

Review

Psychological stress-driven modulation of YAP1 signaling: Mechanistic pathways linking stress biology to tumor progression

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Abstract: Psychological distress is increasingly recognized as a biologically active contributor to cancer progression, and emerging evidence identifies yes-associated protein 1 (YAP1) as a central molecular node through which stress-related signaling influences tumor behavior. As a mechanosensitive transcriptional co-activator within the Hippo pathway, YAP1 integrates neuroendocrine, inflammatory, oxidative, and metabolic cues that become dysregulated under chronic stress, including cortisol elevation, sympathetic activation, pro-inflammatory cytokines, and reactive oxygen species. These stress-induced factors converge on Hippo-dependent and non-canonical regulators such as PI3K–AKT, Ras–MAPK, and integrin–FAK–RhoA, promoting YAP1 dephosphorylation, nuclear translocation, and oncogenic transcriptional activation. Enhanced YAP1 signaling drives proliferation, survival, metabolic rewiring, EMT, metastasis, immune evasion, and resistance to chemotherapy and immunotherapy, while also contributing to pain sensitization and inflammatory cascades. Together, these mechanisms suggest that YAP1 functions as a molecular bridge linking psychological stress with tumor progression, shaping both biological vulnerability and treatment responsiveness. Understanding how psychobiological stress modulates YAP1 opens opportunities for integrative strategies combining pharmacologic YAP1 targeting with psychological interventions that normalize cortisol rhythms, reduce inflammation, and restore autonomic balance, offering a novel framework for stress-responsive precision psycho-oncology

Keywords: Hippo pathway, Mechanotransduction, Psychological stress, Psycho-oncology, Stress biology, Tumor progression, YAP1 signaling

1. Introduction

Yes-associated protein 1 (YAP1) functions as a central transcriptional co-activator within the Hippo signaling pathway, significantly influencing cell proliferation, apoptosis, mechanotransduction, stemness, and tissue repair [1–3]. YAP1's activity is meticulously regulated by phosphorylation events, primarily mediated by MST1/2 and LATS1/2 kinases. When phosphorylated, YAP1 sequesters in the cytoplasm by binding to 14-3-3 proteins, thereby inhibiting its transcriptional activity. Conversely, when the Hippo pathway is inhibited, YAP1 undergoes dephosphorylation and translocates into the nucleus, where it forms a transcriptional complex with TEAD factors to activate proliferative and pro-survival genes such as CTGF and CYR61[1,3–5].

Substantial evidence indicates that dysregulated YAP1 activity is a key contributor to oncogenesis across a wide range of solid tumors. Aberrant nuclear localization of YAP1 fosters epithelial–mesenchymal transition (EMT), enhances metastatic dissemination, promotes immune evasion, and fortifies resistance to

targeted therapies, chemotherapy, and immunotherapy [3,6–8]. Clinically, elevated YAP1 expression correlates with more aggressive tumor phenotypes, shorter progression-free survival, and poor overall prognosis in lung, breast, gastric, pancreatic, and hepatic malignancies [6,9–12].

Parallel to these molecular findings, psychological distress encompassing anxiety, depression, and cancer-related fears is prevalent among individuals with malignancies and is recognized as a biological driver of disease progression [13]. Chronic psychological stress activates multiple physiological systems, including hypothalamic–pituitary–adrenal axis dysregulation, sympathetic–adrenal medullary activation with elevated catecholamines, increased production of inflammatory cytokines such as IL-6 and TNF- α , enhanced oxidative stress driven by reactive oxygen species (ROS), and persistent activation of stress-responsive mitogen-activated protein kinases (MAPKs) such as p38, JNK, and ERK [14–17]. These psychobiological pathways profoundly influence tumor growth, immune surveillance, angiogenesis, metastasis, and patient survival [18].

The positioning of YAP1 at the interface of these stress-responsive networks is particularly notable. As a mechanosensitive and inflammation-responsive co-activator, YAP1 integrates mechanical signals, inflammatory cues, oxidative stress, and metabolic alterations all biological facets dysregulated during prolonged psychological distress. Increased glucocorticoids and ROS disrupt Hippo-mediated inhibition of YAP1 phosphorylation, promoting its nuclear activation and subsequent enhancement of EMT and metastatic behavior [19,20]. Moreover, YAP1 contributes to cancer pain via interactions with TRPV1 channels and IL-1 β /NLRP3 inflammasome signaling pathways strongly influenced by emotional distress and chronic stress [19,21]. These intersections suggest that YAP1 serves not only as a molecular driver of tumor biology but also as a potential mediator of oncogenic effects arising from psychological stress.

