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YAP/TAZ: Drivers of Tumor Growth, Metastasis, and Resistance to Therapy

Barry J. Thompson

The transcriptional co-activators YAP (or YAP1) and TAZ (or WWTR1) are frequently activated during the growth and progression of many solid tumors, including lung, colorectal, breast, pancreatic, and liver carcinomas as well as melanoma and glioma. YAP/TAZ bind to TEAD-family co-activators to drive cancer cell survival, proliferation, invasive migration, and metastasis. YAP/TAZ activation may also confer resistance to chemotherapy, radiotherapy, or immunotherapy. YAP-TEAD cooperates with the RAS-induced AP-1 (FOS/JUN) transcription factor to drive tumor growth and cooperates with MRTF-SRF to promote activation of cancer-associated fibroblasts, matrix stiffening, and metastasis. The key upstream repressor of YAP/TAZ activation is the Hippo (MST1/2-LATS1/2) pathway and the key upstream activators are mechanically induced Integrin-SRC and E-cadherin-AJUBA/TRIP6/LIMD1, growth factor induced PI3K-AKT, and inflammation-induced G-protein coupled receptor (GPCR) signals, all of which antagonize the Hippo pathway. In this review, strategies to target YAP/TAZ activity in cancer are discussed along with the prospects for synergy with established pillars of cancer therapy.

1. Introduction

There are two great theories of metastatic cancer: Theodore Boveri's chromosomal damage theory and Rudolf Virchow's tissue damage and inflammation theory. Boveri's chromosome damage theory underlies all cancer genome sequencing efforts, which have identified a core set of commonly mutated oncogenes and tumor suppressors that primarily affect a handful of signal transduction pathways, most importantly the growth factor induced PI3K-Akt and RAS-RAF signaling pathways (**Figure 1**). Subsequent attempts to develop targeted therapeutics against growth factor signaling have had mixed results, and even the most successful examples increase overall survival for metastatic cancer patients by less than half-a-year compared with conventional chemotherapy, radiotherapy, or immunotherapy. Thus, there remains a major unmet clinical need for new targeted therapies, and Virchow's tissue damage and inflammation theory—restated by Dvorak with the phrasing "cancers: wounds that do not heal"—offers an alternative paradigm for identifying important cancer targets (**Figure 2**).

The transcriptional co-activators YAP (Yes-associated protein) and TAZ (Transcriptional activator with PDZ domain) have recently been demonstrated to be key mediators of the wound healing and tissue regeneration responses to tissue damage as well as important drivers of solid tumor growth, metastasis, and resistance to therapy—making them attractive therapeutic targets for cancer[1,2] (see **Box 1**). Although YAP/TAZ are mutationally activated in a small number of cancers (including chromosomal translocations in epithelioid hemangioendothelioma, ependymoma, poroma, and porocarcinoma—described below), the widespread activation of YAP/TAZ in most solid tumors is best explained by Virchow's theory. Here, I review the roles of YAP/TAZ in wound healing, tissue regeneration and different types of cancer as well as describing the signal transduction pathways that control and cooperate with YAP/TAZ during these events. These concepts inform possible strategies for effectively inhibiting YAP/TAZ activity in cancer patients as monotherapy and as a combination therapy with conventional chemotherapy, radiotherapy, or immunotherapy.

1.1. YAP/TAZ as Mediators of Wound Healing and Tissue Regeneration

The first genetic evidence for a role of Yap in tissue regeneration came from the mouse intestine, where Yap expression and nuclear localization is induced by tissue damage with DSS or gamma-irradiation and intestinal-specific *Villin-CreERt* induced conditional knockout (KO) of a homozygous Lox-flanked *yap* gene ("*floxed*" $yap^{flox/flox}$) prevented regeneration after damage, without affecting normal intestinal turnover.[27,28] Pro-proliferative EGFR ligands[28] and pro-inflammatory signals such as Prostaglandin E_2 (PGE_2) and Interleukin-6 (IL-6) act in a positive feedback loop with Yap after intestinal damage[29,30] (**Figure 3**). Similarly, Yap/Taz are induced and nuclear localized

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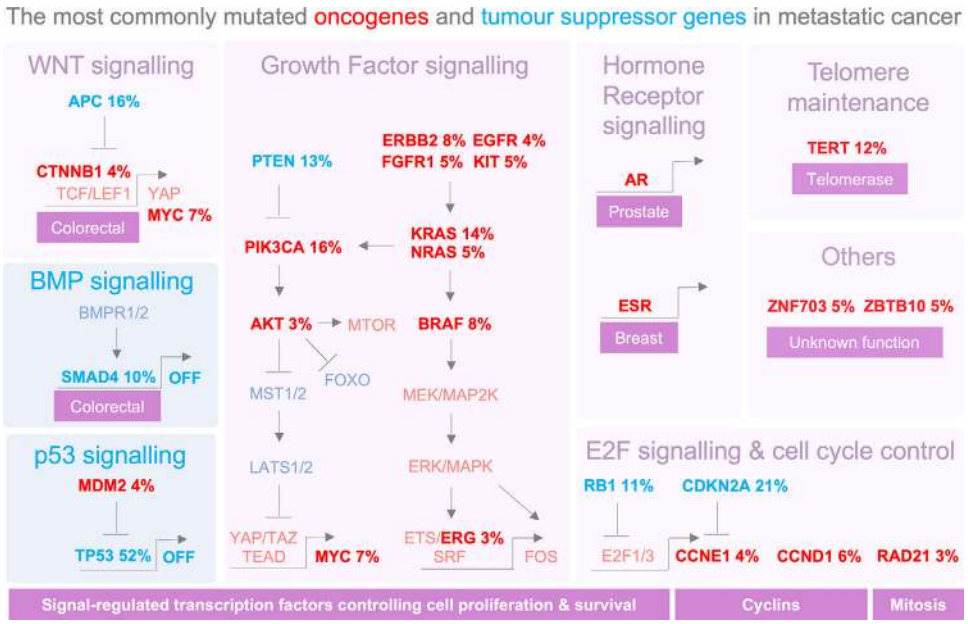

Figure 1. A modern view of Boveri's chromosomal damage theory of metastatic cancer. Boveri's theory postulates that damage to chromosomes (mutations, etc.) might cause cancer. The diagram shows a modern summary of the most commonly mutated oncogenes and tumor suppressor genes in metastatic cancer, assembled into the signaling pathways affected.

