Supplementary Material

**Supplementary Table 1. Abbreviations and glossary.** A full list of abbreviations used multiple times outside their original context in this review, and a glossary of those terms.

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| **Abbreviation** | **Full Name** | **Notes** |
| AP-1 | Activator Protein-1 | Name of complex formed by Jra and Kay in *Drosophila* and their orthologues in mammals |
| aPKC | atypical Protein Kinase C | *Drosophila* apico-basal polarity regulator protein, human orthologues in PRKCI and PCKCZ |
| Ask1 | Apoptotic signal-regulating kinase 1 | *Drosophila* JNKKK, human orthologues in MAP3K15 and MAP3K5 |
| Bsk | Basket | *Drosophila* JNK, human orthologues in MAPK10, MAPK8, and MAPK9 |
| Cher | Cheerio | *Drosophila* F-actin crosslinking protein, human orthologues in FLNA/B/C |
| CIN | chromosomal instability | Phenomenon whereby whole chromosomes or sections thereof duplicate, leading to aneuploidy and potentially tumourigenesis |
| Cno | Canoe | *Drosophila* adherens junction scaffold protein, human orthologue AFDN |
| CycE | Cyclin E | *Drosophila* cell cycle regulator protein, human orthologues in CCNE1/2 |
| Diap1 | Death-associated inhibitor of apoptosis 1 | *Drosophila* apoptosis-inhibiting protein |
| Dlg1 | Discs large 1 | *Drosophila* apico-basal polarity regulator protein, human orthologues in DLG1, DLG2, DLG4, and DLG3 |
| Dpp | Decapentaplegic | *Drosophila* TGF-β ligand, human orthologues in BMP2 and BMP4 |
| Egr | Eiger | *Drosophila* TNF pathway ligand |
| Ena | Enabled | *Drosophila* actin polymerase, human orthologues in ENAH, EVL, and VASP |
| FOS | Fos proto-oncogene, AP-1 transcription factor subunit | Human orthologue of Kay |
| Grnd | Grindelwald | TNF signalling pathway receptor, activated by Egr |
| Hep | Hemipterous | *Drosophila* JNKK, human orthologues in MAP2K4 |
| Hid | Head involution defective | *Drosophila* apoptosis-promoting protein |
| Jak-STAT | Janus kinase-Signal Transduction and Activator of Transcription | Signalling pathway with a diversity of roles, but often involved in intercellular signalling |
| JNK | c-Jun N-terminal Kinase | JNK pathway kinase, activated by JNKKs, and that induces TF activity, also a signalling pathway commonly involved in apoptosis and proliferation regulation |
| JNKK | c-Jun N-terminal Kinase Kinase | JNK pathway kinase kinase, activated by JNKKKs, and that activate JNKs |
| JNKKK | c-Jun N-terminal Kinase Kinase Kinase | JNK pathway kinase kinase kinase, activated by JNKKKKs, and that activate JNKKs |
| Jra | Jun-related antigen | TF downstream of JNK signalling in *Drosophila*, forms AP-1 complex with Kay, human orthologues in JUN and JUND |
| Jub | Ajuba LIM protein | *Drosophila* Wts-inhibiting protein, human orthologues in LIMD1, WTIP, and AJUBA |
| JUN | Jun proto-oncogene, AP-1 transcription factor subunit | Human orthologue of Jra |
| Kay | Kayak | TF downstream of JNK signalling in *Drosophila*, forms AP-1 complex with Jra, human orthologues in FOS, FOSL1, and FOSL2 |
| L(2)gl | Lethal (2) giant larvae | *Drosophila* apico-basal polarity regulator protein, human orthologues in LLGL1 and LLGL2 |
| MAPK | Mitogen Activated Protein Kinase | Class of protein kinase of which JNK is a member, also commonly used as a moniker for signalling pathways proceeding via Egfr and/or Ras85D in *Drosophila* |
| Mbc | Myoblast city | *Drosophila* guanine nucleotide exchange factor protein |
| Mkk4 | MAP kinase kinase 4 | *Drosophila* JNKK, human orthologues in MAP2K7 |
| Mmp1 | Matrix metalloproteinase 1 | *Drosophila* extracellular proteinase, common target of JNK signalling, closest human orthologues in MMP14/24 |
| nTSGs | neoplastic tumour suppressor genes | Class of genes where their inactivation leads to neoplastic tumour growth, characterized by tissue overproliferation and aberrant differentiation |
