has user data with both expression values and gene variants

Network Objects

ENZYMES	GENERIC CLASSES
<p>Generic enzyme</p> <p>KINASE</p> <ul style="list-style-type: none"> Generic kinase Protein kinase Lipid kinase <p>PHOSPHATASE</p> <ul style="list-style-type: none"> Generic phosphatase Protein phosphatase Lipid phosphatase <p>PHOSPHOLIPASE</p> <ul style="list-style-type: none"> Generic phospholipase <p>PROTEASE</p> <ul style="list-style-type: none"> Generic protease Metalloprotease <p>GTPASE</p> <ul style="list-style-type: none"> G-alpha RAS - superfamily 	<ul style="list-style-type: none"> Receptor ligand Transcription factor Protein Compound Predicted metabolite or user's structure Inorganic ion Reaction DNA RNA Generic binding protein Cell membrane glycoprotein
<p>CHANNELS/TRANSPORTERS</p> <ul style="list-style-type: none"> Generic channel Ligand-gated ion channel Voltage-gated ion channel Transporter 	<p>RECEPTORS</p> <ul style="list-style-type: none"> Generic Receptor GPCR Receptors with kinase activity <p>G PROTEIN ADAPTOR/REGULATORS</p> <ul style="list-style-type: none"> G beta/gamma Regulators (GDI, GAP, GET, etc.)
<p>GROUPS OF OBJECTS</p> <ul style="list-style-type: none"> A complex or a group Proteins physically connected into a complex or related as a family Logical association Proteins linked by logical relations or physical interactions Custom association Group of collapsed objects chosen by user 	

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Figure. S22 MetaCore™ “Quick reference guide” (Part 1).

Interactions between objects

EFFECTS

- Positive / activation
- Negative / inhibition
- Unspecified

MECHANISMS

PHYSICAL INTERACTIONS

- B** Binding
Physical interaction between molecules
- C** Cleavage
Cleavage of a protein at a specific site yielding distinctive peptide fragments. Proteolytic cleavage can be carried out by both enzymes and compounds
- CM** Covalent modifications
Covalent binding of a small chemical groups to protein amino acids or DNA/RNA nucleotides.
- +P** Phosphorylation
Protein activity is altered via addition of a phosphate group
- P** Dephosphorylation
Protein activity is altered via removal of a phosphate group
- T** Transformation
Protein activity regulation by binding & hydrolysis of GTP
- Tn** Transport
Transport of a protein or a compound between organelles
- Z** Catalysis
Catalysis of an enzymatic reaction
- Tr** Transcription regulation
Physical binding of a transcription factor to target gene's promoter
- eRT** Co-regulation of transcription
Influences on gene expression by direct binding with transcription machinery or by chromatin remodelling
- Rg** Regulation
Influence on the biochemical reaction by changing its composition
- M** MicroRNA binding
Regulation of gene expression by binding of microRNA to target mRNA

FUNCTIONAL INTERACTIONS

- IE** Influence on expression
Indirect influence of chemical compound or protein on the amount of another protein
- Cn** Competition
When two molecules compete for the interaction with the third molecule
- ?** Unspecified interactions
Influence on activity of protein or RNA without determined mechanism
- PE** Drug-Drug interactions. Pharmacological effect
Drugs change pharmacological effects of other drugs, for instance by competing for drug metabolism enzymes or organic transporters
- TE** Drug-Drug interactions. Toxic effect
Drugs change toxic effects of other drugs, for instance by competing for drug metabolism enzymes or organic transporters

LOGICAL RELATIONS

- BR** Group relation
Object belongs to a generic group of related objects
- CS** Complex subunit
Protein is a subunit of a protein complex
- SR** Similarity relation
Chemically similar compounds with chosen Tanimoto similarity score

LINKS ON NETWORKS

- Incoming interaction
When the molecule is over object, yellow link indicates direction to object
- Outgoing interaction
Cyan link indicates direction FROM the object

INTERACTIONS FROM CUSTOM LIST (MetaLink™)

- Interaction is in the network
Interaction is represented by a thin solid line and is highlighted in blue
- Interaction is in the base, but not in network
Interaction is highlighted in yellow
- Interaction is in the network
Interaction is highlighted in magenta

CANONICAL PATHWAYS

- Canonical pathway
The link is highlighted in a thick cyan or magenta line

LINKS ON MAPS

- Disrupts in disease
- Weakens in disease
- Emerges in disease
- Enhances in disease
- Species specific interactions

Objects on maps

LOCALIZATION

- Mitochondria
- EPR
- Golgi
- Nucleus
- Lysosome
- Peroxisome
- Cytoplasm
- Extracellular

OTHER MAP OBJECTS

Comments

- Note
- Normal process
- Pathological process

Blocks

- Normal process
- Pathological process
- Species specific object
- Path start

For more information, visit clarivate.com/metacore

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Figure. S22 MetaCore™ “Quick reference guide” (Part 2).