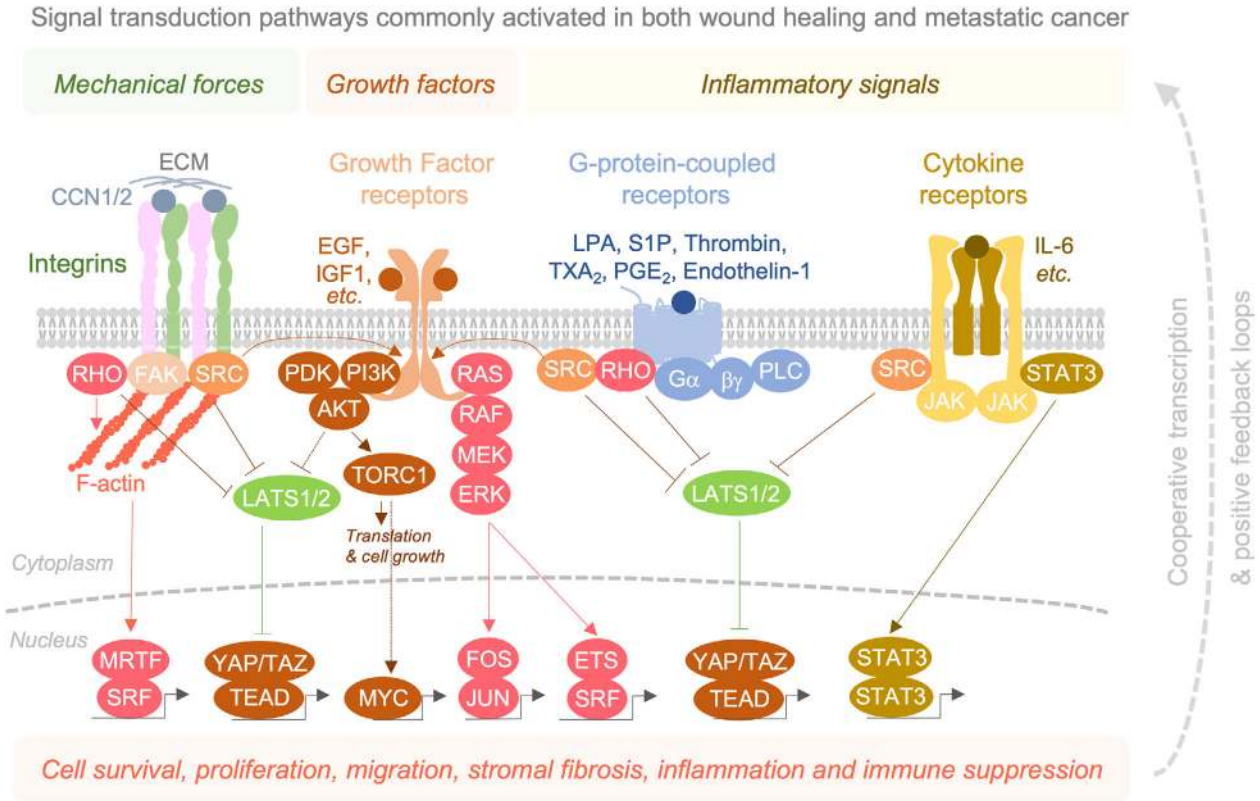

Figure 2. A modern view of Virchow's tissue damage and inflammation theory of metastatic cancer. Virchow's theory postulates the chronic damage or "irritation" of tissues leads to sustained inflammation as the tissue attempts to repair the damage. This theory was restated by Dvorak in the phrasing "cancers: wounds that do not heal." The diagram shows a modern summary of the signal transduction pathways most commonly induced during the regenerative response to tissue damage (wound healing). The same pathways are often chronically activated in metastatic cancer. Note that downstream transcriptional effectors of these pathways exhibit co-operativity in target gene activation and can also induce expression of upstream signaling components in a positive feedback loop that sustains signaling in cancers.

Box 1
A Historical Note on the Discovery of the YAP/TAZ Family

The YAP (Yes-associated protein)[3] and TAZ (Transcriptional co-activator with WW and PDZ domains; WWTR1) were initially characterized as novel transcriptional co-activators[4,5] that interacted with TEAD-family DNA binding transcription factors but had no known biological function.[6] The first evidence for an oncogenic role of YAP/TAZ in driving tumor-like growth and invasive migration came from *Drosophila,* where there is a single YAP/TAZ homolog named Yorkie (Yki) that is the main effector of the Hippo signaling pathway.[7–13] Phosphorylation of Yki by the Warts kinase (and YAP/TAZ by LATS1/2 in humans) induces binding to 14-3-3 proteins and leads to retention in the cytoplasm, preventing nuclear localization and transcription.[7,14] Like YAP/TAZ, Yki acts as a co-activator for a TEAD family transcription factor (named Scalloped or Sd) and drives expression of pro-proliferative and anti-apoptotic target genes including *Myc* and *bantam*.[15–21] Oncogene cooperation between Yki and Ras signaling was also first demonstrated in *Drosophila,* where genome-wide methods revealed that Yki and the Ras-induced AP-1 transcription factor bind to an overlapping set of target genes and exhibit mutual transcriptional cross-regulation in tumors.[22–26] The regulation of Hippo signaling in *Drosophila* has been extensively reviewed elsewhere[9–13] and here the focus is on the regulation and function of YAP/TAZ in wound healing and cancer as well as their potential as therapeutic targets.

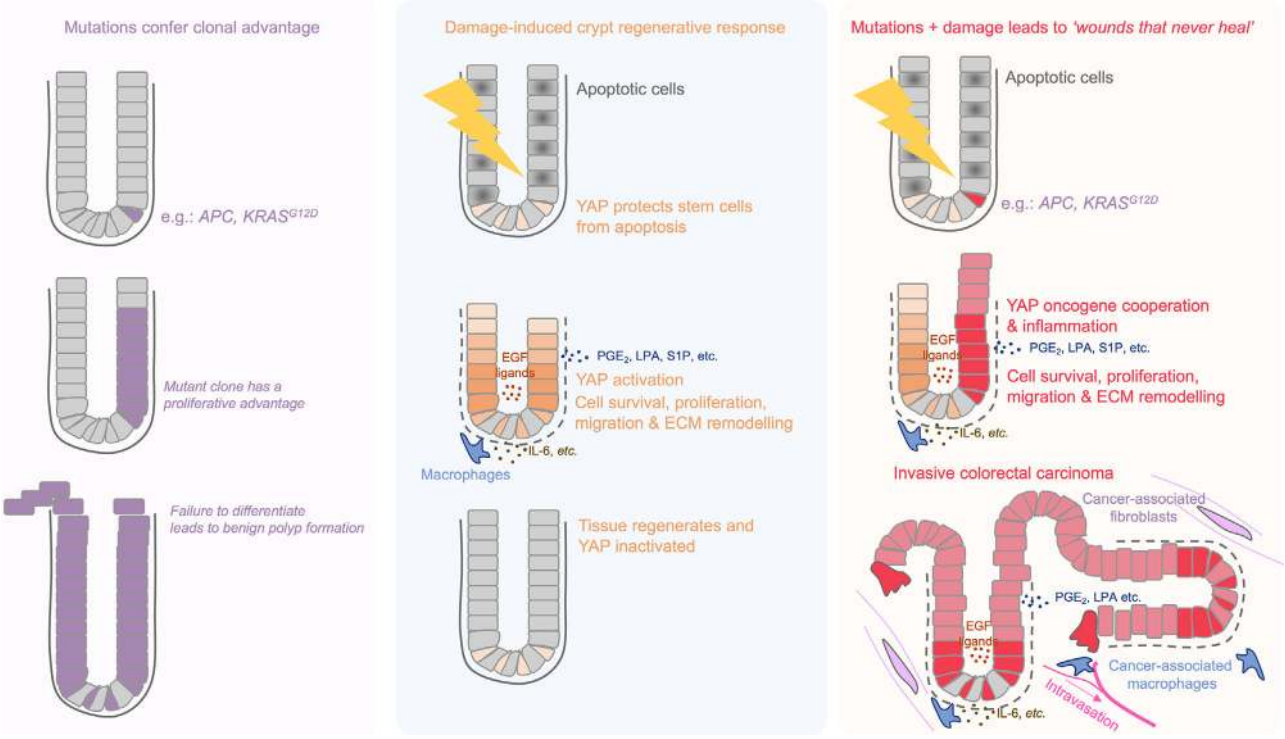

Figure 3. Mutations and tissue damage responses combine to drive colorectal carcinoma. The diagram shows an intestinal crypt with basal stem cells, some of which acquire mutations in APC and KRAS, which produces overproliferation and failure to differentiate and slough off, leading to benign intestinal polyp formation. After intestinal damage (irradiation or DSS treatment), some cells apoptose, while others mount a rapid proliferative regeneration response induced by YAP activation. EGFR ligands, cytokines such as IL-6, and pro-inflammatory GPCR ligands are also induced transiently during regeneration. The combination of mutations plus a chronic regenerative response enables oncogene cooperation between YAP and mutated APC/KRAS to drive colorectal carcinoma formation and invasion.

