Review paper

Journal of High School Science

YAP1 attenuation and its effect on cancer proliferation

Khan Z

Submitted: October 1, 2023, Revised: version 1, January 15, 2024,, version 2, January 20, 2024, version 3, January 21, 2024
Accepted: January 26, 2024

Abstract
The advent of immunotherapy represents a transformative milestone in oncological treatment, affording viable therapeutic options for a substantial cohort of cancer patients. Nonetheless, its applicability remains limited, notably in cases encompassing urothelial bladder cancer, prostate cancer, glioblastoma, and pancreatic cancer, where efficacy wanes. Such refractoriness often ensues from a dearth or depletion of T-cell activity or immune resistance orchestrated by neoplastic cells. In this scenario, the Hippo signaling pathway has emerged as a paramount orchestrator, with the transcriptional co-activator YAP1 (Yes-associated protein 1) and its corollary transcription factors, TEAD; assuming pivotal roles. YAP1, a transcriptional co-activator, assumes a central role in modulating cellular proliferation, survival, and differentiation. Its aberrant regulation has been inextricably linked to diverse malignancies in humans, rendering it an enticing target for anti-cancer therapeutic interventions. Empirical investigations both *in vitro* and *in vivo* corroborate that genetic and pharmacological attenuation of YAP1 engenders favorable outcomes, including the polarization of macrophages towards the M1 phenotype, concomitant downregulation of the IL-6/STAT3 pathway, amplification of anti-cancer extracellular vesicle production, and diminishment of myeloid-derived suppressor cells (MDSCs) within the tumor microenvironment. Each of these phenomena collectively culminate in anti-tumorigenic effects. This comprehensive review endeavors to elucidate the contemporary comprehension of YAP1's intricacies in fostering cancer proliferation and expounds upon the prospective therapeutic ramifications attendant to YAP1 attenuation. It is imperative to acknowledge that further research is requisite to transition these insights into clinically efficacious modalities. Nevertheless, by aggregating extant knowledge, this discourse aims to underscore the pivotal significance of YAP1 as a prospective therapeutic target while also delineating the underlying structure governing its oncogenic or tumor-suppressive propensities.

Keywords
YAP1, TEAD, IL-6, STAT3, Hippo, Upstream regulator, Attenuation, Tumor microenvironment, Transcription factors, Tumor suppression

Zaina Khan, Carmel High School, 520 East Main Street Carmel, Indiana 46032 USA, zaina.khan.ca@gmail.com

1. Introduction

Cancer remains a formidable global health challenge, representing a leading cause of mortality worldwide. Being the sixth leading cause of death with 18.1 million people affected globally, it is clear that cancer represents a significant challenge to healthcare (1). Cancer proliferation occurs when there are alterations in specific genes that regulate cell growth and division. Oncogenes, when mutated or overexpressed, can promote cell proliferation and inhibit cell death, leading to cancer development (2). On the other hand, tumor suppressor genes are responsible for controlling cell growth and division. Mutations in tumor suppressor genes can lead to their inactivation, once again resulting in uncontrolled cell proliferation (3). As the tumor grows, it needs a blood supply to provide nutrients and oxygen to support its expansion. To achieve this, cancer cells can stimulate the formation of new blood vessels through a process called angiogenesis, ensuring a steady supply of resources, and further promoting tumor growth (4). In advanced stages, metastasis causes cancer cells to acquire the ability to invade nearby tissues and migrate to distant parts of the body through the bloodstream or lymphatic system (3, 4).

One cell regulatory process that participates in cancer proliferation is the Hippo signaling pathway. It has emerged as a vital regulator of cellular homeostasis and has been implicated in various biological processes, including organ size control, tissue regeneration, and cell proliferation (5, 6). Within this pathway, YAP1 has garnered considerable attention due to its profound involvement in cancer development and progression. YAP1, a downstream effector of the Hippo pathway, is a transcriptional co-activator that plays a critical role in modulating gene expression programs essential for cell fate determination, proliferation, and survival (5,7). Its dynamic subcellular localization and transcriptional activity are intricately regulated by upstream components of the Hippo pathway, such as MST1/2 and LATS1/2 kinases, which collectively govern YAP1's activity by phosphorylation-dependent cytoplasmic sequestration and proteasomal degradation (7).

In normal physiological conditions, the Hippo pathway tightly restrains YAP1's nuclear translocation and activity, ensuring appropriate cell growth and tissue homeostasis. However, aberrant activation or overexpression of YAP1 has been observed in a wide array of human malignancies, including breast, liver, lung, pancreatic, and prostate cancers, as well as melanoma and glioblastoma (8). This dysregulation of YAP1 in cancer cells not only stimulates uncontrolled proliferation but also promotes tumor progression, metastasis, and therapy resistance (7, 8). Numerous studies have identified YAP1 as a potent driver of cell cycle progression, with its transcriptional co-activator function activating genes involved in G1/S transition and DNA replication. Furthermore, YAP1's interaction with TEA domain (TEAD) transcription factors is pivotal for the transcriptional activation of target genes, many of which are implicated in cancer cell survival, angiogenesis, and evasion of apoptosis (9).

The transcriptional enhanced associate domain (TEAD) proteins constitute a group of

transcription factors, consisting of four distinct family members (TEAD 1–4) (9). They regulate gene expression in response to the HIPPO pathway. TEAD proteins exhibit a strong preference for forming associations with transcriptional co-activators, namely, yes-associated protein 1 (YAP1) or transcriptional co-activators with PDZ-binding motif (TAZ, also known as WWTR1) (9). When bound in complexes with YAP1 or TAZ, TEAD proteins engage with DNA and instigate the transcription of a diverse array of genes intricately involved in processes such as cell proliferation, survival, motility, stemness, and differentiation (10).

Additionally, YAP1's involvement with the IL-6/STAT3 pathway, regulation of MDSCs, and polarization of naive macrophages is hypothesized to aid in the immune evasion of cancer cells (9). Thus, its attenuation could allow for the reduction of tumor growth while making immunotherapy more effective for cancer patients. By modulating peptide MHC exhibition, cancer cells can avoid detection by cytotoxic T cells (10). The production of inhibitory molecules such as PD-L1, and CTLA-4 that bind to corresponding receptors on T cells suppress the activation and function of T cells, preventing them from launching an effective immune response against cancer cells (11). Additionally, YAP1's involvement with the IL-6/STAT3 pathway, regulation of MDSCs, and polarization of naive macrophages is also hypothesized to help cancer cell evade immune attack (9).

Furthermore, the relationship between miRNAs and YAP1 is of particular interest in the context of cancer and other diseases. miRNAs can regulate the presence of YAP1 by binding to its mRNA and inhibiting its translation (3). This regulation can have significant implications for the activity of the YAP1 protein, as it directly impacts the genes controlled by YAP1 (3).

Cancer cells have evolved various strategies to evade immune detection and destruction, allowing them to survive and proliferate despite the presence of an intact immune system. Cancer cells can decrease the presentation of major histocompatibility complex (MHC) molecules on their surface (2, 4). MHC molecules are essential to presenting tumor-specific antigens to immune cells, helping the immune system recognize and attack cancer cells (2). Downregulating corresponding receptors on T-cells suppresses the activation and function of T cells, preventing them from launching an effective immune response against cancer cells (11).

This paper will focus on the ongoing implications of YAP1 and its attenuation as well as its role as a tumor suppressor. It will then discuss in detail the usage of YAP1 in biomedical practices as well as novel ways to counter the cancer-regressive effects of the protein.

1.01 *YAP1 and the Hippo Signaling Pathway*

The Hippo pathway is a complex signaling pathway that is essential to controlling organ size, tissue homeostasis, and cell proliferation in various organisms, including humans (12). It was first identified in fruit flies (Drosophila)

and subsequently found to be highly conserved in mammals (12).

At its core, the Hippo pathway is regulated by a series of protein interactions and modifications that ultimately influence the activity of a transcriptional co-activator called Yes-associated protein (YAP) and its paralog, transcriptional co-activator with PDZ-binding motif (TAZ) (12). YAP and TAZ are pivotal downstream effectors of the Hippo pathway, and their activities are tightly controlled to regulate cell growth and proliferation (13) (Figure I).

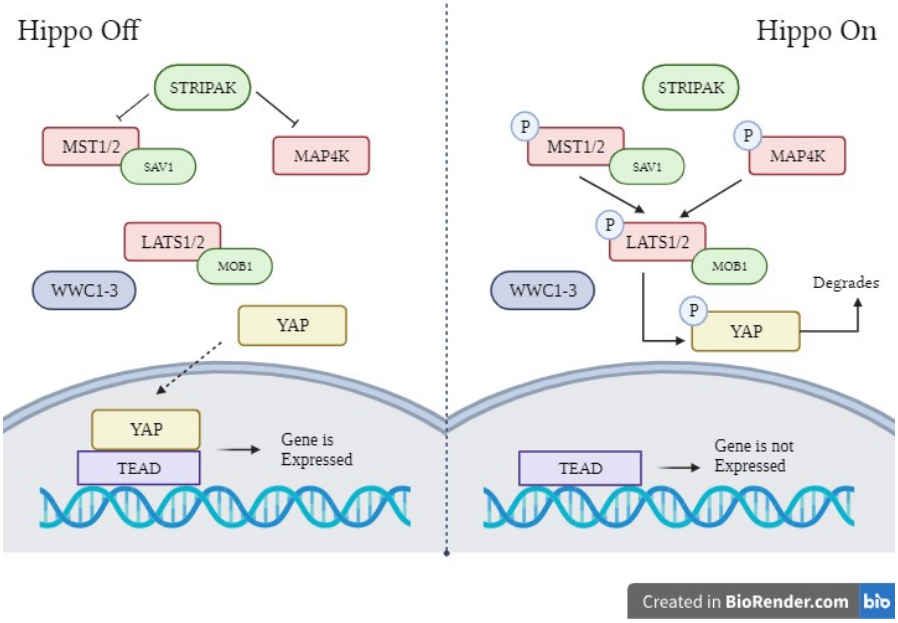

Figure 1. Hippo signaling pathway and YAP1 contributions.

The pathway is activated by a variety of signals, including mechanical cues (such as cell density and extracellular matrix stiffness) and chemical signals (growth elements, cytokines, and hormones) (13). These signals converge on a core kinase cascade consisting of fundamental proteins, including MST1/2 (Mammalian Ste20-like kinases 1 and 2) and LATS1/2 (Large tumor suppressor kinases 1 and 2) (12).

When the Hippo pathway is active, MST1/2 is phosphorylated and activated, which leads to the subsequent phosphorylation and activation of LATS1/2. Activated LATS1/2 then phosphorylates YAP and TAZ, marking them for binding to 14-3-3 proteins in the cytoplasm (13). As a result, YAP and TAZ are isolated in the cytoplasm, preventing their translocation into the nucleus, where they act as transcriptional co-activators (13).

In the absence of Hippo pathway signaling (when growth-promoting signals prevail), MST1/2 and LATS1/2 activities are inhibited or reduced. This leads to reduced phosphorylation of YAP and TAZ, allowing them to translocate into the nucleus. Once in the nucleus, YAP and TAZ are associated with various transcription factors, such as TEAD (TEA domain family members) (14), to regulate the expression of genes involved in cell proliferation, survival, and tissue growth. However, the dysregulation of this pathway often leads to the overactivation of YAP1- a growing issue when it comes to the tumor immune microenvironment.