Given these multifaceted interactions, the present review synthesizes emerging evidence linking psychological stress to YAP1 dysregulation and associated oncogenic pathways. It examines YAP1 as a stress-responsive molecular indicator of psychophysiological burden and explores pharmacologic, molecular, and psychobiological strategies designed to modulate YAP1 activity. By integrating mechanistic oncology with psychoneuroendocrinology, this review proposes a novel conceptual framework aimed at advancing YAP1-informed, stress-sensitive therapeutic strategies in psycho-oncology.

2. Psychological stress and cancer biology

Psychological stress triggers a cascade of interconnected physiological responses that transcend emotional challenges and profoundly affect cancer biology. Activation of primary psychobiological systems collectively shapes the tumor microenvironment and influences cancer progression. The hypothalamic–pituitary–adrenal (HPA) axis becomes highly responsive under chronic stress, resulting in cortisol dysregulation and disrupted glucocorticoid signaling, which impairs immune homeostasis, metabolic regulation, and cell survival pathways [13,22]. Concurrently, psychological stress stimulates sympathetic nervous system (SNS) activation, increasing norepinephrine

and epinephrine release, which engage β -adrenergic receptors on tumor and stromal cells to promote inflammatory signaling, angiogenesis, and metastatic behavior [14,16,17].

Stress further fosters chronic low-grade inflammation, evidenced by elevated IL-6, TNF- α , and C-reactive protein (CRP). These cytokines remodel the immune landscape to support tumorigenesis, promote fibrosis, and amplify metastatic potential [7,23,24]. Additionally, stress elevates oxidative and nitrosative stress through increased reactive oxygen species (ROS) and reactive nitrogen species (RNS), contributing to mitochondrial dysfunction, DNA damage, and redox-sensitive activation of oncogenic cascades [25–27]. Stress-induced activation of MAPKs including p38, JNK, and ERK directly influences cellular proliferation, apoptosis resistance, and adaptation to adverse microenvironments [16,28,29].

Collectively, these alterations create a tumor microenvironment marked by amplified proliferative signaling, enhanced angiogenesis, invasion, and epithelial–mesenchymal transition (EMT), a critical driver of metastasis [7,30]. Immune dysregulation is similarly pronounced; stress promotes immunosuppressive phenotypes such as M2 macrophage polarization and T-cell exhaustion, weakening anti-tumor immunity [31,32]. Metabolic reprogramming under stress shifts cancer cells toward glycolysis and altered oxidative phosphorylation (OXPHOS), supporting tumor survival and growth in hostile environments [33,34]. Clinically, these systemic alterations correlate with cancer-related fatigue, heightened pain sensitivity, and diminished patient functioning under psychological distress [21].

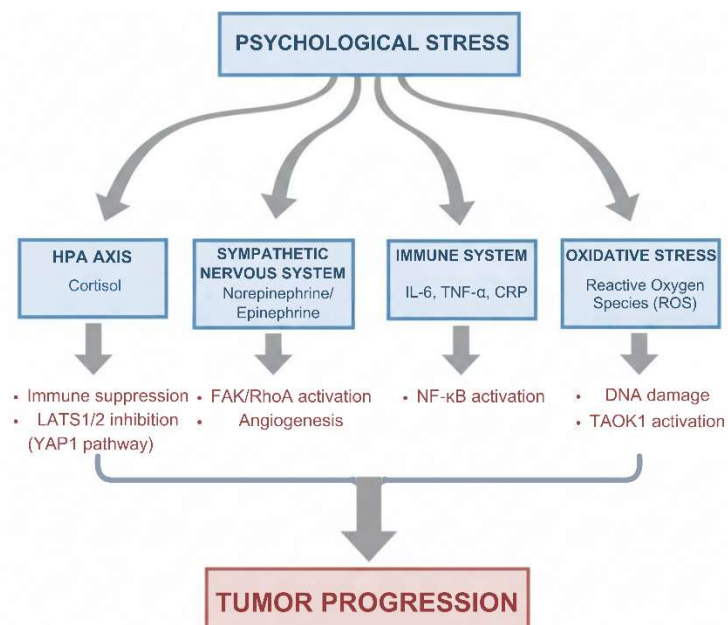


Figure 1. Psychobiological stress and YAP1 pathways relevant to tumour progression.