following skin wounding and skin-specific *K5-CreERt* induced double knockouts (dKO) of $yap^{flox/flox}$ and $taz^{flox/flox}$ had minor effects on normal adult skin proliferation, while strongly impairing cell proliferation during skin wound healing[31] (**Figure 4**). Tissue-specific $yap^{flox/flox}$ $taz^{flox/flox}$ dKO with a variety of different Cre-driver lines also reveals key regenerative functions in mouse heart,[32,33] liver,[34] kidney,[35] and lung[36] as well as in angiogenesis.[37–39] These physiological functions in wound healing and regeneration may explain the widespread activation of YAP/TAZ in human tumors, in accordance with Virchow's tissue damage and inflammation theory of cancer.

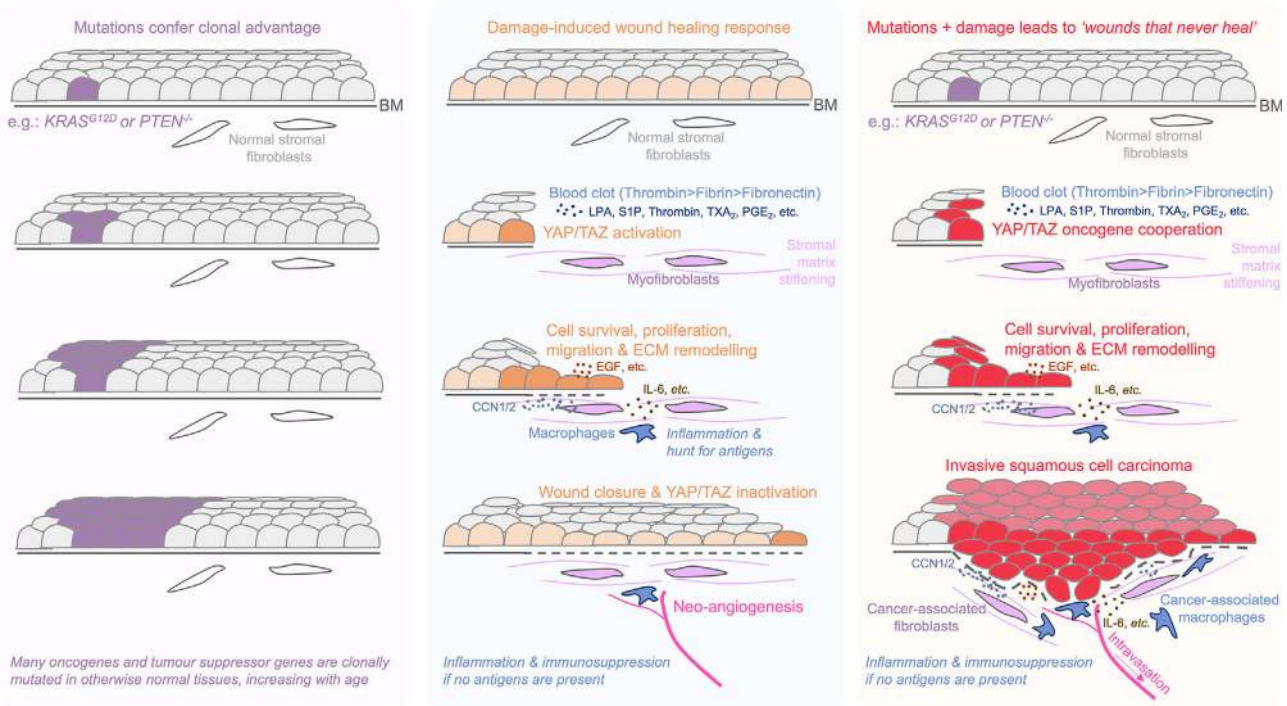

Figure 4. Mutations and tissue damage responses combine to drive squamous cell carcinoma. The diagram shows a stratified squamous epithelium (e.g., skin) with basal layer stem cells, some of which acquire mutations in KRAS or PTEN, which promotes overproliferation and clonal advantage. After wounding, basal stem cells mount a proliferative regeneration response induced by YAP/TAZ activation. EGR ligands, cytokines such as IL-6, and pro-inflammatory GPCR ligands are also induced transiently during regeneration. The combination of mutations plus a chronic regenerative response enables oncogene cooperation between YAP and mutated KRAS/PTEN to drive squamous cell carcinoma formation and invasion.

1.2. YAP/TAZ as Oncogenes: Which Tumor Types?

1.2.1. Squamous Cell Carcinomas of the Skin, Cervix, Vulva, Lung, Esophagus, and Head/Neck

Stratified epithelial tissues such as skin, cervix, lung bronchus, esophagus, or oral mucosa can give rise to different types of squamous cell carcinoma (SCC). Cutaneous SCC (cSCC) is the best studied owing to the experimental tractability of skin, but is highly similar histologically to all other SCCs, including cervical SCC (CVSCC), vulval (VSCC), lung SCC (LUSC; a major subtype of non-small cell lung cancer NSCLC), esophageal SCC (ESCC), as well as head and neck SCC (HNSCC) or oral SCC (OSCC). Although there have been many reports of a strong correlation between high levels of YAP/TAZ expression/nuclear localization with progression and prognosis of many tumor types, here the focus is on experimental evidence for a causative role of YAP/TAZ in tumor growth and metastasis.

In mice, the skin-specific $yap^{flox/flox}/taz^{flox/flox}$ dKO not only affects wound healing,[31] but also completely prevents cSCC formation driven by oncogenic K-Ras signaling to the AP-1 transcription factor, which acts cooperatively with YAP to drive tumor cell proliferation, survival and epithelial-to-mesenchymal transition (EMT).[40–42] Skin-specific overexpression of a $tetO\text{-}YAP^{S127A}$ transgene drives epidermal thickening and produced cSCC-like tumors after transplantation and engraftment into nude mice.[43–45] Expression of a similar skin-specific YAP^{S127A} transgene also produced cervical SCC (CxSCC or CVSCC) tumors within 2–8 months.[46] Expression of a strongly active $nlsYAP^{5SA}$ transgene in skin with *K5-CreERt* produced spontaneous cSCC tumors within 2 weeks in regions of the skin subjected to frequent scratch wounding during grooming.[47] These wound-induced cSCC tumors rapidly formed and progressed via EMT to form invasive spindle cell carcinomas (spSCC).[47] Thus, the genetic evidence demonstrates a fundamental and potent role of YAP/TAZ in skin wound healing and in cooperating with RAS signaling to drive SCC growth and local invasion in mouse models.