| PI3K | Phosphoinositide 3-kinase | Signalling pathway, also known as the AKT or mTOR pathway, with a diversity of roles, but often involved in cell cycle regulation |
| Pvr | PDGF- and VEGF-receptor related | *Drosophila* receptor protein, capable of activating a range of signalling pathways, including PI3K and JNK |
| Raf | Raf oncogene | *Drosophila* kinase protein, lying downstream of Ras85D, human orthologues in BRAF, ARAF, and RAF1 |
| Ras85D | Ras oncogene at 85D | *Drosophila* GTPase protein, human orthologues in HRAS, KRAS, and NRAS |
| Robo2 | Roundabout 2 | *Drosophila* receptor protein, human orthologues in ROBO1/2/3/4 |
| ROS | reactive oxygen species | Reactive chemical species containing oxygen which can be damaging biologically, and can be produced due to cellular stress  |
| Rpr | Reaper | *Drosophila* apoptosis-promoting protein |
| Scrib | Scribble | *Drosophila* apico-basal polarity regulator protein, human orthologue SCRIB |
| Sd | Scalloped | *Drosophila* TF active alongside Yki, human orthologues in TEAD1/3/4/2 |
| Shg | Shotgun | *Drosophila* protein also known as E-cadherin |
| Slpr | Slipper | *Drosophila* JNKKK, human orthologues in MAP3K9, MAP3K10, MAP3K11, and MAP3K21 |
| Src42A | Src oncogene at 42A | *Drosophila* kinase protein, human orthologue FRK |
| Src64B | Src oncogene at 64B | *Drosophila* kinase protein, human orthologues in FYN and SRC |
| SWH | Salvador-Warts-Hippo | Signalling pathway also referred to as the Hippo pathway, suppresses tissue growth by downregulating Yki activity |
| Syx7 | Syntaxin 7 | *Drosophila* endocytic process protein, human orthologues in STX7/12 |
| Tak1 | TGFβ-associated kinase 1 | *Drosophila* JNKKK, human orthologue MAP3K7 |
| TFs | transcription factors | Class of proteins that contribute to gene transcription |
| TGF-β | Transforming Growth Factor-β | Signalling pathway with a diversity of roles, but often involved in cell growth and proliferation |
| TNF | Tumour Necrosis Factor | Signalling pathway capable of activating JNK signalling in *Drosophila* |
| Upd1/2/3 | Unpaired 1/2/3 | *Drosophila* Jak-STAT signalling pathway ligands |
| Wg | Wingless | Signalling pathway also known as the WNT pathway with a diversity of roles in *Drosophila*, but commonly involved in cellular communication and embryogenesis |
| Wgn | Wengen | TNF signalling pathway receptor, activated by Egr |
| Wnd | Wallenda | *Drosophila* JNKKK, human orthologues in MAP3K13 and MAP3K12 |
| Wts | Warts | *Drosophila* kinase protein from the SWH pathway, human orthologues in LATS1/2 |
| Yki | Yorkie | *Drosophila* transcriptional co-activator downregulated by SWH signalling, human orthologue in YAP1 |

**Supplementary Table 2. Conservation of the JNK pathway between *Drosophila melanogaster* and *Homo sapiens*.** The core JNK signalling pathway components in *Drosophila* have orthologues in humans, but with greater genetic redundancy, as is often the case. Note also there are many links between human JNK components and tumourigenesis – here we provide an overview of the various cancers and cancer models to which the human orthologues have been directly linked. However, such links are certain to only scratch the surface regarding how the versatile JNK signalling pathway can affect cancer development in more fundamental ways. We have included the most recent studies for each the human genes where possible, but the field is vast, and we are unable to cover it in its entirety, and so note that it can also be found reviewed in Wagner and Nebreda (2009), Kyriakis and Avruch (2012), Kitanaka et al. (2013), Tournier (2013), Bubici and Papa (2014), Li et al. (2016), Wang and Tai (2016), Yan et al. (2016), Dhanasekaran and Reddy (2017), Wu et al. (2019), Xu and Hu (2020), and Gallo et al. (in press). Note that many more studies than we have cited here link JNK signalling to cancer, but some only explore JNK in a general way, and we tried to limit the studies we have cited to those that were explicit in which JNK pathway gene(s) they examined.