Notably, these psychobiological pathways converge with molecular regulatory networks that govern YAP1 activity. Endocrine mediators including glucocorticoids, catecholamines, inflammatory cytokines, oxidative stress mediators, and MAPK cascades intersect with Hippo, PI3K–AKT, Ras– MAPK, and integrin–FAK–RhoA

pathways that regulate YAP1 phosphorylation, nuclear translocation, and transcriptional output [20,35–37]. This shared regulatory architecture underscores psychological stress as a potent upstream biochemical driver influencing YAP1 oncogenic potential and therapeutic resistance. Accordingly, YAP1 emerges as a crucial molecular bridge linking emotional distress to tumor progression, metastasis, and treatment outcomes. Psychobiological stress and the YAP1 pathway are associated with tumor progression as shown in **Figure 1**.

3. Overview of YAP1 protein

3.1. Structure and function of YAP1

Yes-associated protein 1 (YAP1) is a modular transcriptional co-activator whose structural architecture enables the integration of diverse biochemical and mechanical cues. The N-terminal TEAD-binding domain facilitates formation of the YAP1–TEAD transcriptional complex, which drives transcriptional programs governing proliferation, survival, and extracellular matrix (ECM) remodeling [38]. This interaction is regulated by essential phosphorylation sites particularly Ser127 and Ser381 located in the C-terminal region. Phosphorylation promotes 14-3-3 binding and cytoplasmic sequestration, whereas dephosphorylation promotes nuclear entry and transcriptional activation [39]. YAP1 also operates as a scaffold via WW domains that bind PPxY-containing partners, integrating cytoskeletal dynamics, mechanotransduction, and inflammatory signaling [40].

Physiologically, YAP1 is indispensable for tissue homeostasis, orchestrating cell-cycle progression, stemness maintenance, anti-apoptotic signaling, and organ regeneration [41]. During embryogenesis, YAP1 directs cardiac and hepatic development, and in adult tissues it mediates reparative responses following injury [42]. Its ability to integrate mechanical tension, oxidative stress, inflammatory cytokines, and metabolic cues positions YAP1 as an exceptionally sensitive environmental sensor. In psycho-oncology, this responsiveness suggests that YAP1 may mediate how chronic psychological stress influences tumor growth and microenvironmental adaptation [37].

3.2. Canonical and non-canonical regulation of YAP1

Canonical YAP1 regulation is dominated by the Hippo signaling pathway. The MST1/2–LATS1/2 kinase cascade phosphorylates YAP1, enforcing its cytoplasmic retention through 14-3-3 binding and suppressing TEAD-dependent transcription [43]. Hippo pathway inactivation permits nuclear accumulation of YAP1, enabling transcription of CTGF, CYR61, and other effectors that promote proliferation, migration, and ECM remodeling [44].

YAP1 is also regulated through non-canonical pathways. PI3K–AKT activation modulates YAP1 phosphorylation and enhances nuclear localization [45]. Ras–MAPK signaling including ERK, JNK, and p38 also influences YAP1’s transcriptional activity during inflammation and oxidative stress [39]. Mechanotransduction signals ECM stiffness, cytoskeletal tension, and integrin-mediated FAK–RhoA activation can inhibit LATS1/2, favoring nuclear YAP1 accumulation in tumor and fibrotic

microenvironments [46].

These regulatory pathways exhibit profound sensitivity to psychobiological stress mediators. Cortisol, catecholamines, and inflammatory cytokines modulate Hippo, PI3K–AKT, Ras–MAPK, and FAK–RhoA activity, providing mechanistic insight into how psychological stress may fine-tune YAP1 signaling and transcriptional output [37,47].

3.3. YAP1 and cell proliferation/apoptosis

YAP1 promotes cell proliferation by activating core cell-cycle regulators. In the nucleus, YAP1 upregulates Cyclin D1, c-Myc, E2F transcription factors, and PCNA, supporting G1–S transition and enhancing DNA synthesis [48,49]. These transcriptional effects drive accelerated tumor cell expansion, particularly under mechanical stress, hypoxia, and chronic inflammation.

YAP1 also exhibits strong anti-apoptotic activity. It increases expression of Bcl-2 and Bcl-xL while suppressing Bax and Bad, contributing to cell survival [50]. YAP1 additionally antagonizes p53-dependent apoptosis and enhances adaptation to oxidative, inflammatory, and metabolic stressors in the tumor microenvironment [51,52]. This dual capacity to promote proliferation and inhibit apoptosis fundamentally contributes to oncogenesis and therapeutic resistance.