Human SCC cell lines have also been shown to depend on YAP/TAZ for their proliferation and survival in vitro as well as their ability to metastasize following injection into mice. A genome-wide screen in normal skin (NHK) and cSCC cells (SCC13) identified YAP and TAZ as essential drivers of cell proliferation.[48] In ESCC cells with high YAP activity (KYSE170), siRNA knockdown of YAP reduced cell proliferation in vitro.[49] In ESCC cells with relatively low YAP activity (KYSE1240), overexpression of YAP produced increased proliferation in colony-forming assays in soft agar.[49] In OSCC cells with high YAP activity (SCC2), YAP/TAZ siRNA transfection led to decreased cell proliferation and increased apoptosis as well as reduced migration in scratch wound assays in vitro.[50] Conversely, in OSCC cells with lower YAP activity (CAL27), overexpression of constitutively active YAP5SA increased cell proliferation and decreased apoptosis, as well as increasing

migration in scratch wound assays in vitro.[50] When SCC2 cells were transplanted into the tongue of nude mice in orthotopic xenograft experiments, shRNA knockdown of YAP/TAZ decreased primary tumor volume and almost completely ablated metastasis formation after 22 days.[50] In an OSCC cell line selected for resistance to the chemotherapeutic cisplatin (OSC-19-R), YAP activity was increased compared to the parental line (OSC-19) and silencing of YAP by siRNA knockdown increased the sensitivity of OSC-19-R cells to treatment with cisplatin.[51] Collectively, the above evidence demonstrates a key role for YAP/TAZ in driving the growth, invasion, and metastasis of SCC tumors of many different origins.

1.2.2. Lung Adenocarcinoma

Aside from lung SCC, the second major subtype of non-small cell lung cancer (NSCLC) is lung adenocarcinoma (LUAC or lung ADC). Adenocarcinomas are morphologically distinct from SCC, because they retain their polarized epithelial morphology as sheets, ducts or microcysts. Lung ADC is thought to arise primarily from type II alveolar epithelial cells,[52–54] where YAP/TAZ has roles in pulmonary regeneration.[36,55] In mice, AdenoCre-mediated conditional $yap^{flox/flox}$ homozygous knockout reduced primary tumor growth driven by Cre-inducible $^{LSL}K\text{-}Ras^{G12D}$ and $LKB1^{flox/flox}$.[56] Silencing of *yap* by lentiviral shRNA knockdown in primary mouse lung ADC cells isolated from $K\text{-}Ras^{G12D}$, $LKB^{-/-}$ mice was sufficient to impair tumor cell proliferation in vitro by half and also reduce tumor growth by around half following xenografting into mice.[56] In a follow-up study using an AdenoCre-inducible $^{LSL}K\text{-}Ras^{G12D}$ and $p53^{flox/flox}$ model of lung ADC, introduction of a conditional $yap^{flox/flox}$ allele reduced the number and size of tumors observed and increased survival time by 50%. Immunostaining and genotyping for Yap protein and the *yap* locus indicated that Yap homozygous knockout cells completely fail to form tumors, while Yap heterozygous knockout cells account for the slow growing $^{LSL}K\text{-}Ras^{G12D}$ and $p53^{flox/flox}$ tumors.[57] Overexpression of Yap^{S127A} enhanced tumor grade after 7 months in tumors driven by AdenoCre-inducible $^{LSL}K\text{-}Ras^{G12D}$.[58] Overexpression of Yap specifically in alveolar type II cells with an *SP-C-YAP* transgene led to hyperplasia and accelerated AdenoCre-inducible $^{LSL}K\text{-}Ras^{G12D}$ tumor growth by around twofold.[56] Thus, the genetic evidence demonstrates an essential role for YAP in cooperating with RAS signaling to drive lung ADC growth in mouse models.

Human lung ADC cell lines have also been shown to depend on YAP for their proliferation and migration in vitro as well as their ability to form secondary tumors following injection into mice. In a lung ADC cell line (A549), YAP overexpression promoted proliferation, migration and expression of EMT markers, while YAP inhibition reduced migration and EMT marker expression in vitro and reduced tumor growth by more than half after subcutaneous xenograft transplantation into nude mice.[59] A separate study with the same A549 cell line showed that YAP knockdown sensitized the tumor cells to treatment with the chemotherapy cisplatin.[60] Finally, injection of A549 cells into the tail vein of mice generates lung metastases, whose occurrence was suppressed by lentiviral shRNA knockdown of Taz.[58] Together, the above findings indicate that YAP/TAZ activity is crucial for driving the growth and metastasis of lung ADC tumors.

1.2.3. Colorectal Adenocarcinoma

Colorectal cancer (CRC) arises from large intestinal crypt stem/progenitor cells that normally sustain intestinal homeostasis and can increase their proliferative regeneration after intestinal damage. In mice, *Villin-CreERt* mediated intestinal-specific conditional knockouts of $yap^{flox/flox}$ alone, or both $yap^{flox/flox}$ and $taz^{flox/flox}$, do not impair intestinal homeostasis but strongly prevent proliferative regeneration after damage and *APC* mutant tumor formation.[27,28,61,62] Overexpression of a $tetO\text{-}YAP^{S127A}$ transgene unexpectedly caused arrest of intestinal proliferation,[63] possibly an in vivo manifestation of "oncogene-induced senescence," or an artefact of Yap misexpression in Paneth cells, as activation of endogenous Yap in the intestine with *Sav1* knockout or *Mst1/2* double conditional knockouts causes increased proliferation.[27,64] Thus, more work is needed to clarify whether Yap activation is sufficient to drive intestinal regeneration or to accelerate intestinal tumor growth.

In human colorectal cancer cell lines (HCT116, SW480, SW837, HCA-7, V9P, V9M, V400, VS03, LS174T, DLD1), YAP depletion by lentiviral shRNA inhibited cell proliferation and survival.[64] The capacity of HCT116 cells to migrate invasively in a transwell assay in vitro was also strongly impaired by transfection with siRNAs against YAP and TAZ.[65,66] Although there is some indirect evidence for a role of YAP in CRC metastasis,[67] and knocking down YAP reduced LoVo cell lung met-induced lesions by around half after injection into the tail vein of NOD/SCID mice,[68] further work is needed to investigate YAP/TAZ function in improved models for CRC metastasis. Overall, the existing evidence strongly indicates a role for YAP in CRC tumor growth and suggests a possible role in invasion and metastasis.