1.02 *YAP1 in Cancer Proliferation and Suppression: Increased Cell Cycle Entry*

YAP1 acts as a co-activator, binding to transcription factors, such as TEAD to enhance the transcription of genes promoting cell cycle progression, such as cyclin D1 and c-myc. Cyclin D1 is involved in the G1-S transition, while c-myc promotes cell cycle progression and proliferation (15). Additionally, YAP1 interacts with various cell cycle regulators, including cyclins, cyclin-dependent kinase, and cyclin-dependent kinase inhibitors (15). When these cyclins can no longer function normally, the cells continue to duplicate. These interactions can dysregulate the normal balance of the cell cycle and promote cell proliferation (15). YAP1 can also prevent cell cycle arrest by inhibiting the function of tumor suppressor genes, such as p53. Normally, p53 assumes a vital function in halting the cell cycle and inducing apoptosis (cell death) in response to DNA damage or other cellular stresses (16). However, in cancer cells with YAP1 overexpression, this regulation is disrupted, leading to uncontrolled cell division and proliferation (2).

Most crucially, YAP1 is linked to EMT, a process in which epithelial cells lose their characteristics and gain mesenchymal properties (17). This enables cancer cells to become more motile and invasive, facilitating metastasis and furthering tumor growth (17). The EMT process is regulated by various molecular signaling pathways, including transcription factors such as Snail, Slug, Twist, and ZEB, among others (17). These suppress the expression of genes associated with epithelial characteristics while promoting genes associated with mesenchymal properties (17). This transcriptional reprogramming leads to changes in cell shape, mobility, and behavior, allowing cancer cells to disseminate and colonize distant sites. YAP1's ability to overexpress genes while dysregulated causes it to upregulate these transcription factors leading to increased cell cycle entry and tumor growth (17).

1.03 *Suppression of Cell Death Pathways*

YAP1 plays a role in inhibiting cell death pathways by two methods. YAP1 can regulate the expression of anti-apoptotic genes, such as BIRC5 (Survivin) and BCL-2 family members, which inhibit apoptosis (18). YAP1 can overexpress these genes by binding to specific DNA sequences called enhancers or promoters in the regulatory regions of target genes (18). By promoting the expression of these anti-apoptotic genes, YAP1 can prevent cells from undergoing apoptosis even in conditions where

it would be beneficial for the cell to undergo programmed cell death (18).

On the other hand, YAP1 also can inhibit pro-apoptotic characteristics such as p73, a member of the p53 family of tumor suppressor proteins. In its active form, p73 can induce apoptosis in response to cellular stress or DNA damage (19). It does so by binding to specific DNA sequences in the promoters of target genes, activating or repressing their transcription when encountering stressed or damaged DNA (19). However, when DNA damage is extensive and beyond repair, p73 promotes apoptosis. It activates the expression of pro-apoptotic genes, such as Bax and PUMA, which triggers the intrinsic apoptotic pathway (19). Consequently, YAP1 binding to p73 can block its pro-apoptotic function and, thus, suppress cell death and other cell death pathways (19).

1.04 *Increased Ratio of MDSCs to CD8+ T-cells*

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immune cells that accumulate in the tumor microenvironment and serve a fundamental purpose in suppressing anti-tumor immune responses (20). These cells are known to promote tumor growth and contribute to immune evasion processes employed by cancer cells (20). YAP1 can directly or indirectly influence the expression of the genes involved in immune regulation, often leading to an increase in the recruitment, expansion, or activation of MDSCs within the tumor microenvironment (19). YAP1 can also modulate the production of cytokines and chemokines that attract MDSCs to the tumor site, stimulating their differentiation from precursor cells (19). Various other signaling pathways are known to be involved in MDSC recruitment and function, most notably the STAT3 pathway. YAP1, with its transcriptomic abilities, may enhance the activity of these pathways, once again leading to increased MDSC accumulation (20). The promotion of chronic inflammation within the tumor microenvironment that YAP1 induces is known to support the accumulation and function of MDSCs as well (21). Furthermore, performed migration assays have shown that YAP1-expressing cells cause higher MDSC immigration to tumor sites (21). Alternatively when the YAP1 gene is attenuated a lower amount of MDSC movement is detected. This validates the Cxcl5 and Cxcr2 axis in the recruitment for MDSCs which, in turn, is regulated through YAP1 (21).

Consequently, the higher amounts of MDSCs in the tumor microenvironment lead to a downregulation of CD8+ T-cells. CD8+ T cells are part of the adaptive immune system, meaning they can recognize specific antigens on the surface of infected or cancerous cells (22). Antigens are structures that act as identifying markers, signaling the presence of foreign or abnormal cells (22). When a CD8+ T cell encounters an antigen on the surface of a cancer cell, it becomes activated (22). This activation process involves the interaction between the T cell receptor on the CD8+ T cell and the antigen-presenting molecule on the cancer cell (22). Ultimately this process allows for the CD8+ T-Cell to recognize the tumor cells as a threat and disable them (22). However, when YAP1 increases the expression

of a higher number of MDSCs into the TME, CD8+ T-cells become practically non-functional as they can no longer inhabit the tumor microenvironment (21, 22).

1.05 *Higher M2 Phenotype Expression*

Macrophages are a type of immune cell that is integral to the body's defense against pathogens and cancer cells (23). They are highly versatile and can differentiate into different subtypes based on the microenvironment and signals they receive (23). M1 and M2 macrophages are two distinct activation states of macrophages, and they have contrasting functions in cancer (23).

M1 macrophages, also known as classically activated macrophages, are typically induced by pro-inflammatory signals such as interferon-gamma (IFN-γ) and bacterial components like lipopolysaccharides (LPS) (23). They are potent killers of pathogens and cancer cells and are involved in promoting the inflammatory response (23). In cancer, M1 macrophages can have a positive impact (23). They contribute to the anti-tumor immune response by recognizing and attacking cancer cells directly (23). M1 macrophages can release cytotoxic particles and pro-inflammatory cytokines that help in tumor cell destruction (23). Additionally, they take part in presenting tumor antigens to other immune cells, stimulating an adaptive immune response against the cancer (23).

M2 macrophages, also known as alternatively activated macrophages, are induced by anti-inflammatory signals like interleukin-4 (IL-4) and interleukin-13 (IL-13) (23, 24). They are involved in tissue repair, wound healing, and in downregulating inflammation. M2 macrophages promote tissue remodeling and angiogenesis (the formation of new blood vessels) (23). In the context of cancer, M2 macrophages can have a negative impact and are often associated with promoting tumor progression (23). M2 macrophages can produce elements that promote tissue remodeling, create an immunosuppressive microenvironment, and support tumor angiogenesis, thereby facilitating tumor growth and metastasis (23). They can also inhibit the activation of anti-tumor immune responses by suppressing the function of cytotoxic T cells and natural killer (NK) cells (23).

The spatial and temporal balance between M1 and M2 macrophages in the tumor microenvironment is critical. An abundance of M2 macrophages with a concomittant paucity of M1 macrophages can create an immune-suppressive environment which in turn aids tumor development and progression (23, 24). On the other hand, an abundance of M1 macrophages can enhance the anti-tumor immune response and help in controlling tumor growth (23).

YAP1 expression makes naive macrophages more prone to mature into the M2 phenotype (23). Its interaction with transcriptomic factors allows it to modulate gene expression polarizing genes like F13A1, FUCA1, SDCBP, VSIG4, HLA-E, and TAP2 (24). The upregulation of these genes is associated with M2 polarization. YAP1’s interactions with the STAT3 pathway also increase the transcriptional activity of M2-associated genes

(23, 24). For instance, recent RT-qPCR and ELISA tests have shown abundances of CD206, MerTK, Il-10, Arg-1, and STAT3 (M2 markers) in YAP1-expressing cells (24).

1.06 *YAP1 as a Tumor Suppressor*

Despite the well-established evidence that YAP/TAZ overexpression or activation contributes to tumor progression through various processes, a growing body of research indicates that YAP/TAZ can also exhibit tumor-suppressive functions, albeit in a context-dependent manner (25). Notably, the region where the YAP gene resides, 11q22, frequently experiences loss of heterozygosity (LOH) in certain breast cancers (25). Investigations have found a correlation between the LOH of the 11q22 amplicon, the invasive subtype of breast tumors, and poor survival rates (25).

Consistent with these findings, experiments involving YAP knockdown in breast cancer cells demonstrated increased migration and invasion abilities, reduced responsiveness to Taxol®, and enhanced tumor growth in nude mice (25). Furthermore, recent *in vivo* studies have shown that depleting YAP in breast cancer cells leads to a significant increase in lung metastasis (25). Collectively, these studies underscore a potent tumor-suppressive role for YAP/TAZ.

Some studies have recently proposed a classification of solid tumors into two categories: "YAP on," where YAP is highly expressed and acts as an oncogene, and "YAP off," where its expression is silenced, and it functions as a tumor suppressor (24, 25). Solid cancers classified as "YAP off" typically exhibit RB1 deficiency, encompassing retinoblastoma, small cell lung cancer, and neuroendocrine prostate cancer (24, 25). In "YAP off" solid cancers, the reintroduction of YAP to activate genes associated with the integrin/ECM/adhesion pathway has been shown to induce cytostasis (24, 25).

1.07 *YAP1 as a Prognostic Biomarker*

Sun et al. investigated the prognostic significance of YAP1 expression across various cancer types, with a specific focus on pancreatic ductal adenocarcinoma (PAAD) (26). The analyses found that elevated YAP1 expression was associated with a poorer prognosis in PAAD. Utilizing datasets from Oncomine, TCGA in TIMER, and GEPIA databases, the study demonstrated differential expression of YAP1 between tumor tissues and normal tissues in multiple cancer types (26). Despite heterogeneity among cancer types and databases, a consistent correlation emerged between increased YAP1 expression and adverse prognosis in PAAD (26).

The research further elucidated the role of YAP1 in immune response modulation, particularly in PAAD (26). Strong positive association was identified between YAP1 expression and infiltration levels of CD8+ T cells, along with moderate associations with macrophages, neutrophils, and dendritic cells in PAAD (26). The study also explored the relationship between YAP1 and marker genes of immune cells, revealing the potential contributions of YAP1 to tumor-associated macrophage polarization, Treg responses, and T cell exhaustion. Notably, YAP1 emerged as a crucial regulator of various T cell subsets,

suggesting its involvement in the recruitment and regulation of infiltrating immune cells in PAAD (26).

In summary, the study concluded that YAP1 served as a valuable prognostic biomarker in pancreatic cancer, with implications for patient outcomes (26). Moreover, YAP1 is paramount to the intricate regulation of immune cell infiltration in the context of PAAD, highlighting its potential significance in shaping the tumor microenvironment and influencing the course of the disease (26). In another comprehensive study employing transcriptome and proteome analyses, YAP1 was identified as an indicator of poor overall survival (OS) and disease-free survival (DFS) in pancreatic cancer patients (27). The current gold standard for pancreatic cancer prognostication, the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification system, primarily focuses on the anatomical extent, leading to potential over- or undertreatment (27). The study underscores the need for improved staging systems that incorporate molecular facets to enhance individual prognostication and precision therapy utilization (27).