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| **JNK Pathway Role** | ***Drosophila* Genes** | **Human Orthologues** | **Known Links to Human Tumourigenesis** |
| JNKKKs | *slpr* | *MAP3K9* | * Inactivating mutations found in 24% of tested melanoma cell lines (alongside *MAP3K5*) (Stark et al., 2011)
* Activating mutations found in some non-small cell lung cancers (Fawdar et al., 2013)
* Overexpressed in renal carcinomas, repressed by MicroRNA-148b (Nie et al., 2016)
 |
| *MAP3K10* | * Upregulation promotes proliferation of pancreatic ductal adenocarcinoma cells, and inhibits their sensitivity to gemcitabine treatment (An et al., 2013)
* Likely downregulated by MicroRNA-155 activity in osteosarcoma (Wang et al., 2017a)
 |
| *MAP3K11* | * Dominant-negative MAP3K11 expression suppresses hepatoma cell death (Kim et al., 2004)
* Required generally for growth and invasion of various cancer cells (Chen et al., 2010; Chen and Gallo, 2012; Whitworth et al., 2012; Zhan et al., 2012)
* The oncogenic P252H mutation of MAP3K11 is common in gastrointestinal cancers, and upregulates Wnt, Notch, and MAPK signalling pathways (Velho et al., 2010; Corso et al., 2011; Velho et al., 2014)
* Ectopically activated in Human epidermal growth factor 2 (HER2)-positive cancers, but pro-apoptotic functionality is suppressed by HER2 and restored via drug treatment (Das et al., 2015)
* MicroRNA-199a95p expression suppresses oesophageal tumourigenesis by repressing *MAP3K11* (Byrnes et al., 2016)
* Glioblastoma invasiveness driven by EGFR signalling via DOCK1 and MAP3K11 (Misek et al., 2017)
* Activated in a positive feedback loop with ERK1/2 via oxidative stress to promote colorectal tumourigenesis and invasion (Schroyer et al., 2018)
* Promotes breast tumourigenesis via phosphorylation of p21-activated kinase 1 (Das et al., 2019)
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| *MAP3K21* | * Commonly mutated in in colorectal cancers, where constitutively active alleles can promote tumourigenesis alongside activated KRAS or BRAF (Martini et al., 2013)
* Loss-of-function mutations in colorectal cancer cells reduce growth rates and tumour sizes (Marusiak et al., 2016)
* Found to be overexpressed in triple-negative breast cancers, where it promotes invasiveness (Marusiak et al., 2019)
 |
| *wnd* | *MAP3K13* | * Inactivating mutations in *MAP3K13* have been identified as somatic driver mutations promoting oncogenesis in breast cancers (Stephens et al., 2012)
 |
| *MAP3K12* |  |
| *Tak1* | *MAP3K7* | * Breast tumourigenesis and metastasis can proceed via MAP3K7 activity stimulated by TGF-β signalling (Neil and Schiemann, 2008; Safina et al., 2008)
* Metastatic breast cancers often invade bones, a process mediated by MAP3K7 signalling activity (Safina et al., 2011)
* Necessary in some colon cancers with activated RAS signalling (Singh et al., 2012)
* EMT of skin squamous cell carcinoma is promoted by MAP3K7 downregulation, which is common in said cancers (Lam et al., 2013)
* Overexpression correlates with metastatic tumour behaviour and poor survival in oesophageal squamous cell carcinomas and clear cell renal cell carcinomas (Wei et al., 2013; Wen et al., 2013)
* Overexpressed in renal cell carcinomas, where it acts as an oncogene, upregulating NF-κB signalling (Fandong et al., 2014)
* Overexpressed in many thyroid cancers, with the level of said overexpression correlating with cancer metastasis (Lin et al., 2015)
* Deletion/suppression of *MAP3K7* is strongly associated with prostate tumourigenesis, and also synergises with CHD1 suppression to lead to enhanced cooperative prostate tumourigenesis (Wu et al., 2012; Kluth et al., 2013; Rodrigues et al., 2015)
* Necessary for the survival of lung cancer cells, where it is activated downstream of TGF-β/BMP signalling (Augeri et al., 2016)
* Lies downstream of various metastasis-promoting genes, such as *UBE2N* in breast cancer and *MET* in hepatocellular carcinoma (Wu et al., 2014; Tey et al., 2017)
* Overexpressed in gastric cancer, and its level correlates with reduced survival rates and disease progression (Yang et al., 2017)