1.2.4. Breast Ductal Adenocarcinoma

Breast cancers arise from the mammary glands, which naturally undergo invasive and branching growth during each pregnancy-lactation cycle. Mouse genetics revealed that *MMTV-Cre*-driven $yap^{flox/flox}$ conditional knockout mammary glands were normal in virgin females, but pregnancy-induced growth of alveolar structures was dramatically reduced due to increased apoptosis, as was *PyMT*-driven mammary tumor formation.[69] Activation of endogenous Yap in *MMTV-Cre*-driven $Sav1^{flox/flox}$ conditional knockout mammary glands again had no effect in virgin females but led to a failure in cell differentiation during pregnancy.[69] Overexpression of Yap with *MMTV-rtTA*-driven *TRE-YAP* also caused similar defects in cell differentiation during pregnancy.[69] These results indicate an essential requirement for Yap in the *PyMT*-driven breast cancer model. It will be interesting to test whether Yap and Taz also have an essential function in spontaneous metastasis and also in other mouse models of breast cancer, such as the $PI3K^{H1047R}$-driven model.[70,71]

In a well-studied human breast cell line (MCF10A), YAP/TAZ overexpression and ectopic activation was shown to promote cell proliferation, survival migration after scratch wounding, invasive migration in transwell assays, growth in soft agar, EMT, and resistance to cisplatin.[14,72-75] In breast cancer cell lines (MCF7 and Hs578T), silencing of TAZ alone by siRNA was sufficient to reduce cell migration and invasion.[76] Silencing of TAZ also reduced the growth of MCF7 cells in soft agar and formation of tumors after xenografting into nude mice,[76] and lentiviral TAZ shRNA reduced lung metastasis after orthotopic transplantation of patient-derived breast cancer cells with human HS-27A stromal cells into the cleared fat pad of 6 week old *NOD SCID IL2Rnull* (NSG) mice.[77] In contrast, silencing of both YAP and TAZ by siRNA was necessary to reduce migration of LM2-4 breast cancer cells.[78] YAP shRNA abolished lung metastases when SUM159 with silenced *LIFR* were injected into the tail vein of mice.[79] Overexpression of YAP^{S127A} increased the number and size of lung metastases formed by 67NR or 4T1 breast cancer cells, or even non-transformed mammary NMuMG cells, after injection into the tail vein or via orthotopic transplantation,[79,80] while shRNA depletion of both YAP and TAZ reduced 4T1 lung metastases driven by MRTF-SRF.[81] Finally, YAP or TAZ can enhance PD-L1 levels in MCF10A and MDA-MB-231 breast cancer cells to promote immune evasion (reduced T-cell killing in vitro).[82] Thus, the above evidence supports a key role for either YAP or TAZ, or both, depending on the individual tumor cell type, in driving breast cancer growth, invasion and metastasis.

1.2.5. Pancreatic Ductal Adenocarcinoma

The pancreas has a branched ductal structure surrounded by acinar cells, and either cell type may originate pancreatic ductal adenocarcinoma (PDAC). In mice, *p48-Cre*-driven $^{LSL}K\text{-}Ras^{G12D}$ $p53^{R172H}$ model of PDAC was completely suppressed by crossing to $yap^{flox/flox}$ alone, reducing cell proliferation and reducing expression of *CTGF, CYR61, IL-1A, IL-6, Cox2*, and *Mmp7*, thereby restoring survival.[83] The pancreatic tumor stromal response (α-SMA, vimentin, collagen) was also strongly abrogated by conditional $yap^{flox/flox}$ knockout.[83] The authors proposed an interesting positive feedback model for tumor-stroma interactions involving CTGF, CYR61 signaling to integrins, IL-1A and IL-6 cytokine signaling, and COX2-driven Prostaglandin E2 biosynthesis.[83] Notably the single conditional $yap^{flox/flox}$ knockout did not affect acinar to duct metaplasia (ADM).[83] However, acinar-specific *Ela1-CreERt2* double $yap^{flox/flox}$ $taz^{flox/flox}$ knockout prevented ADM induced by $^{LSL}K\text{-}Ras^{G12D}$ expression and co-incident Caerulein-induced pancreatitis, which induces Yap/Taz nuclear localization.[84,85] Conditional knockout p48-Cre $yap^{flox/flox}$ $^{LSL}K\text{-}Ras^{G12D}$ $^{LSL}p53^{R172H}$ pancreata rapidly resolved Caerulein-induced inflammation and reactivated T-cells compared to $^{LSL}K\text{-}Ras^{G12D}$ $^{LSL}p53^{R172H}$ tumors, which remained inflamed and immunosuppressed, suggesting a key role for Yap in immune evasion.[86] Gain-of-function mouse genetics on Yap/Taz are still needed to confirm that these factors are sufficient to drive PDAC formation and progression to metastasis in either acinar or ductal cell types, although indirect evidence suggests that Yap1 activation can bypass K-Ras addiction in mouse models of pancreatic cancer.[87]

In a human pancreatic cancer cell lines (Colo-357, Panc-1, BxPC-3), YAP shRNA decreased cell proliferation, EMT and invasive migration in transwell chamber assays in vitro.[83] YAP shRNA also reduced BxPC3 tumor size and the stromal response (α-SMA expression) after implantation subcutaneously in to BALB/c nude mice.[88] TAZ shRNA also reduced tumor growth, transwell assay invasion, and EMT in FG and PANC-1 cells.[89] A stiff stromal environment may feedback to promote activation of YAP/TAZ in the tumor cells.[90] Overexpression of YAP promoted invasion in transwell migration assays, EMT and resistance to the chemotherapy gemcitabine.[91] Thus, the above evidence supports a key role for YAP/TAZ in pancreatic cancer growth and invasion, and further work is needed to investigate its function in metastasis.

1.2.6. Hepatocellular Carcinoma

Liver hepatocytes are thought to be the cell of origin for hepatocellular carcinoma (HCC). In mice, whole-liver expression of *ApoE-rtTA TetO-YAP* or *Albumin-Cre* induced conditional knockout of $Mst1/2^{flox/flox}$ or $Sav^{flox/flox}$ produced overgrown livers that progressed to HCC-like tumors.[92–96] Heterozygous deletion of $yap^{-/+}$ largely suppressed HCC-like tumors induced by conditional knockout of $Nf2^{flox/flox}$.[97] Whole liver *Albumin-Cre* $Pten^{flox/flox}$ $Sav^{flox/flox}$ double knockouts rapidly developed HCC tumors within 5 months and this phenotype was suppressed to normal size by crossing with $Yap^{flox/flox}$ and $Taz^{flox/flox}$ to produce a quadruple knockout.[98] Hydrodynamic transfection of both PI3K ($PIK3CA^{H1047R}$) and Yap^{S127A} also produced HCC.[99] Furthermore, expression of strongly active Yap^{5SA} by hydrodynamic transfection of livers was sufficient to induce large HCC-like tumors within 5 months and to recruit type II macrophages to induce immune evasion, which was required for tumorigenesis.[100] The conditional knockout of both *yap* and *taz* specifically in hepatocytes versus bile duct epithelium is necessary to fully understand their cell-type specific functions in normal liver development and in HCC models.

In human HCC cell lines with high and low migratory potential (MHCC97H and MHCC97L), YAP siRNA reduced EMT and invasion in a transwell migration assay.[101] Silencing both YAP and TAZ by shRNA in Huh7 and Hep3B cells increased apoptosis, particularly under hypoxic conditions.[102] Further work is necessary to test whether YAP/TAZ promote HCC metastasis.

1.2.7. Cholangiocarcinoma

Intrahepatic cholangiocarcinoma (ICC or CCA) develops from the oval cells or bile ducts of the liver. Genetically engineered mouse models of Yap/Taz loss and gain of function in bile ducts and ICC have not yet been reported, although specific *Opn-iCreERt2* and *Ck19-CreERt* lines exist.[103] However, activation of Yap/Taz in *Albumin-Cre* $Sav1^{flox/flox}$ mutant livers produced tumors after liver injury (with the hepatotoxin DDC) with mixed features of both cholangiocarcinoma (CCA) and hepatocellular carcinoma (HCC).[94] In addition, hydrodynamic transfection of livers with YapS127A enhanced mixed CCA/HCC tumor formation driven by co-transfection with active PI3K

(*PIK3CA*^{H1047R}).[99] Furthermore, overexpression of Lats2 or dominant-negative TEAD eliminated Akt/Ras-driven CCA liver lesions.[104] Thus, direct manipulation of Yap/Taz specifically in bile duct cells is necessary to confirm their role in genetically engineered mouse models of CCA.