Previous assessments of the prognostic significance of YAP1 protein expression in pancreatic cancer yielded inconclusive results, necessitating larger cohort studies (27). This study, based on a tissue microarray (TMA) and immunohistochemistry analysis of 140 patients, established YAP1 overexpression as an independent factor predicting unfavorable outcomes and disease recurrence (27). These findings were corroborated by public mRNA datasets from The Cancer Genome Atlas (TCGA), reinforcing YAP1's role as a prognostic variable (27). Despite the partial predictability of protein abundances from mRNA levels, the agreement between transcriptome- and proteome-based survival analyses highlights YAP1's clinical significance (27).

Bioinformatic analyses of protein networks revealed direct connections between YAP1 and secreted molecules AREG, CTGF, CYR61, FGF1, and MSLN, implicated in fibrosis and significant signaling pathways involved in tumor-stroma interactions (26, 27). Pancreatic cancer progression is associated with a fibrotic stroma, and YAP1, activated by the stiffening tumor microenvironment, lacks DNA-binding activity and requires interaction with TEAD transcription factors to activate target genes, including AREG, CTGF, CYR61, FGF1, and MSLN (26, 28). The studies propose a paracrine loop whereby YAP1/TEAD target gene products contribute to enhanced fibrotic reactions, influencing the aggressive course of the disease (26, 28).

Experimental validation using the pancreatic cancer cell line Panc-1 demonstrated that disrupting the YAP1/TEAD complex reduced the presence of target gene products in the conditioned medium (28). This suggests that suppressing YAP1 oncogenic activity could modify the tumor microenvironment, presenting a potential approach to control tumor growth and improve prognosis (28). While the clinical utility of such treatment awaits determination, the study emphasizes YAP1's role as a biomarker for individual

prognostication in pancreatic cancer patients and in guiding precision therapy selection. Several studies continue to find YAP1 as a prognostic biomarker for pancreatic cancer which underscores its potential clinical relevance for risk stratification and treatment decision-making in cancer patients. However, the use of YAP1 as a prognostic biomarker is context-dependent, and its significance may vary across different cancer types and patient populations (26-28).

1.08 *Exploration of YAP1 in Specific Cases: Intervertebral Disc Degeneration*

The intervertebral disc, the largest vascular tissue in vertebrates, relies on adjacent endplate micropores for nutrition through diffusion (29). The nucleus pulposus (NP), annulus fibrosus, and cartilaginous endplate (CEP) are interdependent for stability, with CEP proteins crucial for maintaining integrity. Excessive tension load can lead to CEP calcification, affecting nutrient supply and initiating intervertebral disc degeneration (IDD). Histological examinations of patients with lumbar disc herniation (LDH) reveal a degenerated extracellular matrix and decreased collagen-2A (COL-2A) and Sox9 expression, indicating CEP degeneration's impact on IDD progression. Additionally, abnormal mechanical tension is associated with IDD, promoting intervertebral disc cell senescence. SA-β-Gal staining, a senescence biomarker, is higher in LDH, correlating with increased expressions of senescence-related genes. YAP1 is involved in cell proliferation and differentiation regulation. Overexpression of YAP1 slows the degeneration and senescence of endplate chondrocytes. In a rat model, YAP1 injection alleviated IDD-associated changes, suggesting a potential therapeutic role in delaying disc degeneration and senescence (29). These findings highlight the complex interplay between mechanical tension, molecular pathways, and cellular senescence in IDD pathogenesis, with YAP1 emerging as a promising target for intervention.

1.09 *Pressure Overload-Induced Heart Disease*

Pressure overload-induced cardiac hypertrophy has been associated with mitochondrial remodeling and decreased oxidative respiration, although the links between pressure, hypertrophy, and mitochondria are not well understood (30). YAP1, a known mediator of mechanical stress-induced signals, responds to pressure overload in the heart and has often been studied as a possibility for cardiomyocyte regeneration. Previous research identified connections between mechanical stress (found to impair mitochondrial quality control, electron transport chain function, induce ROS accumulation, and disrupted calcium regulation), mitochondrial function, and cardiac hypertrophy, while new studies show that prolonged YAP1 activation was found to trigger hypertrophy by perturbing mitochondria. Simultaneous restoration of mitochondrial fission activator DRP1 and fusion activator MFN1 was necessary to rescue YAP-induced mitochondrial defects and hypertrophy. RNA-seq analyses revealed mitochondrial dysfunction as the major adverse effect of pressure overload, with impaired biogenesis leading to hyperpigmentation. The TEAD1-YAP1 complex was shown to regulate the expression of DRP1 and MFN1 (30). Verteporfin, a YAP1 inhibitor, restored

mitochondrial function, suggesting its potential to alleviate excessive mechanical stress. While YAP signaling is studied for cardiac regeneration, the temporal control of YAP1 activation is crucial, reconciling its roles in promoting both repair and damage. Hence, YAP activation under mechanical stress induces mitochondrial impairment, and verteporfin emerges as a promising candidate for treating cardiac hypertrophy by inhibiting YAP1.

1.10 *Small Cell Lung Cancer*

The innovative classification of small cell lung cancer (SCLC) into four molecular subtypes has stimulated research on the immune landscapes and potential combination therapies for each subtype (31, 32). New research aimed to explore the expression patterns of transcriptional regulators defining these subtypes, utilizing the NMF algorithm to classify clinical samples (31, 32). The SCLC-Y subtype was identified with the worst prognosis, with least susceptibility to immunotherapy. YAP1, known to induce PD-L1 expression in SCLC, played a role in inhibiting immune cell activation. A novel strategy co-targeting YAP1 and PD-L1 was developed, showing significant anti-tumor activity and potential for combination therapy in the SCLC-Y subtype.

The proportions of SCLC molecular subtypes varied, with the SCLC-A and SCLC-N subtypes being the most prevalent. Chen et al. observed a significant difference in recurrence-free survival among the subtypes, with the SCLC-Y subtype exhibiting the least favorable prognosis (31). These findings were consistent with previous reports, although conflicting results were noted in other studies, potentially due to cohort size and follow-up duration differences. Immune cell infiltration analysis found higher proportions of CD3+ and CD8+ T cells in the SCLC-P and SCLC-Y subtypes (32). The SCLC-P subtype showed elevated levels of CD4+ T cells and FOXP3+ Tregs. Co-expression patterns of subtype marker genes and immune checkpoints were proposed, offering insights into potential combined immunotherapy for SCLC.

Owonikoko et al. investigated the complex role of YAP1 in SCLC, demonstrating its impact on stemness and immune microenvironment modulation (32). YAP1's dual effects on immune cell infiltration and its association with poor outcomes across various cancers, including SCLC, were highlighted. The findings suggested that YAP1 enhances immune evasion through PD-L1 induction, immune microenvironment remodeling, and modulation of immune-related signaling pathways.

1.11 *Mechanisms of YAP1-Mediated Cancer Proliferation: IL-6/STAT3 Pathway*

Interleukin-6 (IL-6) is a pro-inflammatory cytokine produced by various cell types, including immune cells and cancer cells. It is a pleiotropic cytokine, meaning it has multiple effects on different cells and tissues. It is produced by various cell types, including T cells, B cells, macrophages, fibroblasts, and endothelial cells, in response to infections and other inflammatory stimuli (33). More notably it is a potent activator of STAT3 signaling. In the context of cancer, elevated IL-6 levels have

been observed in many tumor types, and this cytokine is known to promote tumor growth, invasion, and metastasis. STAT3 is a transcription factor that, when activated by phosphorylation, translocates to the nucleus and regulates the expression of genes involved in cell survival, proliferation, and immune responses (33). Aberrant STAT3 activation is associated with many cancer types and has been linked to tumor development and progression as well.

Studies on YAP1 and STAT3 crosstalk have shown that YAP1 and STAT3 can interact and influence each other's activities selectively (34). YAP1 can promote STAT3 activation by several processes. One is through direct physical interaction, where YAP1 binds to STAT3 and enhances its phosphorylation and activation. Additionally, YAP1 can induce the expression of IL-6 through a positive feedback loop system, which, as mentioned earlier, activates STAT3. The activation of STAT3 by YAP1 leads to the upregulation of STAT3 target genes, many of which are involved in promoting cell survival and proliferation. The overall relationship between YAP1, STAT3, and IL-6 can form a positive feedback loop that sustains their activation (33, 34). YAP1 induces IL-6 expression, which activates STAT3, and active STAT3 can enhance YAP1 activity. As YAP1 and STAT3 promote each other's activation, this loop can lead to persistent activation of pro-cancer signaling pathways, promoting tumor growth and progression.

When examining these phenomena on a protein level, RNA analysis showed that pharmacological attenuation of YAP1 caused the downregulation of IL-6 (34). Since STAT3 is directly activated by IL-6 its phosphorylation is also positively correlated with YAP1 expression.

1.12 *Transcription Factors (TEADs)*

TEADs (TEA domain transcription factors) are a family of transcription factors that interact with YAP1 to regulate the transcription of target genes. TEADs are the major DNA-binding partners of YAP1, and together, they form a transcriptional complex that promotes the expression of genes involved in cell proliferation, survival, and epithelial-mesenchymal transition (EMT) (35). The YAP1-TEAD complex binds to specific DNA sequences called TEAD-binding elements (TEBs) within the promoters or enhancers of target genes (36). In cancer, the YAP1-TEAD signaling axis can be aberrantly activated, leading to increased cell proliferation and tumor growth. This dysregulation can be caused by mutations or amplifications of YAP1 and TEAD genes which result in increased expression and activity of YAP1-TEAD complexes, promoting uncontrolled cell growth. The Hippo pathway, which normally negatively regulates YAP1 by promoting its cytoplasmic retention and degradation, can be disrupted in cancer, leading to the nuclear accumulation of YAP1 and enhanced YAP1-TEAD transcriptional activity (35). Physical forces and cues from the tumor microenvironment can activate YAP1-TEAD signaling in cancer cells, contributing to cancer progression.

Once YAP1 translocates into the nucleus and forms a complex with TEADs, it can activate

the transcription of genes that promote cell proliferation, inhibit apoptosis, and enhance tumor cell survival. In many forms of cancer, the YAP1-TEAD complex promotes the expression of various target genes, including CTGF (Connective Tissue Growth Factor), CYR61 (Cysteine-rich angiogenic inducer 61), and AXL, among others (36). These genes are associated with cell survival, proliferation, and invasion, thereby contributing to cancer development and progression.

1.13 *Wnt Oncogenic Pathway*

The Wnt signaling pathway is a highly conserved pathway that is vital for embryonic development, tissue homeostasis, and stem cell maintenance (37). Wnt signaling is initiated by the binding of Wnt ligands to Frizzled receptors and co-receptors, leading to the stabilization and nuclear translocation of β-catenin. In the nucleus, β-catenin interacts with TCF/LEF transcription factors to activate the expression of Wnt target genes involved in cell proliferation, survival, and differentiation. Aberrant activation of the Wnt pathway is a common feature of many cancers. Mutations in essential components of the pathway, such as the APC (adenomatous polyposis coli) gene or β-catenin itself, can lead to constitutive activation of Wnt signaling (37). This sustained Wnt pathway activity can drive uncontrolled cell proliferation, cell transformation, and the formation of tumors. The Wnt pathway is particularly well-known for its role in colorectal cancer, where APC mutations are frequently observed.

Emerging evidence suggests that YAP1 and Wnt signaling pathways can interact and cooperate to promote tumorigenesis in certain contexts (38). YAP1 has been shown to directly interact with β-catenin, leading to enhanced Wnt signaling activity. Additionally, YAP1 can induce the expression of Wnt ligands and receptors, further potentiating Wnt pathway activation. The crosstalk between YAP1 and Wnt pathways can lead to a positive feedback loop, sustaining tumorigenic signals and driving cancer progression.