4. Mechanistic pathways linking psychological stress to YAP1 activation

Psychological stress exerts profound molecular influence by modulating biochemical systems that converge on YAP1 regulation. Glucocorticoid signaling, sympathetic–adrenergic activity, inflammatory cytokines, oxidative stress, and stress-responsive MAPKs all operate as upstream regulators of canonical and non-canonical Hippo pathways, influencing YAP1 phosphorylation, stability, and transcription. Through these mechanisms, YAP1 functions as a convergence hub that integrates environmental, metabolic, mechanical, and immunological cues [53]. This integrative capacity provides a mechanistic rationale for how chronic psychological distress can reshape tumor biology and enhance oncogenic potential.

4.1. Glucocorticoid-dependent modulation

Chronic psychological stress is associated with sustained cortisol elevation and dysregulated diurnal rhythm, exposing tissues to prolonged glucocorticoid signaling [54]. Cortisol suppresses LATS1/2 activity, decreasing inhibitory phosphorylation of YAP1 and promoting its nuclear accumulation [55], favoring transcription of proliferative and survival-related genes [56]. However, some stress and depression models demonstrate paradoxical Hippo activation with decreased nuclear YAP1, suggesting context-dependent glucocorticoid effects shaped by tissue type, microenvironmental cues, and stress chronicity [57,58]. These findings indicate that glucocorticoid dysregulation does not uniformly activate YAP1 but instead rewires signaling pathways that may support tumor adaptation under psychological stress [59].

4.2. Mechanical stress and cytoskeletal tension

A key but underrecognized pathway connecting psychological stress to YAP1 activation is adrenergic–mechanotransductive signaling. Sympathetic activation elevates circulating catecholamines, which enhance actomyosin contractility through RhoA–ROCK signaling [60]. Increased cytoskeletal tension activates focal adhesion kinase (FAK) and RhoA, inhibiting LATS1/2 and increasing nuclear YAP1 accumulation [61]. Mechanical forces within the tumor microenvironment amplify these responses, especially in stiff, collagen-rich matrices where activated fibroblasts further promote YAP1 activation [62]. YAP1-mediated mechanotransduction enhances tumor survival, invasion, and metastatic dissemination by supporting EMT and cytoskeletal remodeling [63]. From a psycho-oncology perspective, adrenergic signaling induced by psychological stress may potentiate these mechanotransductive pathways, thereby intensifying YAP1-driven oncogenic behavior.

4.3. Inflammatory cytokines and NF- κ B/MAPK crosstalk

Psychological stress promotes chronic low-grade inflammation with elevated IL-6, TNF- α , and other mediators [64]. These cytokines directly influence Hippo pathway components; IL-6 and TNF- α activate NF- κ B, which modulates MST1/2 and LATS1/2 phosphorylation, thereby altering YAP1 stability and localization [65]. Cytokine signaling further activates MAPKs including JNK and p38 that inhibit or redirect Hippo signaling, promoting nuclear YAP1 accumulation [64]. These interactions reinforce YAP1-driven stemness, proliferation, and EMT programs. Persistent psychological distress sustains inflammatory cytokine production [63], creating continuous pressure on YAP1 regulatory networks and fostering a tumor microenvironment primed for aggressive behavior [53].

4.4 Oxidative stress and TAOK1–Hippo regulation

Oxidative stress represents another critical conduit linking psychological distress to YAP1 activation. Chronic stress elevates ROS and RNS through mitochondrial dysfunction, glucocorticoid-induced metabolic changes, and cytokine-driven free radical production [53,56]. ROS activates TAOK1 and MST1/2 kinases, altering LATS1/2 phosphorylation and YAP1 localization [55]. Long-term stress also reduces Nrf2-mediated antioxidant defense, increasing oxidative load and sensitizing YAP1 to ROS-mediated activation [54]. Conversely, YAP1 promotes resistance to oxidative injury by upregulating antioxidant enzymes such as SOD and GPx [57]. This bidirectional feedback loop ROS activating YAP1, and YAP1 increasing ROS tolerance supports tumor persistence during psychological stress.

4.5 Integrated stress sensing through YAP1

YAP1 acts as an integrative sensor consolidating multiple stress-related biological inputs. Cortisol, catecholamines, IL-6, TNF- α , mechanical tension, and oxidative stress converge on Hippo and non-Hippo pathways to coordinate YAP1 activation. Under sustained psychological distress, these inputs collectively promote a YAP1-activated phenotype characterized by enhanced proliferation, metabolic adaptability, EMT, metastasis, immune evasion, and PD-L1 upregulation [56]. Through these coordinated mechanisms, YAP1 serves as a molecular interface linking

psychosocial states to oncogenic behavior, underscoring the biological relevance of mind–body interactions in cancer progression.

