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Authors

Rozengurt, Enrique
Eibl, Guido

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REVIEW

Central role of Yes-associated protein and WW-domain-containing transcriptional co-activator with PDZ-binding motif in pancreatic cancer development

Enrique Rozengurt, Guido Eibl

ORCID number: Enrique Rozengurt (0000-0002-7838-9170); Guido Eibl (0000-0003-3497-4527).

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Enrique Rozengurt, Department of Medicine, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA 90095, United States

Enrique Rozengurt, Guido Eibl, CURE: Digestive Diseases Research Center, Los Angeles, CA 90095, United States

Guido Eibl, Department of Surgery, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA 90095, United States

Corresponding author: Guido Eibl, MD, Director, Professor, Department of Surgery, David Geffen School of Medicine, University of California at Los Angeles, 72-236 CHS, 10833 Le Conte Avenue, Los Angeles, CA 90095, United States. geibl@mednet.ucla.edu
Telephone: +1-310-7949577
Fax: +1-310-2062472

Abstract

Pancreatic ductal adenocarcinoma (PDAC) remains a deadly disease with no efficacious treatment options. PDAC incidence is projected to increase, which may be caused at least partially by the obesity epidemic. Significantly enhanced efforts to prevent or intercept this cancer are clearly warranted. Oncogenic *KRAS* mutations are recognized initiating events in PDAC development, however, they are not entirely sufficient for the development of fully invasive PDAC. Additional genetic alterations and/or environmental, nutritional, and metabolic signals, as present in obesity, type-2 diabetes mellitus, and inflammation, are required for full PDAC formation. We hypothesize that oncogenic *KRAS* increases the intensity and duration of the growth-promoting signaling network. Recent exciting studies from different laboratories indicate that the activity of the transcriptional co-activators Yes-associated protein (YAP) and WW-domain-containing transcriptional co-activator with PDZ-binding motif (TAZ) play a critical role in the promotion and maintenance of PDAC operating as key downstream target of KRAS signaling. While initially thought to be primarily an effector of the tumor-suppressive Hippo pathway, more recent studies revealed that YAP/TAZ subcellular localization and co-transcriptional activity is regulated by multiple upstream signals. Overall, YAP has emerged as a central node of transcriptional convergence in growth-promoting signaling in PDAC cells. Indeed, YAP expression is an independent unfavorable prognostic marker for overall survival of PDAC. In what follows, we will review studies implicating YAP/TAZ in pancreatic cancer development and consider different approaches

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to target these transcriptional regulators.

Key words: Pancreatic cancer; Yes-associated protein and WW-domain-containing transcriptional co-activator with PDZ-binding motif; Oncogenic Kras; Obesity; Signaling network and loops

Core tip: The identification of signaling networks that underlie risk factor promoted pancreatic cancer development and progression is of paramount importance to prevent or intercept this lethal disease. Accumulating evidence suggests that several core signaling pathways downstream of oncogenic Kras, augmented by environmental conditions, *e.g.*, obesity, converge on Yes-associated protein (YAP) and WW-domain-containing transcriptional co-activator with PDZ-binding motif (TAZ), transcriptional co-activators in the Hippo pathway. Statins and metformin, widely used Food and Drug Administration-approved drugs, show great promise to intercept this disease by disrupting or inhibiting this amplifying network at multiple points converging onto YAP/TAZ.

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INTRODUCTION

Despite advances in our understanding of genetics and basic biology, imaging, surgical treatments, and adjuvant therapy, pancreatic ductal adenocarcinoma (PDAC), which represents 90% of all pancreatic cancers, is a disease with dismal prognosis with an overall 5-year survival rate of only about 7%[1]. The incidence in the general population is estimated to be 8 cases per 100000 person-years, and the worldwide mortality about 7 deaths per 100000 person-years[2,3]. PDAC is already the 3rd leading cause of cancer-related mortalities in the United States[4]. Indeed, deaths due to PDAC are predicted to increase markedly. Indeed, the disease is expected to become the 2nd leading cause of cancer-related mortality in the United States in the next few years[5]. Given that only a minority of patients diagnosed with PDAC are eligible for surgical intervention, the research is gradually shifting to identify novel approaches in early diagnosis, prevention and interception, a novel concept, which attempts stopping transformed cells from progressing to frank cancer[6-10]. The elucidation of the molecular mechanisms of risk-factor associated PDAC promotion will be of paramount importance to facilitate the discovery of novel targets and agents for prevention and identify robust biomarkers to stratify patients for selective and individualized therapeutics.

KRAS MUTATIONS AND PDAC

Oncogenic *KRAS* mutations were first reported to be associated with PDAC more than 30 years ago[11,12]. Although the genetic landscape of PDAC is complex, since the initial reports extensive research in both humans and mice have substantiated the critical significance of *KRAS* mutations in the early stages of PDAC. In fact, many studies have confirmed that over 90% of PDAC harbors *KRAS* mutations[13,14] and KRAS signaling is one of the core signaling pathways in human PDAC[13]. Most *KRAS* mutations in PDAC are found at position G12, of which the single amino acid replacement G12D is the most predominant[15]. Mutations at position G13 or Q61 have been detected at lower frequency, 21% or 28%, respectively[15]. Using deep whole exome sequencing an integrated genomic characterization of PDAC revealed several different *KRAS* mutations in a subset of tumors, with some PDACs showing biallelic mutations[16]. Mechanistically, mutations at position G12 with a single amino acid substitution induce conformational changes that interfere with the intrinsic GTPase