1.14 *Notch Pathway*

The Notch signaling pathway is an evolutionarily conserved pathway that plays a fundamental role in cell fate indicators, tissue development, and cell differentiation (39). The pathway consists of four transmembrane receptors (Notch1-4) and five ligands (Jagged1, Jagged2, Delta-like 1, Delta-like 3, and Delta-like 4) in mammals. The pathway is activated when Notch receptors on the cell surface bind to specific ligands on neighboring cells, leading to proteolytic cleavage of the receptor and release of the Notch intracellular domain (NICD). The NICD translocates to the nucleus and interacts with transcription factors, leading to the expression of target genes involved in various cellular processes. In cancer, the Notch pathway can be both oncogenic and tumor-suppressive, depending on the context and specific tissue types (40). Aberrant activation of the Notch pathway has been observed in several cancer types and can promote tumor growth, angiogenesis, and metastasis. Conversely, in some cases, Notch signaling can act as a tumor suppressor by inhibiting cell proliferation or inducing differentiation.

Aster et al. (41) found that crosstalk and regulatory interactions between the YAP1 and Notch pathways in cancer can regulate Notch signaling by directly influencing the expression of Notch receptors or ligands or through other intermediaries. In turn, Notch pathway components can modulate the activity of YAP1. This occurs through various methods including tumor cell proliferation, epithelial-mesenchymal transition, and immune modulation. Overall the interplay impacts various aspects of cancer biology, including tumor initiation, maintenance, and response to therapies.

1.15 *TGF-β Pathways*

The TGF-β pathway takes on a dual role in cancer biology, acting as both a tumor suppressor and a tumor promoter, depending on the context and stage of the disease (42). In normal tissues, TGF-β acts as a tumor suppressor by inhibiting cell proliferation, inducing apoptosis (programmed cell death), and promoting differentiation. However, during cancer development, the TGF-β signaling pathway can be altered, leading to a switch from its tumor-suppressive to its tumor-promoting functions. Mutations or alterations in components of the TGF-β pathway can lead to uncontrolled cell proliferation, invasion, and metastasis. These changes often occur in various types of cancers, such as breast cancer, colorectal cancer, pancreatic cancer, and others. Tumor cells can become insensitive to TGF-β's growth-inhibitory effects, and instead, they exploit the pathway to promote tumor progression and immune evasion.

There is an intricate interplay between the TGF-β and YAP1 pathways in cancer (43). Cross-talk between these two pathways can lead to synergistic effects, promoting cancer progression. YAP1 can modulate the TGF-β pathway by physically interacting with Smad proteins, which are crucial mediators of the TGF-β pathway. This interaction enhances the transcriptional activity of TGF-β-responsive genes, further promoting tumor growth and invasion. TGF-β itself can also regulate YAP1 activity affecting its subcellular localization or stability. TGF-β-induced YAP1 activation may also contribute to cancer cell proliferation and metastasis. Lastly, YAP1 and TGF-β pathways can form complex feedback loops (44), where one pathway's activity influences the other's expression or activity. These loops can amplify oncogenic signals and contribute to cancer progression. The positive feedback nature of their interactions causes uncontrollable tumorigenesis.

1.16 *Upstream Regulator Mutations*

In lung adenocarcinoma cells, the activation of TAZ triggers the expression of a set of target genes (Table 1), such as ABL2, AXL, and L1CAM, promoting brain metastasis (45). Through ChIP-qPCR, it was demonstrated that activated TAZ binds to the ABL2 promoter. This creates a positive feedback loop, wherein increased ABL2 production activates TAZ, leading to enhanced transcription of AXL and L1CAM. The TAZ-ABL2-AXL axis contributes to the elevated expression of brain metastatic targets, including L1CAM, crucial for lung adenocarcinoma brain metastasis. Treatment with the ABL kinase inhibitor

ABL001 impedes the expression of TAZ targets, reducing brain metastasis outgrowth.

Table 1: YAP/TAZ Transcriptional Targets and Mechanisms (45)

Target Gene	Mechanism	Target Gene	Mechanism
AXL	Invasion, Stemness, Seeding, Colonization, Therapy Resistance	FOXM1	Cell Proliferation, EMT Invasion
ABL2	Seeding, Colonization	ARHGAP29	Cell Motility, Invasion
L1CAM	Seeding Colonization, Perivascular Extension	MSLN	Cell Motility, Invasion
THBS1	Cell Motility, Invasion	COX-2	Cell Proliferation, Colonization
CTGF	Cell Motility, Invasion, Therapy, Resistance	CD44	Cell Motility, Invasion
RHAMM	Cell Motility, Invasion	PD-L1	Immune Evasion

Additionally, AXL expression is regulated by YAP/TAZ signaling independently of ABL kinases (45). The AXL promoter contains four TEAD binding sites, with YAP binding to the AXL promoter region in hepatocellular carcinoma. In osteosarcoma, AXL is linked to YAP/TAZ signaling, promoting cell stemness and enhancing metastasis. YAP-dependent upregulation of AXL contributes to resistance to targeted therapies in non-small-cell lung cancer, and inhibiting AXL kinase activity restores drug sensitivity. AXL also engages in diverse roles in promoting invasion, metastasis, and drug resistance associated with YAP signaling in melanoma.

Thrombospondin 1 (THBS1), a YAP target gene, regulates cell adhesion. TSP1, the protein encoded by THBS1, promotes FAK phosphorylation and activation, enhancing tumor cell motility and invasiveness (45). THBS1 mediates invasion in melanoma models. Similarly, ITGAV, a TAZ target gene encoding integrin-αV, is overexpressed in various solid tumors. In hepatocellular carcinoma, the TAZ/TEAD complex binds the ITGAV promoter to induce its expression.

Connective tissue growth factor (CTGF), a YAP and TAZ target gene, and CYR61, another TAZ target gene, are members of the connective tissue factor family (45). They function as integrin ligands, influencing cell proliferation, apoptosis, migration, and angiogenesis. CTGF activity in breast cancer enhances migration, while both CTGF and CYR61 collaborate to promote drug resistance in breast cancer. CYR61 is implicated in melanoma metastasis by increasing cell invasion, and in osteosarcoma, it induces epithelial-mesenchymal transition (EMT) and promotes lung metastatic invasion.

The FOXM1 transcription factor, an essential player in cancer progression and metastasis, is upregulated by the YAP/TEAD4 complex

binding to its promoter. Inhibition of FOXM1 results in decreased cell proliferation, migration, metastasis, and drug resistance in various cancers, including breast, lung, and colorectal cancers.

The YAP target gene ARHGAP29 correlates with the metastatic potential of several cancers (45). Increased ARHGAP29 expression induces changes in actin dynamics, softening the cytoskeleton and promoting cell migration. Mesothelin (MSLN), a YAP target linked through YAP/TEAD1 binding, is overexpressed in various cancers and promotes invasion and migration (45). MSLN enhances cancer cell invasion by increasing MMP-7 expression through MAPK/ERK and JNK signaling pathways. CD44 and RHAMM, both YAP target genes, upregulated in various cancers, promote cell invasion by binding hyaluronic acid, and are involved in ERK1/2 regulation (45). Other YAP and TAZ targets include COX-2 and PD-L1. COX-2, activated directly by YAP in colorectal cancer, is involved in drug resistance, increasing cell proliferation and colony-forming ability [108]. PD-L1 expression in cancer cells, mediating immune evasion, is regulated by TAZ activity in breast cancer through TAZ binding to the PD-L1 promoter region. Notably, some genes are specific targets of either TAZ or YAP, emphasizing their distinct functions (45). Further research is needed to elucidate the specific transcriptional programs governed by these components and their diverse roles in the metastatic cascade across various tumor types.

1.17 *Nuclear Condensates*

Nuclear condensates represent dynamic and highly organized structures within the cell nucleus, with a pivotal role in orchestrating various cellular processes (46). These condensates arise from phase separation phenomena, wherein biomolecules undergo liquid-liquid phase transitions, leading to the formation of membrane-less organelles with distinct biochemical compositions. Recent investigations have unveiled the participation of the transcriptional co-activator YAP1 in the modulation and regulation of nuclear condensates. YAP1, a key effector in the Hippo signaling pathway, engages in intricate molecular interactions that influence the spatial and temporal organization of nuclear condensates (46). The specific impact of YAP1 on the biophysical properties and functionality of these condensates remains an active area of exploration, contributing to our evolving comprehension of the nuanced interplay between cellular signaling pathways and nuclear architecture.

In the context of nuclear condensates, YAP1 emerges as a multifaceted regulator, influencing not only the assembly dynamics but also the composition of these subnuclear structures (46). YAP1's translocation to the nucleus is contingent upon its activation and subsequent complex formation with transcriptional partners, such as TEAD (47). Once localized within the nucleus, YAP1 interfaces with various molecular components that contribute to the formation and maintenance of nuclear condensates. The interplay between YAP1 and nuclear condensates extends beyond mere structural considerations, as YAP1 has been implicated in the modulation of gene expression within these specialized nuclear domains (47). Elucidating

the intricate molecular instruments underpinning the crosstalk between YAP1 and nuclear condensates presents a compelling avenue for advancing our understanding of nuclear organization and its implications for cellular homeostasis and pathological states (46). As research endeavors progress, unraveling the nuanced interdependencies between YAP1 and nuclear condensates holds promise for unveiling novel regulatory paradigms with far-reaching implications for cellular function and disease pathogenesis.

1.18 *Emerging Epigenetic Discoveries with YAP : YAP in Epigenetic Regulation*

Current evidence underscores the significant involvement of epigenetic processes in the intricate regulation of transcription by YAP/TAZ, evident in both Drosophila and mammalian cells (48). This regulatory process hinges on the recruitment of chromatin remodeling features and chromatin-modifying enzymes by YAP/TAZ, ultimately influencing the accessibility of regulatory regions such as promoters and enhancers. Noteworthy among the identified epigenetic regulators contributing to YAP/TAZ-dependent transcriptional control are the SWI/SNF complex, p300, BRD4, and chromatin methylation (48). The SWI/SNF complex, implicated in chromatin remodeling, has been suggested to collaborate with YAP/TAZ, although conflicting evidence exists regarding its role in YAP/TAZ-dependent transcription. Additionally, p300 and BRD4, both histone acetyltransferases, are recruited by YAP/TAZ to enhance chromatin acetylation, promoting enhancer–promoter remodeling and facilitating RNA polymerase binding and activity (48). Chromatin methylation, specifically the methylation of histone H3 at lysine 4, is associated with gene activity, and NCOA6, a subunit of the Trithorax-related MLL2/3 HMT complex, acts as a cornerstone regulating Hippo-mediated transcriptional responses. Lastly, the NuRD repressor complex is implicated in the repression of transcription by YAP/TAZ, limiting genome accessibility around bound regulatory regions through histone deacetylation and chromatin remodeling activities. These findings provide a comprehensive overview of the multifaceted epigenetic landscape underlying YAP/TAZ-mediated transcriptional control, emphasizing the intricate interplay between these regulators in various cellular contexts (48). Further biochemical studies and context-specific genome-wide chromatin mapping are warranted to address remaining questions and enhance our understanding of these regulatory agents.