5. Downstream oncogenic outputs of YAP1 under psychological stress

YAP1 activation drives a broad spectrum of oncogenic programs that shape tumor aggressiveness, adaptability, and therapy resistance. These downstream transcriptional and phenotypic effects documented across multiple solid tumors are further intensified under chronic psychological stress, which amplifies many molecular pathways controlled by YAP1 [66–68]. Understanding these convergent mechanisms is essential for elucidating how stress biology worsens clinical outcomes through YAP1-dependent processes.

A principal consequence of YAP1 activation is the enhancement of cell proliferation. Nuclear YAP1 upregulates cell-cycle regulators including Cyclin D1, c-Myc, E2F, and PCNA, promoting G1–S transition and rapid tumor expansion [68]. Concurrently, YAP1 exerts strong anti-apoptotic effects by elevating Bcl-2 and Bcl-xL while suppressing pro-apoptotic mediators such as Bax and Bad [68]. Through additional suppression of p53-mediated apoptotic responses, YAP1 facilitates tumor cell survival under mechanical stress, hypoxia, inflammation, and cytotoxic therapy [69].

YAP1 is also central to the maintenance of cancer stemness an attribute linked to therapeutic resistance and tumor recurrence. The FDX1/FOXO3 axis and BCL-xL–dependent pathways mediate YAP1-driven self-renewal and sustain tumor-initiating subpopulations [68]. These YAP1-regulated stemness programs are further potentiated in microenvironments shaped by psychological stress, where cytokine-rich and metabolically altered conditions promote stem-like phenotypes [67].

YAP1 further drives metastasis by inducing epithelial–mesenchymal transition (EMT) via activation of transcription factors and ECM-remodeling genes that enhance motility, invasion, and cytoskeletal reorganization [69]. YAP1-driven EMT is synergistically amplified by inflammatory cytokines and mechanical cues both elevated during psychological stress which promote metastatic competence and pre-metastatic niche formation [70]. YAP1 also contributes to metabolic reprogramming through dynamic shifts between glycolysis and oxidative phosphorylation (OXPHOS), enabling tumor adaptation to fluctuating oxygen and nutrient availability [71]. This metabolic flexibility supports tumor survival in hypoxic, metabolically stressed microenvironments associated with chronic stress and inflammation [72].

Immune evasion represents an additional major downstream output of YAP1. By upregulating PD-L1 expression in a TEAD-dependent manner, YAP1 promotes CD8⁺ T-cell exhaustion and reduces antitumor immunity [67]. Because psychological stress induces immunosuppressive phenotypes such as M2 macrophage polarization and impaired T-cell function stress may potentiate YAP1-mediated immune escape, undermining immunotherapy responsiveness [69].

An emerging dimension of YAP1 function is its role in cancer pain sensitization. Through the IL-1 β /NLRP3–YAP1–TRPV1 axis in dorsal root ganglia, YAP1 contributes to heightened nociception and chronic inflammatory pain. This pathway is

strongly modulated by oxidative stress and cytokines both markedly elevated under psychological distress [66,68]. Thus, YAP1 may serve as a mechanistic bridge linking emotional suffering to amplified cancer-related pain.

Importantly, psychological stress amplifies many YAP1-driven oncogenic processes. Cortisol and catecholamines enhance proliferation and suppress apoptosis; IL-6 and TNF- α reinforce EMT, stemness, and immune escape; and ROS drives oxidative stress-mediated YAP1 activation [71]. Together, these stress-induced mediators synergize with YAP1 to accelerate tumor progression, exacerbate pain, and worsen treatment outcomes. This convergence highlights the need to integrate psychophysiological stress management into cancer care and positions YAP1 as a central molecular mediator of the stress–cancer axis.

6. YAP1 in cancer therapy and psychobiological modulation

The clinical significance of YAP1 extends beyond its oncogenic role; substantial evidence shows that YAP1 influences therapeutic response across chemotherapy, targeted therapy, and immunotherapy. As an integrator of mechanical, metabolic, oxidative, and inflammatory cues, YAP1 contributes to chemotherapy resistance, targeted therapy escape, and immune tolerance [73,74]. Importantly, psychological stress alters many of these same pathways, suggesting that YAP1 is a mediator through which psychobiological factors shape treatment efficacy. This section integrates pharmacologic YAP1-targeting strategies with psychosocial approaches capable of indirectly modulating YAP1 activity.