* Tumour suppressor role of MicroRNA-146a in gastric cancer due to its targeted inhibition of *MAP3K7* (Chen et al., 2017)
* Upregulation in pancreatic ductal adenocarcinoma associated with apoptosis suppression and lymph node metastasis (Melisi et al., 2011; Huang et al., 2017a)
* Overexpressed in many breast cancers, and inhibition of MAP3K7 suppresses triple-negative breast cancer metastasis to the lungs in animal models (Huang et al., 2015; Iriondo et al., 2018)
* Commonly constitutively active in cutaneous T-cell lymphoma cells, and acts upstream of NF-κB and β-catenin signalling (Gallardo et al., 2018)
 |
| *Ask1* | *MAP3K15* |  |
| *MAP3K5* | * Found to be commonly mutated in melanoma samples, where the R256C mutation led to increased proliferation, and apoptosis is induced by MAP3K5 in response to novel atmospheric gas plasma treatment (Ishaq et al., 2014; Prickett et al., 2014)
* CLDN6 acts as a breast cancer tumour suppressor, and this effect correlates with MAP3K5 expression in multiple cancers (Guo et al., 2012; Zhang et al., 2015; Guo et al., 2016)
* Lung adenocarcinoma cells survive based on downregulation of MAP3K5 activity by ROR1 (Ida et al., 2016)
* Multiple drugs activate MAP3K5 signalling in hepatocellular carcinoma cells, where it is known to promote apoptosis – 4SC-202 does so independently, while ABT-737 synergises with curcumin (Fu et al., 2016; Jiang et al., 2016; Zhang et al., 2016; Zheng et al., 2016)
* Deletion in platelets non-autonomously reduces lung cancer metastasis (Kamiyama et al., 2017)
* In neuroblastoma cells, MAP3K5 is active and stabilises NR2E1, which promotes cell survival (Sobhan et al., 2017)
* Sensitivity of colorectal cancer cells to drug treatment was enhanced after MAP3K5 was derepressed (Zhang et al., 2018)
* SLC35F2 is commonly overexpressed in cancers, and in papillary thyroid carcinoma promotes tumourigenesis via MAP3K5 (He et al., 2018)
* Overexpression in gastric cancer cells inhibits proliferative and migratory behaviours via JNK and p38 signalling (Wan et al., 2018)
 |
| JNKKs | *hep* | *MAP2K4* | * Implicated as having tumour suppressor functionality in both ovarian cancer and lung adenocarcinoma (Ahn et al., 2011; Yeasmin et al., 2011)
* Expression strongly correlates with multiple osteosarcoma progression parameters, as well as cell proliferation in pancreatic ductal adenocarcinoma (Handra-Luca et al., 2012; Tesser-Gamba et al., 2012)
* Promotes metastatic behaviour independently of JNK or p38 downstream targets in some prostate cancers (Pavese et al., 2014)
* MicroRNA-27a downregulates *MAP2K4* – in osteosarcoma cell lines this then promotes tumourigenic behaviour, but in prostate cell lines this suppresses it (Pan et al., 2014; Wan et al., 2016)
* Low MAP2K4 activity, as measured by phosphorylation, is correlated with increases metastatic capability in colorectal cancer samples (Wang et al., 2017b)
* MicroRNA-802 targets *MAP2K4*, but is downregulated in some tongue squamous cell carcinomas, contributing to tumourigenesis (Wu et al., 2017)
* Resistance of triple-negative breast cancers to PI3K signal inhibition has been linked to MAP2K4 activity (Mundt et al., 2018)
* High MAP2K4 (alongside MAP2K7) expression is linked to favourable prognoses in some pancreatic ductal adenocarcinomas (Lu et al., 2019)
 |
| *Mkk4* | *MAP2K7* | * Hepatoma treatment via flavonoid drugs occurs in part via the induction of MAP2K7 activity (Tang et al., 2012)
* Elevated MAP2K7 activity contributes to hepatocellular carcinoma tumourigenesis (Guo et al., 2013)
* MicroRNA-493-based inhibition of *MAP2K7* likely contributes to preventing the metastasis of colon cancers to the liver (Sakai et al., 2014)
* Drug-based suppression of the capacity of multiple myeloma to suppress MAP2K7-mediated apoptosis may be a promising treatment avenue (Tornatore et al., 2014)
* MAP2K7 is thought to play a role in breast cancer development, where the post-translational modification of neddylation regulates its activity (Zhu et al., 2016)
* Certain *MAP2K7* alleles may indicate a higher risk of certain lung cancers (Qiu et al., 2016; Jia et al., 2017)