1.19 *SCML2 and YAP1 interactions*

Studies have explored novel biochemical and functional interactions between YAP1 and SCML2 proteins in human cells (48). Mass spectrometry-based proteomics, co-immunoprecipitation, immunological assays, GST pulldown assays, and gene silencing data were utilized to demonstrate the interaction and functional antagonism between YAP1 and SCML2. SCML2 acts as a growth suppressor in androgen-sensitive cells while functioning as a survival factor in androgen-insensitive cells, suggesting context-dependent roles. Several RNA-binding proteins associated with YAP1 were identified, indicating potential crosstalk between RNA regulation and YAP1 functions. The connection between SCML2, YAP1, and

the androgen receptor (AR) was explored, proposing a process where androgen exposure induces the interaction of SCML2 with YAP1. The findings suggest that the YAP1 and SCML2 interaction is critical in cellular biology and diseases such as cancer, particularly in the context of androgen/AR signaling. Potential influences that may facilitate or mediate the YAP1 and SCML2 interaction were identified, emphasizing the complexity of their protein network. Additionally, SCML2 regulates cell growth and survival through potentially divergent means, involving crosstalk with YAP1 and modulation of the Hippo/STK4 signaling pathway.

While valuable insights into the YAP1-SCML2 axis are being investigated, there are limitations, and further research is needed to elucidate detailed physiological significance and potential therapeutic implications of this interaction in the context of cellular physiology and cancer development. Therefore, these discoveries underscore the need for future investigations aimed at elucidating the molecular foundation and physiological importance of the interaction between SCML2 and YAP1, which governs histone modifications and gene expression. Such studies may identify the SCML2-YAP1 axis as a vital pathway that significantly influences cellular physiology and contributes to human diseases, notably the development, and progression of cancer, especially in the context of steroid hormones such as androgens.

1.20 *Pluripotent Cell Differentiation*

Other studies have aimed to elucidate the specific functions of the mechanotransducer YAP1 in the growth and differentiation of pluripotent cells, addressing existing controversies in the literature (49). YAP1 knockout induced pluripotent cell (iPSC) lines were generated, mimicking features observed in previous YAP1 knockout embryonic stem cell (ESC) lines. Surprisingly, YAP1-deficient iPSCs exhibited colony formation and upregulation of the pluripotency marker OCT4, maintaining a positive Epi-Pluri-Score. However, gene expression analysis found significant differences, with mesoderm-associated genes being upregulated in YAP1-deficient iPSCs, supporting previous suggestions of YAP1 inhibiting differentiation toward mesoderm lineages (49). The study demonstrated differential activation of NODAL and related TGF-β and WNT pathways in YAP1-deficient iPSCs, aligning with YAP1's known role in regulating these pathways in pluripotent stem cells. Additionally, the study explored the involvement of YAP1 in epigenetic changes and observed distinct and reproducible DNA methylation modifications in YAP1-deficient iPSCs, indicating an apparatus yet to be elucidated. Despite the heterogeneity of iPSC colonies, particularly in the expression of NODAL and LEFTY, the self-organization of YAP1 knockout colonies was not affected. While YAP1 was not essential for maintaining pluripotency and colony self-organization, it assumed a vital function in the regulation of directed differentiation, with evidence of impaired cell-fate decisions in YAP1 knockout iPSCs during 3D multi-lineage differentiation. The study concluded that YAP1 controls the TGF-β pathway, influencing self-organized germ layer specification in early iPSC aggregates.

1.21 *TET1*

Neuroblastoma, the most common tumor in children, poses a high risk of recurrence, emphasizing the need for a comprehensive understanding of genetic variations associated with the disease (4, 50). Studies have focused on polymorphisms of m5C modification core genes, particularly the m5C demethylase gene TET1 (which is induced by the expression of YAP), which operates as a central element in the occurrence and development of some cancers (50). A case–control study in children from Jiangsu, China, found that TET1 gene polymorphisms (rs3998860 G > A and rs12781492 A > C) were associated with an increased risk of neuroblastoma. Logistic regression analysis indicated that the GG genotype of TET1 rs3998860 significantly elevated neuroblastoma risk compared to the AA genotype, particularly in the recessive model. Risk SNPs could accumulate, contributing to neuroblastoma. Stratification analysis revealed increased neuroblastoma risk associated with TET1 rs3998860 in subgroups >18 months of age and males. Site of origin stratification indicated a significant association with retroperitoneal neuroblastoma, emphasizing the impact of variable sites on the results. Additionally, TET1 gene polymorphisms were associated with an increased risk of retroperitoneal neuroblastoma across various clinical staging subgroups (50).

The GTEx database was used to analyze the impact of rs3998860 and rs12781492 on nearby gene expression. Both alleles were associated with increased STOX1 mRNA expression, a gene implicated in pre-eclampsia and shown to regulate cell cycle and proliferation in neuroblastoma. High STOX1 expression correlated with poor prognosis. The study also identified associations between the alleles and increased expression of CCAR1, KIF1BP, SLC25A16, and RUFY2, suggesting potential systems for neuroblastoma risk. While these studies provide valuable insights into the association between TET1 gene polymorphisms and neuroblastoma risk, limitations include single-center recruitment and the need for further research to elucidate specific mechanisms. Overall, this research contributes to the understanding of genetic determinants influencing neuroblastoma susceptibility in children.

2. YAP1 Attenuation

Various methods of YAP1 attenuation have been explored over the last decade. Attenuating YAP1 can be achieved through various molecular and pharmacological approaches, to mitigate its oncogenic effects.

2.01 *Verteporfin*

Repurposing Verteporfin can have an impact on endometrial cancer, where YAP levels correlate with clinical characteristics, and TP53 is often wild-type (51). Verteporfin, known for its use as a photosensitizer with limited toxicity, is proposed as a cancer therapeutic due to its ability to alter functions associated with tumor pathophysiology (Figure 2). The compound is shown to decrease nuclear YAP levels by increasing cytosolic 14-3-3σ, trapping YAP in the cytosol (51). This effect is supported by Reverse Phase Protein Array (RPPA) data indicating an increase in multiple 14-3-3 family members.

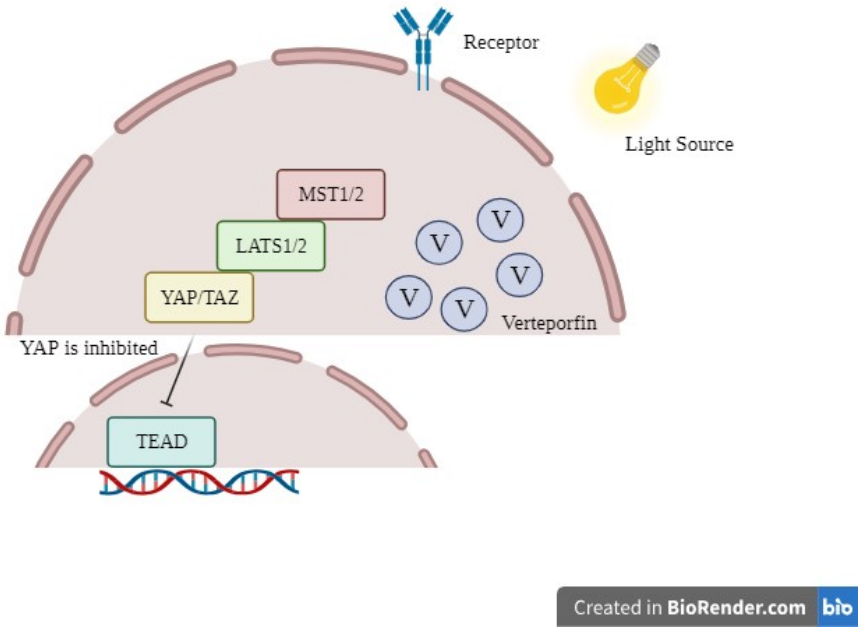

Figure 2. Exposure to light inhibits signal between YAP1 and TEAD receptors

The 14-3-3 family of proteins, involved in various cellular processes, is suggested to contribute to Verteporfin's impact on autophagy, apoptosis, cell cycle progression, and transcriptional regulation (51). Verteporfin's ability to induce 14-3-3σ, an essential member sequestering phosphorylated proteins in the cytosol, aligns with its effects on YAP1 and tumor pathophysiology. YAP1 homolog TAZ is also modulated, with both YAP and TAZ sequestered in the cytosol by 14-3-3, diminishing their transcriptional co-activation functions. Phosphorylation of specific motifs, including a consensus 14-3-3 binding motif, contributes to this sequestration. Verteporfin-induced DNA damage increases 14-3-3σ, dependent on TP53, and Wei et al. identified a feed-forward loop involving 14-3-3σ and p53 activation (51).

Notably, Verteporfin increased p53 levels, and p53 is identified as crucial for Verteporfin's effects on 14-3-3σ and cell proliferation (52). The potential therapeutic application of Verteporfin was suggested, especially in tumors where YAP signaling is critical and p53 is the wild type. Type 1 endometrial cancer was proposed as a suitable candidate for Verteporfin evaluation. However, the effectiveness of Verteporfin in the BrafCA; Tyr-CreERT2; Ptenf/f transgenic model of melanoma was unsatisfactory (52). While other treatments like siRNA targeting YAP and TAZ induced an elongated bipolar cell morphology,

this response was not replicated with Verteporfin treatment across a broad range of drug concentrations (0.1 ng to 10 μM). Furthermore, Verteporfin's effectiveness depended on the specific cellular context, tissue type, or genetic background. YAP1 functions in a highly context-dependent manner and the response to Verteporfin could vary across different cell types or disease models.

Further research should be conducted on biomarker identification for Verteporfin responsiveness. Identifying predictive biomarkers that indicate which patients are most likely to benefit from Verteporfin treatment is a critical knowledge gap. Understanding the molecular profiles associated with responsiveness to Verteporfin could guide patient stratification and enhance the precision of treatment strategies.

2.02 *MicroRNA*

Hu et al. investigated the role of miR-181a in the proliferation and differentiation of skeletal muscle satellite cells (SMSCs) in Hu sheep (46). Previous studies highlighted the involvement of various microRNAs (miRNAs), including miR-378 and miR-125b, in sheep muscle growth. MiR-181a, known for its participation in muscle growth, cancer progression, and disease occurrence, was examined in the differentiation process of SMSCs (46). O'Brien et al. observed that miR-181a expression increased initially and then decreased during the differentiation process, leading the researchers to suggest its involvement in SMSC differentiation (53). Through experimental methods such as qRT-PCR, Western blot, cck-8, flow cytometry, and EDU, it was found that miR-181a suppressed the proliferation of SMSCs. Additionally, the expression of integral genes (MyHC, MyoD, and MyoG) in muscle satellite cell differentiation was facilitated by miR-181a, indicating its role in this process. Immunofluorescence experiments further supported the hypothesis that miR-181a promoteed the formation of myotubes, contributing to the differentiation of SMSCs. The study also focused on identifying the target gene of miR-181a and found YAP1 to be a potential target. Experimental validation through dual-luciferase reporter assays, qRT-PCR, and Western blot confirmed that YAP1 was indeed the target gene of miR-181a. YAP1, a downstream gene of the Hippo pathway, is known to participate in cell proliferation, apoptosis, and migration. The results showed that miR-181a binds to the 3′UTR region of the YAP1 gene, leading to a reduction in YAP1 expression at both the mRNA and protein levels. In summary, the research indicated that miR-181a suppressed SMSC proliferation, promoting differentiation, and targeting YAP1 in Hu sheep.