6.1. Pharmacologic YAP1 targeting

Multiple therapeutic strategies have been developed to inhibit YAP1 or disrupt its transcriptional output. One of the most established approaches is interference with the YAP1–TEAD complex. Verteporfin prevents YAP1 from binding TEAD, reducing expression of pro-survival and pro-metastatic genes [75]. Epigenetic modulators, including histone acetyltransferase inhibitors such as CPTH6, also suppress YAP1 transcription and restore chemosensitivity in resistant tumors [73].

RNA-based therapeutics represent another avenue. Nanoparticle delivery of YAP1-directed siRNA significantly reduces lung metastasis in triple-negative breast cancer models [76]. Dual-pathway inhibitors such as MT-001, targeting YAP1 and MEK signaling simultaneously, show synergistic induction of apoptosis and inhibition of proliferation [76]. Gene-manipulation tools, including CRISPR/dCas9-mediated repression, provide precise approaches for silencing YAP1-driven programs.

Clinically, YAP1 expression holds prognostic and predictive value. High YAP1 correlates with poorer survival in gastric cancer and NSCLC [77,78]. In NSCLC, YAP1 positivity predicts reduced progression-free survival in patients receiving EGFR-TKI therapy [78]. In melanoma, YAP1 inhibition synergizes with PD-1 blockade to enhance tumor regression [79]. Collectively, these findings support YAP1 as a critical therapeutic target in both conventional and immune-based therapies.

6.2. Psychological stress during treatment and impact on YAP1

Cancer diagnosis and treatment are periods of profound psychological distress.

Anxiety, fear of recurrence, treatment-related uncertainty, and depressive symptoms activate the HPA axis and sympathetic nervous system, increasing cortisol, catecholamines, IL-6, TNF- α , and oxidative stress [74]. These biomarkers often remain elevated throughout chemotherapy, radiotherapy, immunotherapy, and survivorship.

These psychobiological factors influence YAP1 regulation at multiple levels. Cortisol suppresses MST/LATS activity; cytokines modulate NF- κ B and MAPK signaling; ROS activates kinases controlling YAP1 phosphorylation; and adrenergic signaling strengthens mechanotransduction inputs [73,80]. Collectively, these effects bias YAP1 toward nuclear accumulation and transcription of pro-survival genes, contributing to the emergence of resistant clones capable of evading chemotherapy, surviving targeted therapy, and impairing immunotherapy response [81].

YAP1-driven therapy resistance manifests through:

- reduced chemotherapy-induced apoptosis,
- sustained proliferative and metabolic programs, and
- enhanced immune evasion via PD-L1 upregulation and suppression of cytotoxic T-cell activity [82].

Psychological stress amplifies these mechanisms, suggesting that psychophysiological burden may directly compromise treatment efficacy through YAP1-centered pathways.

6.3. Psychological factors modulating YAP1

Psychological interventions including cognitive behavioral therapy (CBT), mindfulness-based stress reduction, supportive-expressive group therapy, and multimodal psychosocial care have documented biological effects overlapping with YAP1 regulatory pathways. Such interventions lower cortisol, reduce IL-6 and TNF- α , attenuate sympathetic overactivation, and decrease oxidative stress, while improving neuroinflammatory and pain-related signaling [83].

These improvements generate meaningful molecular changes that restore Hippo pathway activity, increasing LATS1/2 phosphorylation, promoting cytoplasmic sequestration of YAP1, and suppressing its nuclear transcriptional output [82]. This shift decreases EMT and stemness signatures, reduces PD-L1 expression, and enhances immune responsiveness. Preclinical evidence indicates that psychological interventions may synergize with pharmacologic YAP1 inhibitors to reduce metastasis, proliferation, and tumor-initiating cell populations [83].

Collectively, these findings demonstrate that YAP1 is influenced not only by pharmacologic therapeutics but also by psychosocial interventions. Psychobiological modulation therefore represents a complementary strategy to enhance treatment responsiveness and improve outcomes in cancer patients.

7. YAP1 as a therapeutic target in psycho-oncology

Yes-associated protein 1 (YAP1) has emerged as a significant player in both oncology and psychobiology, particularly within the context of psycho-oncology. Growing evidence indicates that YAP1 is not merely an oncogenic driver but also a stress-sensitive molecular hub through which psychological factors influence tumor

behavior. YAP1 integrates neuroendocrine signals, immune responses, metabolic alterations, and oxidative stress, thereby serving as a critical junction linking psychophysiological stress with malignant progression [1,30,84]. This dual role elevates YAP1 from a conventional molecular target to a strategic therapeutic axis in psycho-oncology, where psychological conditions significantly affect oncogenic outcomes.