In human cholangiocarcinoma cell lines, YAP shRNA knockdown inhibited HCCC9810 cell proliferation, EMT, migration, and invasion in vitro and also reduced tumor size and metastasis after xenografting intraperitoneally into nude mice.[105] The sensitivity of HCCC9810 xenograft tumors in nude mice to chemotherapy with 5-FU was dramatically increased after YAP knockdown.[105,106] These results clearly define a key role for YAP in CCA cell line tumorigenicity and suggest possible roles in CCA metastasis.

1.2.8. Gastric Cancer

In mice, activation of Yap/Taz in the intestine with Lgr5-Cre mediated double knockout of *Lats1/2* produced gastric cancers (GC) due to strong Myc expression.[107] In human GC cells (HFE-145), overexpression of YAP^{5SA} or TAZ^{4SA} increased growth in soft agar and increased invasion in transwell migration assays.[107] In other GC cell lines, knockdown of YAP reduced tumor growth after xenografting into mice and promoted resistance to chemotherapy,[108] as well as reducing EMT induced by *Helicobacter pylori* infection of GC cells.[109] This preliminary evidence supports a key role for YAP/TAZ in gastric cancer growth and invasion.

1.2.9. Melanoma

Melanocytes are a mesenchymal cell type derived from the neural crest via a developmental EMT and melanoma can become rapidly invasive and metastatic. Genetically engineered mouse models have not yet been employed to investigate the loss or gain of function of Yap and Taz in melanoma models. However, in a human melanoma cell line (A375), YAP^{S127A} overexpression enhanced tumor formation following injection subcutaneously into mice and strongly enhanced lung metastasis formation following injection into the tail vein.[80] Silencing of YAP or TAZ by shRNA knockdown reduced 1205Lu cell proliferation in soft agar and ability to form lung metastasis following tail vein injection.[110] YAP shRNA also reduced the ability of B16F10 melanoma cells to spread to lymph nodes following implantation into footpads.[111] YAP shRNA knockdown reduced, and YAP^{5SA} overexpression increased, the expression of PD-L1 in treatment-resistant melanoma cells (A375SM), suppressing T-cell killing.[112] Thus, the evidence from cell lines supports a possible role for YAP/TAZ in melanoma metastasis and resistance to immunotherapy.

1.2.10. Brain Cancer

Glioblastoma multiforme (GBM) is a rapidly lethal brain tumor that is thought to originate from neural stem cells. In the chicken embryo neural tube, overexpression of YAP increased cell proliferation and progenitor cell number and reduced differentiation, while transfection with YAP shRNA increased apoptosis.[113] In mice, proliferation of basal neural progenitors in the subventricular zone was increased by *Tis21-CreERt2* conditional YAP overexpression and decreased by dominant-negative YAP overexpression or treatment with Verteporfin.[114] Verteporfin also suppressed *GFAP-Cre*-driven *Pik3ca*^{H1047R} induced neural overproliferation in mice.[115] In zebrafish, co-expression of YAP^{5SA} with H-Ras^{V12} induced aggressive brain tumors.[116] Thus, while there is strong evidence for a role of Yap/Taz in neural stem cell proliferation and tumor formation, further work is necessary to examine the function of Yap and Taz in mouse models of GBM brain tumor formation.

In human GBM cell lines, shRNA knockdown of YAP attenuated proliferation, migration and colony/neurosphere formation in vitro and produced 100-fold smaller tumors after orthotopic xenograft into immunodeficient mice.[117,118] Interestingly, mosaic expression of YAP in GBM cells also promoted clonal dominance in part by inducing cell competition (apoptosis of neighboring cells with low YAP).[119]

1.2.11. Role of YAP/TAZ as Oncoproteins in Other Solid Tumors

Histological staining of tumors and experiments in cancer cell lines have implicated YAP/TAZ in several other solid tumor types, including ovarian,[120–127] prostate,[128–134] bladder,[135–139] endometrial,[140,141] kidney,[142–144] thyroid,[145–149] adrenal,[150] mesothelioma,[151,152] sarcomas,[153–156] and epithelioid hemangioendothelioma.[157,158] In all the above cases, genetically engineered mouse models are still necessary to establish the causative role of Yap/Taz in these tumors in vivo.

1.2.12. Tumors without YAP/TAZ: Hematological Malignancies and Testicular Cancer as Exceptions to the Rule

Despite the widespread activation of YAP/TAZ in many solid tumor types (**Figure 5**), there are two striking exceptions to this rule. The first is hematological tumors, where Yap/Taz double knockouts confirm they are dispensable for both normal and malignant hematopoiesis.[159] The second is testicular cancer, which lacks detectable YAP and TAZ expression, and is interestingly also the tumor type that is most sensitive to chemotherapy.[160,161]

1.3. Mutations and Signals Regulating YAP/TAZ in Cancer

1.3.1. Mutations, Amplifications, and Translocations at the YAP and TAZ Loci

The *YAP (or YAP1)* gene is located within the mouse 9qA1 amplicon[73,162] and syntenic human 11q22 amplicon that is detected in around 10% of HNSCC.[49,50,163] A more comprehensive analysis revealed both YAP and TAZ copy number amplifications in 15% of CVSCC, LUSC, and HNSCC.[164] In addition, chromosomal translocations at the *YAP (YAP1)* and *TAZ (WWTR1)* loci have been observed in ependymoma, epithelioid hemangioendothelioma, poroma, and porocarcinoma.[157,158] Rare activating point mutations in *YAP* have also been found in melanoma.[165]

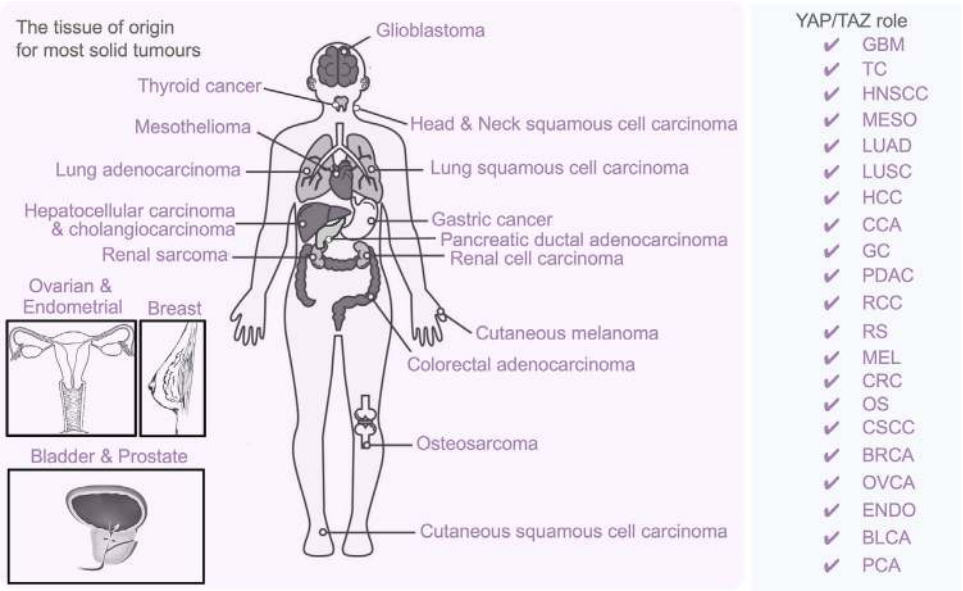

Figure 5. YAP/TAZ have an oncogenic function in most solid tumors. The diagram shows the tissue of origin for the most common solid tumors. YAP/TAZ has been implicated as having an oncogenic role in all of these tumor types.