Chen et al. Studied the effect of miR-15a-5p in cervical cancer (CC) (54). They found that miR-15a-5p was decreased in CC tissues and cell lines and was associated with CC metastasis. Overexpression of miR-15a-5p inhibited CC cell viability, invasion, and migration, and promoted apoptosis. YAP1 was identified as a functional target of miR-15a-5p, and its overexpression reversed the suppressive effects of miR-15a-5p. The study suggested that miR-15a-5p functions as a tumor suppressor in CC progression by inhibiting

YAP1 expression. The researchers compared miR-15a-5p with other miRNAs involved in CC development, highlighting its potential as a therapeutic target. Previous studies showed miR-15a-5p's tumor-suppressive role in various cancers (53). The study confirmed that miR-15a-5p inhibited cell viability, migration, and invasion while inducing apoptosis in CC cells (54).

YAP1 was identified as a target of miR-15a-5p (54). YAP1 overexpression partly counteracted the inhibitory effects induced by enhanced miR-15a-5p expression in CC cells. Studies concluded that miR-15a-5p suppressed CC cells by directly targeting YAP1. However, further research, especially *in vivo* studies and clinical trials, is needed to validate these findings and explore potential downstream targets of miR-15a-5p in CC. The miR-15a-5p/YAP1 axis was proposed as a potential biomarker and therapeutic target for CC therapy.

Circular RNA is also being investigated as a therapeutic modulator of YAP1 (55). Circular RNAs (circRNAs) are proposed to play an important role in regulating the Hippo signaling pathway, particularly in the context of cancer. The Hippo-YAP axis and its interactions with various signaling pathways, including the regulatory role of non-coding RNAs, were discussed. The focus was on circRNAs and their potential involvement in modulating the components of the Hippo pathway. The miRNA sponging employed by circRNAs, emphasized the need for precise methods to elucidate circRNA functions (55). This raises questions about the efficiency and significance of circRNA-miRNA interactions, the influence of circRNA tertiary structures, and the potential impact on gene expression.
Additionally, the diverse regulatory functions of circRNAs related to the Hippo-YAP axis, including their roles as protein binding partners, transcriptional regulators, and modulators of protein translocation were investigated (55). The findings suggested the possibility of circRNAs being translated into proteins, highlighting questions about the variables influencing circRNA translation efficiency. The review also suggested the existence of a potential feedback regulation of circRNAs by the Hippo signaling pathway, posing questions about their regulation of splicing events, circRNA biogenesis, transcription, and translation. However, several research directions and unresolved questions are proposed, such as the exploration of circRNA interactions with splicing components, their involvement in circRNA translation, and the feedback regulation of circRNAs by the Hippo pathway. Further experimental and in silico analyses to address these questions are required along with more comprehensive studies to elucidate their roles.

2.03 *ION-537*

ION-537 is currently in the developmental stages as a potential treatment for solid tumors, with a specific focus on metastatic castration-resistant prostate cancer (mCRPC) (56). This investigational drug operates by targeting YAP1, which regulates cellular processes associated with cancer development and progression. What sets ION-537 apart is its utilization of antisense drug discovery technology in its development. This innovative

approach involves the use of antisense oligonucleotides to modulate gene expression, ultimately influencing the activity of YAP1. By leveraging antisense technology, ION-537 aims to interfere with the expression of YAP1, potentially disrupting the pathways that contribute to the growth and survival of cancer cells. The focus on metastatic castration-resistant prostate cancer underscores the critical need for novel therapeutic options in addressing advanced stages of prostate cancer, and ION-537's unique system of action positions it as a candidate for further exploration in the realm of cancer therapeutics. ION-537 is currently under clinical development by Ionis Pharmaceuticals and is going through Phase II for Metastatic Castration-Resistant Prostate Cancer (56).

2.04 *Targeting YAP-Fusion Proteins (Phase Separation)*

The nuclear localization of the transcriptional co-activator YAP and the subsequent activation of TEA domain family (TEAD) transcription factors regulate cell proliferation, differentiation, and stem cell fate (57). Disruptions in the regulation of YAP are associated with developmental defects and the progression of cancer. The Hippo pathway, a conserved signaling pathway responsive to mechano-chemical changes in tissue architecture and osmolarity, regulates YAP's nuclear localization. Despite the recognized importance of YAP, the precise alterations in gene expression patterns upon YAP redistribution into the nucleus remain largely unknown. Cai et al. Has observed the phenomenon of phase separation in cells, leading to the formation of liquid-like or gel-like condensates (referred to as 'droplets') involving weak multivalent interactions among proteins and nucleic acids. (57). In the nucleus, this phase separation contributes to heterochromatin formation, transcriptional upregulation, and the clustering of nuclear enhancer elements into super-enhancers (SEs) that transcribe specific gene sets crucial for cell identity or cancer malignancy.

YAP has been identified in interactions with various transcription elongation factors and has been associated with SE regions in the genome. Building upon the concept of liquid-liquid phase separation in SE formation, Cai et al. investigated whether YAP forms phase condensates to activate its gene expression program. Notably, under hyperosmotic stress, known to activate YAP downstream signaling, YAP was observed to form nuclear and cytoplasmic phase condensates (57). These condensates contained distinct proteins contributing to both YAP's redistribution into the nucleus and its role in transcriptional control. Within the nucleus, YAP droplets were demonstrated to reorganize the genome, facilitating sustained YAP target gene expression. This research sheds light on the involvement of phase condensates in YAP-mediated transcriptional regulation, revealing new insights into the complex situation of governing gene expression in response to cellular stress.

2.05 *Targeting Heparan Sulfation*

Through a genome-wide screening in melanoma cells characterized by varying YAP1 activity levels, vulnerabilities associated with YAP1/TAZ activity were identified,

particularly in the context of MAPKi treatment (58). Of particular interest was the sulfate transporter SLC35B2, which was found to be significantly overexpressed in primary tumors and metastases compared to normal tissue, making it an appealing anti-cancer target (58). Elevated SLC35B2 expression across various cancers correlated with shorter progression-free interval (PFI), notably significant in BRAFV600E mutant melanomas, indicating its potential relevance in the context of MAPKi treatment, a standard for advanced BRAFV600 mutant melanoma.

Functioning as a sulfate transporter in the Golgi membrane critical for sulfation, SLC35B2's knockout hindered HS surface expression and limited the activity of YAP1-stimulated RTKs, including ERBB3, EGFR, and AXL. The loss of HS expression following SLC35B2 knockout led to the re-sensitization of YAP1-activated melanoma cells to MAPKis, proposing SLC35B2 as a novel approach to suppress RTK activity and overcome RTK-mediated drug resistance.

Despite the downregulation of SLC35B2 being associated with YAP1/TAZ activity, its pronounced overexpression may result from the suppression of the tumor suppressor microRNA miR-22 (58). YAP1/TAZ activation, contributing to MAPKi resistance, stimulated HS expression via overexpressed EXT1, a potential anti-cancer target. However, SLC35B2 knockout more efficiently abrogated HS expression and exhibited a more significant antiproliferative effect in the presence of Vemurafenib compared to EXT1 knockout, suggesting a higher therapeutic potential for SLC35B2. Although SLC35B2 has not been previously considered a target for anti-cancer therapies, its overexpression in tumors and non-essentiality in normal cells define a therapeutic window. While specific inhibitors for SLC35B2 are currently unavailable, the potential "druggability" based on the broader SLC family of transporters indicates promising avenues for future exploration.

The study further highlights the positive correlation between YAP1/TAZ activity and resistance to MAPKis in melanoma cell lines, independent of additional genetic aberrations (58). The MITFlow/AXLhigh phenotype, associated with increased YAP1/TAZ activity and MAPKi resistance, may be a biomarker for identifying melanomas responsive to co-treatments targeting the MAPK pathway and heparan sulfation. In conclusion, the research introduces SLC35B2 as a potential therapeutic target to overcome compensatory pathway activation and underscores the significance of the MITFlow/AXLhigh phenotype in guiding treatment strategies for RTK-driven resistant melanomas.

2.06 *Metabolic Reprogramming*

In gastric cancers, elevated YAP mRNA and protein expression levels are associated with metastases and malignant behavior, indicating a poor prognosis for patients (59). While the mechanical regulation of YAP by nuclear-cytoplasmic shuttling is recognized, some studies have further explored the role of mechanical cues in the regulation of YAP mRNA transcription. Jiang et al. observed epigenetic reprogramming that ensured transcriptional regulation of YAP in response

to increased matrix stiffness (59). Promoter hypomethylation of YAP1 is reversed upon *in situ* matrix softening in a time-dependent and memory-operable manner, accompanied by an immediate phenotypic conversion of tumor cells. The results of this study align with recent findings on mechanosensitive responses involving epigenetic changes, including DNA methylation, histone modification, and chromatin remodeling, resulting in heritable changes in gene expression. Promoter hypomethylation, a critical factor in cancer through the transcriptional activation of oncogenes, is highlighted in the context of tissue stiffness as a crucial epigenetic regulator of tumorigenesis.

The investigation also explores the effects of DNA methylation inhibitors on mechanosensitive YAP activation. Transcriptional silencing of YAP affected protein expression levels of DNA methylation inhibitors (GRHL2, TET2, and KMT2A) in the stiff matrix. Depletion of these inhibitors led to changes in YAP expression, cellular localization, and promoter methylation. The study proposes a positive feedback loop between YAP activation and epigenetic alteration in response to matrix stiffness, providing insights into potential mechanotherapeutic strategies for targeting ECM-mediated tumor progression. The reversible nature of DNA methylation makes it a promising target for therapeutic interventions in cancer. While speculative, it may be possible that direct collagen depletion may act as a YAP1 inhibitor. Given that fibrillar collagen significantly contributes to elevated extracellular matrix (ECM) stiffness, the targeted removal of collagen through recombinant collagenase may be a potential avenue for cancer therapeutics. Moreover, there have been developments in inhibitors targeting Hsp47, LOX, LOXL2, LOXL3, integrin, Piezo1, TRPV4, ILK, YAP/TAZ, and TEAD. Many of these inhibitors which work similarly to collagen depletion have demonstrated anticancer activities in preclinical studies. Thus it would be intriguing to investigate whether preemptive collagen administration could reduce the risk of cancer development in individuals exhibiting either a gain of function of YAP1 or an overexpression of plasma YAP1.

3. Conclusion

YAP1, through its transcriptional regulatory activity, influences various cellular processes within the tumor microenvironment, such as cell proliferation, apoptosis, invasion, and extracellular matrix remodeling. Additionally, YAP1 can modulate immune responses, angiogenesis, and the secretion of various cytokines and growth contributors in the tumor microenvironment. These multifaceted effects collectively contribute to promoting tumor progression, metastasis, and evasion of immune surveillance, thus enhancing the overall aggressiveness of cancer cells.

The connection between YAP1 and the IL-6 pathway in the context of cancer and the tumor microenvironment has shown that YAP1 can regulate the expression of IL-6 and IL-6R, and *vice versa*, IL-6 stimulation can activate YAP1 signaling. This reciprocal crosstalk between YAP1 and the IL-6 pathway creates a positive feedback loop, leading to enhanced YAP1

activity and IL-6 production in the tumor microenvironment. Hence, the upregulation of these signals leads to tumor expansion and immune evasion. Furthermore, the concurrent signals that YAP1 sends to MDSCs lead to the downregulation of CD8+ T-cells which are crucial for the attack on the TME. The association of YAP1 with the M2 macrophage phenotype further inhibits the immune system's ability to counteract cancer proliferation.