7.1 Conceptual role of YAP1 in integrative cancer care

The regulatory architecture of YAP1 enables it to respond to diverse environmental conditions, including stress-related biochemical signals amplified during chronic psychological distress. Glucocorticoids, catecholamines, inflammatory cytokines, ROS, and mechanical cues converge on Hippo and non-Hippo pathways that control YAP1 phosphorylation, nuclear shuttling, and transcriptional output [1,85]. YAP1 thus functions as a stress-responsive oncogenic switch, orchestrating proliferation, apoptosis resistance, metastasis, immune escape, and metabolic adaptation [30,84].

Enhanced YAP1 activation under chronic psychological stress correlates with increased oncogenic signaling, whereas improved psychological states may reduce YAP1-driven malignant behaviors [86,87].

7.2 Integrated therapeutic strategy: Combining pharmacologic and psychobiological approaches

Effective cancer care requires integrative strategies targeting both YAP1-driven oncogenesis and the psychological stressors that potentiate YAP1 activity. Pharmacologic inhibitors including YAP–TEAD disruptors, RNA-based silencing tools, and CRISPR/dCas9-mediated repression provide direct suppression of YAP1 output [87,88]. However, persistent stress-related biochemical signaling may diminish their efficacy.

Complementary psychological interventions such as cognitive behavioral therapy, mindfulness-based stress reduction, and supportive-expressive therapies can lower cortisol, reduce IL-6 and TNF- α , modulate adrenergic activity, and decrease oxidative stress [89,90]. Such reductions in upstream mediators restore Hippo pathway restraint and reduce nuclear YAP1 activity.

By modulating stress biology, psychological interventions may synergize with pharmacologic YAP1 inhibitors, enhancing suppression of metastasis, reducing stemness, improving immunotherapy responsiveness, and elevating quality of life [77,91,92]. This integrated framework positions YAP1 not only as a molecular therapeutic target but also as a mechanistic bridge linking mental health and tumor biology a perspective that may transform therapeutic strategies in psycho-oncology [91].

8. Future research directions

Despite growing recognition of YAP1 as a stress-responsive molecular hub linking psychological distress to tumor progression, significant gaps remain in understanding how psychobiological processes shape YAP1 signaling and its

oncogenic consequences. Advancing this field requires integrated mechanistic, translational, and clinical research strategies that bridge psychoneuroendocrinology with molecular oncology. The following priorities outline a roadmap for future investigations.

8.1. Mechanistic studies: Defining how psychological stress regulates YAP1

A central challenge is to delineate the biochemical mechanisms through which stress mediators alter YAP1 phosphorylation, stability, and transcriptional output. Future studies should examine how cortisol, catecholamines, and inflammatory cytokines (IL-6, TNF- α) modulate upstream Hippo kinases (MST1/2, LATS1/2) to regulate YAP1 nuclear activation [51,93,94]. Stress-responsive MAPKs including p38, JNK, and ERK must also be clarified, particularly how they integrate redox and cytokine signals to regulate YAP1 in tumor cells exposed to psychological distress [51,95]. Additionally, research is needed to determine how chronic stress affects YAP1 ubiquitination, degradation, and protein turnover. Key questions include whether YAP1 can function as a stress-responsive molecular sensor predicting therapy resistance, metastatic potential, or psychosocial vulnerability [96–98].

8.2. Development of psychobiological tumor models

Preclinical models capable of reproducing the psychophysiological environment of distressed cancer patients are urgently needed. Integrating chronic stress paradigms such as restraint stress, social defeat stress, and unpredictable mild stress into tumor-bearing rodents would enable direct examination of stress-regulated YAP1 dynamics [99].

Multi-omics platforms (phosphoproteomics, epigenomics, metabolomics) should be applied to map the architecture of YAP1-centered networks under psychological stress [100]. Organoid and organ-on-chip systems exposed to glucocorticoids, catecholamines, cytokines, and ROS may reveal neuroendocrine–tumor interactions and distinct stress-activated YAP1 signatures [101].

8.3. Psychosocial modulation of YAP1: A translational frontier

A promising frontier involves psychological interventions as regulators of YAP1 signaling. Clinical and preclinical studies should test whether psychotherapy or structured stress-reduction programs alter YAP1 phosphorylation by lowering cortisol, IL-6, TNF- α , oxidative stress, and sympathetic activation [102,103].