Such amplification and translocation events are consistent with Boveri's theory but not sufficient to explain the frequent activation of YAP/TAZ expression and nuclear localization in many solid tumors, suggesting a primary role for other mechanisms including altered upstream signaling during tissue damage and inflammation, consistent with Virchow's theory.

1.3.2. Regulation of YAP/TAZ by Hippo (MST1/2-LATS1/2) Signaling

As mentioned above, YAP and TAZ are the main effectors of the Hippo (MST1/2-LATS1/2) signaling pathway.[7–14] The Hippo pathway is strongly activated at the apical domain of polarized epithelial cells.[13] Interestingly, mechanical stretching of epithelial cells can directly inhibit Hippo signaling in cultured epithelial cells[166] and in *Drosophila*,[167] suggesting that mechanical strain might also contribute to activation of YAP/TAZ in epithelial tumors.[13] More dramatically, loss of the apical domain during progression from adenoma to carcinoma may also contribute to activation of YAP/TAZ.[13] Although there are a variety of mutations in Hippo pathway components in cancer, the frequency of such mutations is relatively rare compared to other tumor suppressor pathways,[164] indicating that mutations affecting other signaling pathways, and/or non-mutational mechanisms such as tissue damage and inflammatory responses must be responsible for frequently observed activation of YAP/TAZ expression and nuclear localization in cancer.

1.3.3. Regulation of YAP/TAZ by Growth Factor-PI3K-AKT Signaling

PI3K-Akt signaling is normally induced by growth factors (e.g., IGF-1, EGF) acting via receptor tyrosine kinases and is the signaling pathway most commonly activated by mutations in human cancer.[168,169] One major effector of Akt is the TORC1 complex, whose activation causes benign harmatomas, indicating that it is not the only Akt effector in malignant human cancer.[169] Akt also inhibits FOXO transcription factors to promote cell survival.[169] Recent evidence suggests that PI3K-Akt signaling also inhibits the Hippo pathway to promote YAP/TAZ activation to drive cell proliferation and malignancy.[99,115,170-178] Importantly, further work is necessary to identify the molecular mechanism by which PI3K-Akt signaling inhibits the Hippo pathway. In addition, while PI3K-Akt signaling appears necessary to promote YAP/TAZ activation, it is apparently not sufficient, as cells also require mechanical stimulation or other additional inputs to activate YAP/TAZ.

1.3.4. Regulation of YAP/TAZ by Mechanical Stimulation of INTEGRIN-SRC Signaling

A stiff stromal extracellular matrix (ECM) is a hallmark of both the wound healing response and formation/progression of solid tumors.[179] Tumor cells interact with the ECM via Integrins, which respond to ligand binding and mechanical stress by signaling through FAK and SRC family kinases[180–182] to inhibit Hippo signaling and activate YAP/TAZ.[31,61,183-199] SRC family kinases appear to act primarily by direct tyrosine phosphorylation of LATS1, but can also directly phosphorylate YAP/TAZ.[30,31,61,183-199] Importantly, there is extensive signaling cross-talk between Integrin-SRC signaling and Growth factor-PI3K-Akt signaling.[200–206] In addition, mechanotransduction via Integrin-SRC signaling also promotes formation of focal adhesions and stress fibers, a process involving increased Rho GTPase mediated actomyosin contractility.[179,207,208] Notably, it has been proposed that extreme actomyosin-mediated forces pulling on

the nuclear envelope in vitro may increase its permeability to any small molecule to allow YAP/TAZ to diffuse into the nucleus,[209] but it remains unclear whether this mechanism operates in vivo.

1.3.5. Regulation of YAP/TAZ by Forces Acting on Adherens Junctions

Activation of the RhoGTPase induces actomyosin contractility and thus mechanical forces acting on cell adhesions, including both Integrins and E-cadherin. Tension on E-cadherin-based adherens junctions can recruit molecules such as the LIM-domain family Ajuba/LIMD1/TRIP6 to inhibit LATS1/2 kinases by an unknown mechanism.[210–214] Interestingly, tension on adherens junctions also activates SRC,[215–219] which can directly phosphorylate TRIP6[220,221] and regulate LIMD1,[188] as well as directly phosphorylating and inhibiting LATS1.[185] Thus, further work is needed to clarify the mechanisms by which tension at adherens junctions regulates LATS1/2 kinase activity and YAP/TAZ activation. Importantly, tumor cells lacking E-cadherin based adherens junctions, such as those cultured as single cells or those having undergone EMT, are still subject to mechanical regulation of YAP/TAZ via Integrin adhesions.

1.3.6. Regulation of YAP/TAZ by GPCR Signaling

G-protein coupled receptors (GPCRs) are large family of 7-transmembrane "serpentine" receptors that upon ligand binding activate intracellular G-proteins. Ectopic activation of GPCRs with agonists such as the serum components LPA, S1P, Thrombin, Thromboxane A2, and Endothelin-1, as well as Wnt3a and Wnt5a/b, can induce G_q or $G_{12/13}$ activity, which leads to inhibition of LATS1/2 and YAP/TAZ activation in cell culture.[222–225] Downstream of G-proteins, activation of Rho is necessary to activate YAP/TAZ.[222–225] Since the wound healing process involves exposure of cells to LPA, S1P and Thrombin, these findings could help explain the activation of YAP/TAZ after wounding, and underscore the importance of YAP/TAZ activation as a link between wound healing and cancer. For the GPCR ligand PGE_2, there is evidence that it contributes to YAP activation in vivo during intestinal regeneration, colitis, and colorectal cancer.[29] The GPCR pathway is also mutationally activated in some cancers, as activating mutations in G_q (*GNAQ/GNA11*) occur in 83% uveal melanoma[226,227] and the Kaposi sarcoma virus encodes a GPCR that activates YAP/TAZ.[228] As noted above, how Rho activation leads to inhibition of LATS1/2 is still unclear, but could involve increased tension on Integrin adhesions and thus FAK-SRC signaling. In addition, classic GPCR signaling studies implicate SRC family kinases as key downstream effectors, particularly in cross-talk between GPCR and growth factor signaling[220,221,229-242] and cytokine signaling.[196,229] Consistent with this view, in uveal melanoma, mutations in G_q require FAK activation to activate YAP.[243] Thus, further work is needed to clarify how GPCRs control LATS1/2 kinase activity and activate YAP/TAZ. Nevertheless, GPCR signaling is an important mechanism linking tissue inflammation and activation of YAP/TAZ