Thus, the inhibition of YAP1 expression using using approved drugs, combinatorial treatment, or genetically, has promising therapeutic potential for controlling cancer growth and improving patient outcomes. The attenuation of YAP1 opens up avenues for personalized treatment since different cancer types may exhibit distinct responses to YAP1 modulation, calling for a tailored approach to treatment.

Importantly, the potential of YAP1 attenuation as a therapeutic approach has been demonstrated in preclinical studies. The inhibition of YAP1 activity has consistently resulted in reduced cancer cell proliferation and induction of apoptosis. Although more research is needed to determine the proper implications of YAP1 modulation in human cells, current studies have found that the use of Verteporfin, AZD2858 and varlitinib, or combinatorial treatment decreases the risk of cancer proliferation and downregulates immunosuppression in cancer cells.

YAP1's pivotal role in cancer proliferation positions it as an attractive therapeutic target with the potential to significantly impact cancer treatment strategies. By further elucidating the mechanisms underlying YAP1-mediated tumorigenesis and addressing the challenges in developing effective therapies, we can pave the way for novel and more personalized approaches to combat cancer and improve patient outcomes. Continued research in this field holds promise for the future, bringing us closer to realizing the full potential of YAP1 modulation as a viable anticancer strategy.

Acknowledgment

I sincerely thank my mentors Pritam Sadhukhan and Mohammad Obaidul Hoque for their guidance and assistance throughout the research and editing process of this review.

Abbreviations

ADCY1 - Adenylate Cyclase 1, AJCC - American Joint Committee on Cancer, APC - Adenomatous Polyposis Coli, AREG – Amphiregulin, Arg-1 – Arginase-1, BRD4 - Bromodomain-containing Protein 4, CC - Cervical cancer, CD206 - Cluster of Differentiation 206, CD44 - Cluster of Differentiation 44, CCAR1 - Cell division cycle and apoptosis regulator 1, ChIP-qPCR - Chromatin Immunoprecipitation coupled with quantitative Polymerase Chain Reaction, COL-2A – Collagen-2A, CTCF - CTC-Binding Factor, CTGF - Connective Tissue Growth Factor, CYR61 - Cysteine-rich 61, CYR61 - Cysteine-rich Angiogenic Inducer 61, DFS - Disease-Free Survival, DNA - Deoxyribonucleic Acid, DRP1 - Dynamin-Related Protein 1, ECM - Extracellular matrix, ELISA - Enzyme-Linked Immunosorbent Assay, EMT - Epithelial-Mesenchymal Transition, ESC - Embryonic Stem Cell, F13A1 - Coagulation Factor XIII A

Chain, FGF1 - Fibroblast Growth Factor 1, FOXP3 - Forkhead Box P3, FOXM1 - Forkhead Box M1, FUCA1 - Alpha-L-Fucosidase 1, GEPIA - Gene Expression Profiling Interactive Analysis, GST - Glutathione S-Transferase, HLA-E - Human Leukocyte Antigen E, IDD - Intervertebral Disc Degeneration, IFN-γ – Interferon-gamma, IL-4 – Interleukin-4, IL-6 – Interleukin-6, IL-10 – Interleukin-10, IL-13 – Interleukin-13, KIF1BP - Kinesin family member 1 binding protein, LATS1/2 - Large Tumor Suppressor Kinases 1 and 2, LEFTY - Left-Right Determination Factor, LOH - Loss of Heterozygosity, MAPKi - Mitogen-activated protein kinase inhibitor, MDSCs - Myeloid-Derived Suppressor Cells, MERKT - Mer Tyrosine Kinase, MST1/2 - Mammalian Sterile 20-like Kinases 1 and 2, MSLN – Mesothelin, miR-181a – microRNA-181a, m5C – 5-Methylcytosine, MSLN – Mesothelin, MyHC - Myosin heavy chain, MyoD - Myogenic Differentiation 1, MyoG – Myogenin, NICD - Notch Intracellular Domain, NK cells - Natural Killer cells, NMF - Non-negative Matrix Factorization, NODAL - Nodal Growth Differentiation Factor, NP - Nucleus Pulposus, OCT4 - Octamer-Binding Transcription Factor 4, OS - Overall Survival, PAAD - Pancreatic Ductal Adenocarcinoma, PD-L1 - Programmed Death Ligand 1, PDZ - PSD95/Discs Large/ZO-1, RUFY2 - RUN and FYVE domain-containing protein 2, RB1 - Retinoblastoma Protein, RHAMM - Receptor for Hyaluronic Acid-Mediated Motility, RT-qPCR - Reverse Transcription Quantitative Polymerase Chain Reaction, SA-β-Gal - Senescence-Associated Beta-Galactosidase, SCML2 - Sex Comb on Midleg-Like 2, SDCBP - Syndecan Binding Protein, SLC25A16 - Solute carrier family 25 member 16, SLC35B2 - Solute carrier family 35 member B2, SMSCs - Skeletal muscle satellite cells, Smad - Small Mothers Against Decapentaplegic, SCLC - Small Cell Lung Cancer, STAT3 - Signal Transducer and Activator of Transcription 3, STOX1 - Storkhead box 1, SWI/SNF - Switch/Sucrose Non-Fermentable, TAP2 - Transporter Associated with Antigen Processing 2, TCF/LEF - T-cell Factor/Lymphoid Enhancer Factor, TCGA - The Cancer Genome Atlas, TEAD - TEA Domain Transcription Factor, TET1 - Ten-Eleven Translocation 1, THBS1 - Thrombospondin 1, TIMER - Tumor Immune Estimation Resource, TGF-β - Transforming Growth Factor-beta, TNM – Tumor-Node-Metastasis, VSIG4 - V-set and Immunoglobulin domain containing 4, WNT – Wingless/Integrated, YAP1 - Yes-Associated Protein 1

4. References

1. Ahmad, F.B., Anderson, R.N. (2021). The Leading Causes of Death in the US for 2020. JAMA, 325(18), 1829–1830. https://doi.org/10.1001/jama.2021.5469

2. Lee, E.Y., Muller, W.J. (2010). Oncogenes and tumor suppressor genes. Cold Spring Harbor perspectives in biology, 2(10), a003236. https://doi.org/10.1101/cshperspect.a003236

3. Jiang, X., Wang, J., Deng, X., Xiong, F., Zhang, S., Gong, Z., et al. (2020). The role of microenvironment in tumor angiogenesis. J Exp Clin Cancer Res 39. https://doi.org/10.1186/s13046-020-01709-5

4. Watnick, R.S. (2012). The role of the tumor microenvironment in regulating tumor angiogenesis. Cold Spring Harbor Perspectives in Medicine, a006676. https://doi.org/10.1101/cshperspect.a006676

5. Shibata, M., Ham, K., Hoque, M.O. (2018). A time for YAP1: Tumorigenesis, immunosuppression, and targeted therapy. International journal of cancer, 143(9), 2133–2144. https://doi.org/10.1002/ijc.31561

6. Szulzewsky, F., Holland, E.C., Vasioukhin, V. (2021). YAP1 and its fusion proteins in cancer initiation, progression, and therapeutic resistance, Developmental Biology, Volume 475, 2021, Pages 205-221, ISSN 0012-1606, https://doi.org/10.1016/j.ydbio.2020.12.018

7. Sun, K., Zhang, X., Liu, X.,Lu, P. (2021). YAP1 is a prognostic biomarker and is correlated with immune cell infiltration in pancreatic cancer. Frontiers in Molecular Biosciences, 8. https://doi.org/10.3389/fmolb.2021.625731

8. Zhou, T.Y., Zhou, Y.L., Qian, M.J., Fang, Y.Z., Ye, S., Xin, W.X., Yang, X.C. et al. (2018). Interleukin-6 induced by YAP in hepatocellular carcinoma cells recruits tumor-associated macrophages. Journal of Pharmacological Sciences, 138(2), 89–95. https://doi.org/10.1016/j.jphs.2018.07.013

9. Baek, S.W., Mun, J.Y., Jang, I.H., Yang, G.E., Jeong, M.S., Kim, S.K., et al. (2022). YAP1 activation is associated with the progression and response to immunotherapy of non-muscle invasive bladder cancer. EBioMedicine, 81, 104092. https://doi.org/10.1016/j.ebiom.2022.104092

10. Spranger, S., Gajewski, T.F. (2018). Mechanisms of tumor cell–intrinsic immune evasion. *Annual Review of Cancer Biology*, *2*(1), 213–228. https://doi.org/10.1146/annurev-cancerbio-030617-050606

11. Luo, J., Deng, L., Zou, H. Guo, Y., Tong, T., Huang, M., et al. (2023). New insights into the ambivalent role of YAP/TAZ in human cancers. J Exp Clin Cancer Res 42, 130. https://doi.org/10.1186/s13046-023-02704-2

12. Badouel, C., McNeill, H. (2011). SnapShot: The hippo signaling pathway. Cell, 145(3), 484–484.e1. https://doi.org/10.1016/j.cell.2011.04.009

13. Werneburg, N., Gores, G.J., Smoot, R.L. (2020). The Hippo Pathway and YAP Signaling: Emerging Concepts in Regulation, Signaling, and Experimental Targeting Strategies With Implications for Hepatobiliary Malignancies. Gene expression, 20(1), 67–74. https://doi.org/10.3727/105221619X15617324583639

14. Yuan, Y., Park, J., Feng, A., Awasthi, P., Wang, Z., Chen, Q., et al. (2020). YAP1/TAZ-TEAD transcriptional networks maintain skin homeostasis by regulating cell proliferation and limiting KLF4 activity. Nat. Commun. 11, 1472. https://doi.org/10.1038/s41467-020-15301-0

15. Malumbres, M. (2014). Cyclin-dependent kinases. Genome Biol 15, 122. https://doi.org/10.1186/gb4184

16. Ding, L., Cao, J., Lin, W., Chen, H., Xiong, X., Ao, H., et al. (2020). The Roles of Cyclin-Dependent Kinases in Cell-Cycle Progression and Therapeutic Strategies in Human Breast Cancer. International journal of molecular sciences, 21(6), 1960. https://doi.org/10.3390/ijms21061960

17. Kalluri, R., Weinberg, R.A. (2009). The basics of epithelial-mesenchymal transition. The Journal of Clinical Investigation, 119(6), 1420–1428. https://doi.org/10.1172/JCI39104

18. Zhang, X., Abdelrahman, A., Vollmar, B., Zechner, D. (2018). The Ambivalent Function of YAP in Apoptosis and Cancer. International journal of molecular sciences, 19(12), 3770. https://doi.org/10.3390/ijms19123770

19. Raj, N., Bam, R. (2019). Reciprocal crosstalk between yap1/hippo pathway and the p53 family proteins: Mechanisms and outcomes in cancer. *Frontiers in Cell and Developmental Biology*, *7*. https://doi.org/10.3389/fcell.2019.00159

20. Wu, Y., Yi, M., Niu, M., Mei, Q., Wu, K. (2022). Myeloid-derived suppressor cells: an emerging target for anticancer immunotherapy. Mol Cancer 21, 184. https://doi.org/10.1186/s12943-022-01657-y