Research should also investigate whether psychosocial interventions can reverse YAP1-driven EMT, stemness, metabolic rewiring, or immune evasion. Identifying mediators that link psychological well-being with restored Hippo activity would deepen understanding of the mind–tumor interface [104]. Early translational studies combining psychological therapy with YAP1 inhibitors may reveal synergistic therapeutic effects [105].

8.4. Combining YAP1 inhibitors with psychotherapy and molecular targeted approaches

Given extensive pathway compensation in aggressive cancers, combination strategies are required for durable suppression of YAP1-driven oncogenesis. Rational combinations include YAP1 inhibitors with immunotherapy, anti-MET, anti-MEK, or anti-Wnt agents [105].

Integrating psychological interventions with YAP1-targeted therapy reduces upstream stress mediators contributing to YAP1 activation. Lifestyle and antioxidant strategies may further attenuate oxidative stress a major regulator of YAP1 [95,98]. Such approaches simultaneously address psychobiological and molecular contributors to tumor progression, exploiting stress biology as a modifiable co-driver of oncogenic YAP1 activity.

8.5. Clinical translation: Toward mind–body integrated cancer trials

The ultimate goal is to incorporate YAP1-informed psychobiological mechanisms into clinical research and oncology practice. Future randomized trials should determine whether psychotherapy reduces YAP1 activation or modifies YAP-related transcriptomic signatures.

Biomarker studies should evaluate YAP1 as an index of psychophysiological burden and a predictor of treatment response. Longitudinal tracking of cortisol, cytokines, oxidative stress markers, and YAP1 status may uncover temporal interactions between psychological states and tumor biology [106].

Finally, multidisciplinary protocols combining mental health interventions with precision oncology and YAP1-targeted agents may redefine treatment paradigms by demonstrating measurable molecular and clinical benefits [107].

9. Conclusion

Yes-associated protein 1 (YAP1) has emerged as a pivotal transcriptional co-activator at the intersection of tumor biology and psychophysiological stress. As a highly responsive integrator of mechanical tension, inflammatory signaling, oxidative stress, metabolic perturbation, and neuroendocrine input, YAP1 embodies a molecular conduit through which chronic psychological distress can shape malignant behavior. This convergence enables YAP1 to influence core cancer processes including proliferation, survival, metastatic progression, immune evasion, metabolic reprogramming, pain sensitization, and therapeutic resistance thereby positioning it as a central mediator of mind–body interactions in oncology.

The evidence reviewed highlights YAP1 not only as an oncogenic driver but also as a potential indicator of psychophysiological burden. Its activity reflects upstream fluctuations in cortisol, catecholamines, cytokines, ROS, and MAPK signaling biological systems that are profoundly altered in patients living with persistent anxiety, depression, and cancer-related fear. This dual role suggests that YAP1 may help explain why psychological distress predicts poorer clinical outcomes and provides a mechanistic rationale for integrating psychosocial care into standard cancer treatment.

Targeting YAP1 pharmacologically through TEAD inhibitors, epigenetic modulators, siRNA approaches, or dual-pathway blockade offers powerful avenues for suppressing YAP1-driven oncogenic programs. Yet these strategies are likely to be strengthened by concurrent interventions that reduce the stress biology fueling

YAP1 activation. Structured psychological therapies, such as cognitive behavioral therapy, mindfulness-based stress reduction, and supportive–expressive approaches, can modulate key upstream pathways by lowering cortisol, dampening inflammatory cytokines, improving autonomic regulation, and reducing oxidative stress. An integrated model combining direct molecular inhibition of YAP1 with psychobiological modulation therefore represents a compelling strategy for improving treatment efficacy, reducing metastatic potential, alleviating pain, and enhancing quality of life.

Future research should deepen mechanistic understanding of how stress-responsive pathways regulate YAP1; develop psychobiologically informed tumor models that capture real-world patient physiology; and evaluate combination strategies involving psychotherapy, lifestyle interventions, and YAP1-targeted therapeutics. Clinical trials incorporating mind–body interventions alongside precision oncology will be essential to validate YAP1 as both a biomarker and a therapeutic node within psycho-oncology.

Ultimately, advancing YAP1-focused, stress-informed cancer care holds the potential to transform how clinicians conceptualize and treat malignancy recognizing the biological reality that psychological distress is not separate from cancer biology, but intricately woven into the molecular circuits that govern tumor progression and treatment response.

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