* High MAP2K7 (alongside MAP2K4) expression is linked to favourable prognoses in some pancreatic ductal adenocarcinomas (Lu et al., 2019)
* A review of the potential of MAP2K7 as a therapeutic target in cancer has also recently been published (Park et al., 2019)
 |
| JNKs | *bsk* | *MAPK10* | * Tumour suppressor CDKN2A acts to inhibit MAPK10 activity and so prevents tumourigenesis (Choi et al., 2005)
* May act as a tumour suppressor in chromophobe renal cell carcinoma depending on its epigenetic status (Yoo et al., 2011)
* Expression positively correlates with disease progression in various cancers (Dai et al., 2014)
* MicroRNA-27a-3p downregulates *MAPK10* to promote tumourigenesis in nasopharyngeal carcinoma (Li and Luo, 2017)
 |
| *MAPK8* | * Estrogen signalling may act alongside JNK signalling via MAPK8 activity to affect breast cancer and cervical epithelial cancer progression (Fogarty et al., 2012; Sun et al., 2012)
* Multidrug resistance of colon cancer is mediated in part by JNK signalling via MAPK8 (Zhu et al., 2012)
* Stromal MAPK8 signalling in breast cancers is highly important in their progression and in developing malignance (Lisanti et al., 2014)
* Pro-apoptotic MAPK8 signalling is suppressed in hepatocellular carcinoma to facilitate aerobic glycolysis (Iansante et al., 2015)
* FXR suppresses MAPK8 activity to inhibit chemically-induced liver tumourigenesis (Wang et al., 2015)
* MAPK8 expression positively regulates vitamin D receptor expression, which then facilitates vitamin D-mediated colorectal cancer cell proliferation inhibition (Bi et al., 2016)
* JNK signalling via MAPK8 (and MAPK9) is activated by hepatitis B virus X protein, and overcomes tumour suppressor TGF-β signalling in hepatocellular carcinoma (Wu et al., 2016)
* Gastric cancer cells undergo apoptosis after dihydroartemisinin administration via JNK signalling through MAPK8 (and MAPK9) (Zhang et al., 2017)
* JNK signalling through MAPK8 (and MAPK9) activates Notch signalling in triple-negative breast cancer cells to promote tumourigenesis (Xie et al., 2017)
* Expression is reduced in oesophageal squamous cell carcinomas, and expression in the stromal cells specifically correlates with tumourigenesis (Bao et al., 2018)
 |
| *MAPK9* | * Overexpressed in many non-small cell lung carcinomas, and is necessary for their growth, as well as in some cases their capacity to initiate tumourigenesis (Nitta et al., 2011; Okada et al., 2013)
* Decreasing MAPK9 activity may contribute to the effectiveness of ulinastatin on inhibiting breast cancer cell growth (Wang et al., 2012)
* Constitutively activated MAPK9 is found and necessary in various multiple myeloma tumours (Barbarulo et al., 2013)
* MAPK9 (and MAPK8) may be necessary for the resistance of prostate cancers to certain drug treatments (Parra and Ferreira, 2013)
* JNK signalling via MAPK9 and downstream of KRAS contribute to tumour-initiation by pancreatic cancer stem cells (Okada et al., 2014)
* Colorectal cancer metastasis may depend in part on downregulation of MicroRNA-200c and the concomitant upregulation of *MAPK9* (Sui et al., 2014)
* MAPK9 (and MAPK8) contribute to the capacity of chemoresistant cell lines to initiate tumourigenesis (Liu et al., 2015)
* Non-small cell lung carcinonoma cells undergo apoptosis after MAPK9 (and MAPK8) upregulation in response to phloretin treatment (Min et al., 2015)
* MAPK9 is misregulated in ulcerative colitis, which can lead to cancer, but restoring its functionality might be preventative with regards to this tumourigenesis (Lessel et al., 2017; Reissig et al., 2017)
* Upregulating *MAPK9* by downregulating MicroRNA-200c can contribute to bladder cancer invasiveness (Huang et al., 2017b)
* MAPK9 (and MAPK8) contribute to osteosarcoma invasiveness, which is suppressed by inhibiting their activity (Lu et al., 2018)
* MAPK9 (and MAPK8) activity is suppressed in many lung squamous cell carcinomas, with increased activity being indicative of better survival rates amongst similar cancers (Liu et al., 2019)
* Contributes to melanoma cell tumourigenesis and drug resistance (Du et al., 2019)
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