21. Wang, G., Lu, X., Dey, P., Deng, P., Wu, C. C., Jiang, S. et al. (2016). Targeting YAP-Dependent MDSC Infiltration Impairs Tumor Progression. Cancer Discovery, 6(1), 80–95. https://doi.org/10.1158/2159-8290.CD-15-0224

22. Lesokhin, A.M., Merghoub, T., Wolchok, J.D. (2013). Myeloid-derived suppressor cells and the efficacy of CD8+ T-cell immunotherapy. Oncoimmunology, 2(2), e22764. https://doi.org/10.4161/onci.22764

23. Gao, J., Liang, Y., Wang, L. (2022). Shaping polarization of tumor-associated macrophages in cancer immunotherapy. Frontiers in Immunology, 13. https://doi.org/10.3389/fimmu.2022.888713

24. Yang, W., Yang, S., Zhang, F., Cheng, F., Wang, X., Rao, J. (2020). Influence of the Hippo-YAP signaling pathway on tumor-associated macrophages (TAMs) and its implications on cancer immunosuppressive microenvironment. Annals of translational medicine, 8(6), 399. https://doi.org/10.21037/atm.2020.02.11

25. Luo, J., Deng, L., Zou, H. et al. (2023). New insights into the ambivalent role of YAP/TAZ in human cancers. J Exp Clin Cancer Res 42, 130. https://doi.org/10.1186/s13046-023-02704-2

26. Sun, K., Zhang, X.D., Liu, X.Y., Lu, P. (2021). YAP1 is a Prognostic Biomarker Correlated with Immune Cell Infiltration in Pancreatic Cancer. Frontiers in molecular biosciences, 8, 625731. https://doi.org/10.3389/fmolb.2021.625731

27. Ling, C., Xie-Wan, C., Ling, F., Chun-Li, J., Yong-Xin, Y., Xing-Yun, L., Jian-Guo, S. (2023). "YAP1 as a Novel Negative Biomarker of Immune Checkpoint Inhibitors for EGFR-Mutant Non-Small-Cell Lung Cancer", Canadian Respiratory Journal, vol. 2023, Article ID 4689004, 14 pages.. https://doi.org/10.1155/2023/4689004

28. Ramadan, R., Elkarmouty, A. Elnaggar, M. (2019). Aberrant methylation of yes-associated protein (YAP1) as a potential biomarker in breast cancer. Egypt J Med Hum Genet 20, 24. https://doi.org/10.1186/s43042-019-0038-x

29. Kong, L., Xie, Y.S., Ma, X.D. Huang, Y., Shang, X.F. (2023). Mechanism of YAP1 in the senescence and degeneration of endplate chondrocytes induced by intermittent cyclic mechanical tension. J Orthop Surg Res 18, 229. https://doi.org/10.1186/s13018-023-03704-w

30. Kashihara, T., Mukai, R., Oka, S.I., Zhai, P., Nakada, Y., Yang, Z., et al. (2022). YAP mediates compensatory cardiac hypertrophy through aerobic glycolysis in response to pressure overload. The Journal of Clinical Investigation, 132(6), e150595. https://doi.org/10.1172/JCI150595

31. Chen, P., Sun, C., Wang, H., Zhao, W., Wu, Y., Guo, H. (2023). YAP1 expression is associated with survival and immunosuppression in small-cell lung cancer. Cell Death Dis 14, 636. https://doi.org/10.1038/s41419-023-06053-y

32. Owonikoko, T. K., Dwivedi, B., Chen, Z., Zhang, C., Barwick, B., Ernani, V., et al. (2021). YAP1 Expression in SCLC Defines a Distinct Subtype With T-cell-Inflamed Phenotype. Journal of Thoracic Oncology: official publication of the International Association for the Study of Lung Cancer, 16(3), 464–476. https://doi.org/10.1016/j.jtho.2020.11.006

33. Huang, B., Lang, X., Li, X. (2022). The role of IL-6/JAK2/STAT3 signaling pathway in cancers. Frontiers in oncology, 12, 1023177. https://doi.org/10.3389/fonc.2022.1023177

34. Johnson, D.E., O'Keefe, R.A., Grandis, J.R. (2018). Targeting the IL-6/JAK/STAT3 signaling axis in cancer. Nature reviews. Clinical oncology, 15(4), 234–248. https://doi.org/10.1038/nrclinonc.2018.8

35. Cunningham, R., Hansen, C.G. (2022). The Hippo pathway in cancer: YAP/TAZ and TEAD as therapeutic targets in cancer. Clinical science (London, England: 1979), 136(3), 197–222. https://doi.org/10.1042/CS20201474

36. Yuan, Y., Parra, N.S., Chen, Q., Iglesias-Bartolome, R. (2020). Yap1-Taz/TEAD Transcriptional Networks Restrain Differentiation Downstream of Oncogenic Hedgehog-Smo Activity. https://doi.org/10.1101/2020.12.28.424593

37. Deng, F., Peng, L., Li, Z. Tan, G., Liang, E., Chen, S., et al. (2018). YAP triggers the Wnt/β-catenin signaling pathway and promotes enterocyte self-renewal, regeneration, and tumorigenesis after DSS-induced injury. Cell Death Dis 9, 153. https://doi.org/10.1038/s41419-017-0244-

38. Komiya, Y., Habas, R. (2008). Wnt signal transduction pathways. Organogenesis, 4(2), 68–75. https://doi.org/10.4161/org.4.2.5851

39. Kopan R. (2012). Notch signaling. Cold Spring Harbor perspectives in biology, 4(10), a011213. https://doi.org/10.1101/cshperspect.a011213

40. Lobry, C., Oh, P., Mansour, M.R., Look, A.T., Aifantis, I. (2014). Notch signaling: Switching an oncogene to a tumor suppressor. Blood, 123(16), 2451–2459. https://doi.org/10.1182/blood-2013-08-355818

41. Aster, J.C., Pear, W.S., Blacklow, S.C. (2017). The Varied Roles of Notch in Cancer. Annual review of pathology, 12, 245–275. https://doi.org/10.1146/annurev-pathol-052016-100127

42. Tzavlaki, K., Moustakas, A. (2020). TGF-β Signaling. Biomolecules, 10(3), 487. https://doi.org/10.3390/biom10030487

43. Qin, Z., Xia, W., Fisher, G.J., Voorhees, J.J., Quan, T. (2018). YAP/TAZ regulates TGF-β/Smad3 signaling by induction of Smad7 via AP-1 in human skin dermal fibroblasts. Cell Commun Signal 16, 18. https://doi.org/10.1186/s12964-018-0232-3

44. Maity, S., Gridnev, A., Misra, J.R. (2022). Assays Used for Discovering Small Molecule Inhibitors of YAP Activity in Cancers. Cancers, 14(4), 1029. https://doi.org/10.3390/cancers14041029

45. Thrash, H.L., Pendergast, A.M. (2023). "Multi-Functional Regulation by YAP/TAZ Signaling Networks in Tumor Progression and Metastasis" Cancers 15, no. 19: 4701. https://doi.org/10.3390/cancers15194701

46. Hu, X., Wu, X., Berry, K., Zhao, C., Xin, D., Ogurek, S., et al. (2023). Nuclear condensates of YAP fusion proteins alter transcription to drive ependymoma tumourigenesis. Nature Cell Biology, 25(2), 323–336. https://doi.org/10.1038/s41556-022-01069-6

47. Cai, D., Feliciano, D., Dong, P., Flores, E., Gruebele, M., Porat-Shliom, N., et al. (2019). Phase separation of YAP reorganizes genome topology for long-term YAP target gene expression. Nature cell biology, 21(12), 1578–1589. https://doi.org/10.1038/s41556-019-0433-z

48. Lopez-Hernandez, A., Silvia S., and Stefano, C. (2021). "Emerging Principles in the Transcriptional Control by YAP and TAZ" Cancers 13, no. 16: 4242. https://doi.org/10.3390/cancers13164242

49. Heng, B.C., Zhang, X., Aubel, D., Bai, Y., Li, X., Wei, Y., Fussenegger, M., Deng, X. (2020). Role of YAP/TAZ in Cell Lineage Fate Determination and Related Signaling Pathways. Frontiers in cell and developmental biology, 8, 735. https://doi.org/10.3389/fcell.2020.00735

50. Wu, B.K., Mei, S.C., Chen, E.H., Zheng, Y., Pan, D. (2022). YAP induces an oncogenic transcriptional program through TET1-mediated epigenetic remodeling in liver growth and tumorigenesis. Nature Genetics, 54(8), 1202–1213. https://doi.org/10.1038/s41588-022-01119-7

51. Wei, L., Ma, X., Hou, Y., Zhao, T., Sun, R., Qiu, C., et al. (2023). Verteporfin reverses progestin resistance through the YAP/TAZ-PI3K-Akt pathway in endometrial carcinoma. Cell Death Discov. 9, 30. https://doi.org/10.1038/s41420-023-01319-y

52. Feng, J., Gou, J., Jia, J., Yi, T., Cui, T., Li, Z. (2016). Verteporfin, a suppressor of the YAP-TEAD complex, presents promising antitumor properties on ovarian cancer. OncoTargets and therapy, 9, 5371–5381. https://doi.org/10.2147/OTT.S109979\

53. O'Brien, J., Hayder, H., Zayed, Y., Peng, C. (2018). Overview of microRNA biogenesis, mechanisms of actions, and circulation. Frontiers in Endocrinology, 9. https://doi.org/10.3389/fendo.2018.00402

54. Chen, X., Cao, R., Liu, H., Zhang, T., Yuan, X., Xu, S. (2020). MicroRNA-15a-5p-targeting oncogene YAP1 inhibits cell viability and induces cell apoptosis in cervical cancer cells Retraction in /10.3892/ijmm.2024.5348. International Journal of Molecular Medicine, 46, 1301-1310. https://doi.org/10.3892/ijmm.2020.4704

55. Liu, H., Liu, Y., Bian, Z. Zhang, J., Zhang, R., Chen, X., et al. (2018). Circular RNA YAP1 inhibits the proliferation and invasion of gastric cancer cells by regulating the miR-367-5p/p27 Kip1 axis. Mol Cancer 17, 151. https://doi.org/10.1186/s12943-018-0902-1

56. Barry, E.R., Simov, V., Valtingojer, I., Venier, O. (2021). Recent Therapeutic Approaches to Modulate the Hippo Pathway in Oncology and Regenerative Medicine. Cells, 10(10), 2715. https://doi.org/10.3390/cells10102715

57. Cai, D., Feliciano, D., Dong, P., Flores, E., Gruebele, M., Porat-Shliom, N., et al. (2019). Phase separation of YAP reorganizes genome topology for long-term YAP target gene expression. Nature cell biology, 21(12), 1578–1589. https://doi.org/10.1038/s41556-019-0433-z

58. Dieter, S.M., Lovecchio, D., Pataskar, A. Zowada, M.K., Korner, P.R., Khalizieva, A., et al. (2022). Suppression of heparan sulfation re-sensitizes YAP1-driven melanoma to MAPK pathway inhibitors. Oncogene 41, 3953–3968. https://doi.org/10.1038/s41388-022-02400-z

59. Jiang, Y., Zhang, H., Wang, J., Liu, Y., Luo, T., Hua, H. (2022). Targeting extracellular matrix stiffness and mechanotransducers to improve cancer therapy. J Hematol Oncol 15, 34. https://doi.org/10.1186/s13045-022-01252-0