1.4. Signals Cooperating with YAP/TAZ to Drive Oncogenic Transformation in Cancer

1.4.1. MRTF-SRF Signaling

A second mechano-regulated signal are the myocardin-related transcription factors MRTF-A (also called MAL or MKL-1) and MRTF-B (MKL-2), which bind to serum response factor (SRF) DNA-binding transcription factors.[244–247] In *Drosophila*, the MRTF homolog Mal-d promotes invasive migration of border cells, similar to the YAP/TAZ homolog Yorkie.[8,248,249] In vertebrate development, SRF is required for formation of mesoderm (which involves EMT and migration of mesodermal cells)[250–252] and for activation of fibroblasts by mechanical stress.[253] MRTF-SRF can drive tumor cell EMT[254–257] and metastasis[258] as well as matrix stiffening via activation of cancer-associated fibroblasts.[259] Like YAP/TAZ, MRTF is activated by translocation to the nucleus in response to Rho-mediated actomyosin contractility.[244-246,253,260-263] However, the mechanism of MRTF activation is unique: Rho activation causes F-actin polymerization, which depletes G-actin, which otherwise binds directly to MRTF to localize it to the cytoplasm[264,265] by promoting nuclear export.[266] Thus, simultaneous activation of MRTF-SRF and YAP/TAZ-TEAD signaling can occur in response to Rho activation by mechanical forces or GPCR signaling, and the two transcription factors share a common set of target genes, including *CYR61 (CCN1), CTGF (CCN2)* and many cytoskeletal regulators whose expression feeds back positively on both of these mechano-regulated transcription factors in a mutually reinforcing manner to promote stromal matrix stiffness, tumor cell proliferation, invasive migration, and metastasis.[81,117,259,267] Further work is needed to examine cooperation between MRTF-SRF and YAP/TAZ-TEAD in different cancer types in vivo.

1.4.2. RAS-RAF Signaling

Growth factor signaling through receptor tyrosine kinases (RTKs) activates the small GTPase RAS, which can contribute to PI3K-AKT activation by these same RTKs, but importantly also signals via the classical RAF-ERK pathway to phosphorylate and activate TCF (ETS-family SRF co-factors, which induce FOS expression) and AP-1 (FOS/JUN) transcription factors[268] (Figure 2). Oncogene cooperation between YAP-TEAD and AP-1 on target gene promoters is now well established as a driver of tumor cell proliferation in various cancer types.[23,25,40,42,57,83] Since RAS signaling is so commonly mutationally activated in human cancers, it may function by altering the normal wound healing/regeneration response, synergizing with activated YAP/TAZ to bring about tumor formation rather than allowing the normal cessation of proliferation once regeneration is complete (Figure 4).

1.4.3. WNT Signaling

Wnt signaling via beta-catenin/TCF transcription is of fundamental importance in intestinal homeostasis, regeneration and colorectal cancer.[269] Mouse knockouts indicate that Yap

is essential for Wnt-induced intestinal tumor formation[27,28,62] (Figure 3). How Wnt signaling regulates YAP in the intestine is a subject of some controversy and further work is necessary to resolve the relationship between the two pathways. Finally, Wnt signaling also appears to cooperate with YAP/TAZ in other tissues, such as skin.[270,271]

1.4.4. Cytokine Signaling

Pro-inflammatory cytokines, such as IL-6, signal via cytokine receptors and the JAK-STAT3 pathway.[272,273] There is evidence for cooperation and positive feedback between IL-6 signaling and YAP/TAZ during intestinal regeneration and tumor formation,[30,193] in pancreatic cancer,[84] in renal cell carcinoma,[196] and in lung cancer.[198] There is also evidence for cross-talk between cytokine signaling and pro-inflammatory GPCR signaling[229] (Figure 2).

1.4.5. HIF Signaling?

Hypoxia is sensed by tumor cells via the hypoxia-inducible factor family (HIF-1alpha, -2alpha and -3alpha) of transcription factors, which play important roles in tumor progression.[274] Hypoxia was reported to repress LATS1/2 gene expression to promote YAP activation during endometriosis,[275] while another group found that hypoxia induced expression of an orphan GPCR, the *GPCR5A* gene, to activate YAP in colonic epithelial cells.[276] YAP was also reported to maintain HIF-1alpha expression.[277] Others reported that Hypoxia promoted YAP nuclear localization via direct YAP-HIF-1alpha binding.[278,279] Finally, HIF-2alpha was also reported to induce YAP expression and activity in colorectal cancer cell lines and mouse models.[280] Thus, various different mechanisms have been proposed for cooperation between HIF factors and YAP, and further work is needed to explore this connection in different tumors in vivo.

1.5. Therapeutic Strategies for Inhibiting YAP/TAZ Activation

1.5.1. SRC Family Kinase Inhibitors

Broad spectrum SRC family tyrosine kinase inhibitors such as dasatinib potently inhibit YAP/TAZ activation[31,61,183,185-190,195,281] and are effective in treating tumors in mice,[180,188,193,282] but suffer from toxicity in patients owing to inhibition of many other tyrosine kinases. Thus, there is a major unmet need for new and highly specific SRC family kinase inhibitors that are well tolerated.

1.5.2. PI3K-AKT Inhibitors

Specific inhibitors of PI3K and AKT are in clinical trials for cancer therapy.[169] Treatment of cancer cells with these inhibitors decreases YAP/TAZ nuclear translocation and activity,[170,172,173,176] suggesting a possible mechanism by which these inhibitors may reduce cancer growth and progression. Complete inhibition of YAP/TAZ in tumors may require dual inhibition of both PI3K-AKT and SRC signaling.

1.5.3. YAP/TAZ-TEAD Binding Disruptors

Verteporfin was the first characterized YAP-TEAD binding inhibitor,[283] but this compound suffers from low potency in vivo.[59,122,135,138,141] Thus, it will be of great interest to develop new and more potent inhibitors of this binding interaction, and the compound flufenamic acid is the first of a new wave of such small molecules.[284,285]

1.6. YAP/TAZ Inhibitors May Exhibit Synergy with Chemotherapy, Radiotherapy, and Immunotherapy

1.6.1. Chemotherapy

YAP appears to confer resistance to chemotherapeutics such as Cisplatin in multiple cancer cell types.[51,60,105,108,127,138] These results suggest that effective YAP/TAZ inhibitors could synergize with chemotherapy as a treatment combination for patients.

1.6.2. Radiotherapy

Treatment of tumors with radiation remains a crucial method of cancer therapy. Radiotherapy operates by inducing DNA damage and cell death, similar to chemotherapy. Whether YAP/TAZ confers resistance to radiotherapy is an important open question.

1.6.3. Immunotherapy

Antibodies against PD-1 and CTLA-4 are important immune checkpoint inhibitors that boost T-cell killing of tumor cells and are highly effective in some cancer patients, while others are resistant. There is some evidence that YAP/TAZ may confer resistance of cancer cells to immunotherapy, through upregulation of PD-L1 expression,[82] or through regulation of macrophages/myeloid derived suppressor cell (MDSC) cell infiltrates.[86,100,177,178,286] Thus, targeting YAP/TAZ may be an ideal "adjuvant" for combination with immunotherapy.

2. Conclusion and Outlook

YAP and TAZ have emerged as key drivers of wound healing, tissue regeneration and tumor progression, in accordance with Virchow's theory of metastatic cancer in which chronic inflammation and regeneration are crucial drivers in many solid tumor types. In addition, some cancer types exhibit mutational activation of YAP or TAZ in accordance with Boveri's chromosomal damage theory of cancer. New drugs targeting YAP/TAZ are likely to be effective therapeutics in most forms of metastatic cancer, particularly in combination with the established pillars of cancer

therapy. Demonstrating the effectiveness of these compounds in pre-clinical models will be an essential first step towards clinical trials in human patients.

Conflict of Interest

The author declares no conflict of interest.

Keywords

cancer, Hippo pathway, tissue growth, YAP/TAZ

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