activity of KRAS and prevent the interactions between KRAS and GTPase-activating proteins (GAPs), which stimulate the conversion of KRAS-GTP (active state) to KRAS-GDP (inactive state), thereby ending KRAS activation. In this manner, the KRAS mutations lead to its prolonged activation and consequently to the persistent stimulation of downstream signaling effectors[15,17]. It is becoming clear that different mutations of G12 lead to different conformational states that differ in their affinity for interacting effectors[18]. Although mutations in *KRAS* is an early and essential step in PDAC, it is insufficient to stimulate development of frank, invasive PDAC. Activation of other pathways by additional mutations (*e.g.*, in tumor suppressor genes, including p53, p16 and SMAD4) or environmental stimuli, including obesity and metabolic syndrome are required for the promotion of invasive PDAC[19-24].

In addition, the "efficacy" of oncogenic KRAS to initiate and promote PDAC is influenced and modulated by the presence of common susceptibility genes. Recent genome-wide association studies (GWAS) of PDACs in populations of European ancestry have identified additional common pancreatic cancer risk loci carrying pancreatic cancer risk signals, including *NR5A2*, *PDX1*, *AB0*, *NOC2L*, *HNF1B*, *GRP*[25-28]. Moreover, an elegant study demonstrated that variations in oncogenic dosage have a critical role in PDAC biology and phenotypic diversification[29], with the highest oncogenic Kras levels underlying aggressive undifferentiated phenotypes. Activation of other pro-oncogenic pathways, including *Myc*, *Yap1* or *Nfkb2*, which collaborate with heterozygous mutant Kras in driving tumorigenesis have been shown to have a lower metastatic potential[29]. It seems that evolutionary constraints direct oncogenic dosage gain and variation along defined routes to drive the early progression of PDAC and shape its downstream biology[29]. Integrated genomic and global gene expression analyses have classified human pancreatic cancers into several distinct subtypes that may dictate and predict clinical outcomes and therapeutic responses. Collison and colleagues defined three subtypes: classical, quasi mesenchymal, and exocrine-like[30], while Bailey *et al*[31] classified four subtypes: squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine exocrine (ADEX). By separating tumor cells and stromal components, Moffitt and colleagues identified two stromal subtypes: normal and activated, and two tumor-specific subtypes: classical and basal-like[32]. Using whole genome sequencing and copy number variation analysis Waddell *et al*[33] categorized PDAC into four subclasses based on patterns of structural variation (variation in chromosomal structure): stable, locally rearranged, scattered, and unstable. Taken together, these large genomic efforts clearly demonstrate that pancreatic cancer is a genetically complex and heterogeneous disease, which has significant implications in prognosis and therapeutic response, and classifying pancreatic cancers into subtypes may assist and pave the way to more efficacious personalized treatment strategies.

PROGRESSION MODEL OF PDAC

It is estimated that PDACs develop over many years from non-invasive precursor lesions. The non-cystic lesion is called pancreatic intraepithelial neoplasia (PanIN) and is usually diagnosed in histological preparation of tissue removed during surgery or in biopsy specimens[34-37]. These PanINs progress from early PanIN-1 lesions to advanced PanIN-3 (carcinoma *in situ*) and finally to frank invasive PDAC. Besides this classical view of gradual step-wise PanIN progression and PDAC formation, in at least a subset of PDACs there seem to be catastrophic genetic events (*e.g.*, chromothripsis) necessary for the transition from preinvasive to invasive PDAC (punctuated equilibrium)[38-41]. The pathological characteristics of cystic precursor lesions, including intraductal papillary mucinous neoplasm (IPMN) have been recently reviewed elsewhere[42]. Most low-grade PanIN lesions contain oncogenic *KRAS* mutations[43]. This finding provided further evidence in support of the step-wise carcinogenesis model, in which *KRAS* mutations are envisioned as initiating events[15,44,45].

Genetically engineered mouse models of PDAC have corroborated this paradigm[46-49]. In the KC model, mutated *Kras* is expressed from its endogenous locus (by crossing *LSL-KrasG12D* mice with *PDX-1-Cre* or *p48-Cre* mice, *i.e.*, KC model)[48-50]. This KC mouse model shares similar histopathologic and genetic features to the human disease including the development and progression of PanINs[46]. In addition to the role of oncogenic KRAS in the initiation of PDAC, *Kras* mutations have also been shown to be important for PDAC maintenance[51,52]. In line with the notion that mutated *Kras* is necessary but not fully sufficient for the development of invasive PDAC, only few animals (5%-10%) in the KC model (without additional genetic alterations) develop frank PDAC very late (usually after 9 mo)[46]. Cell senescence has

been proposed as a barrier to the malignant progression of tumors[53]. The formation of PDAC can be greatly accelerated by the presence of another mutation (*e.g.*, *Trp53*)[47,54].

Besides additional genetic mutations, several studies have convincingly demonstrated that environmental, nutritional, and metabolic factors, including obesity, type-2 diabetes mellitus (T2DM) and inflammation efficiently promote PDAC formation[55-59]. This notion is substantiated by several preclinical studies. Expression of physiologic levels of oncogenic *Kras* in murine models efficiently transformed only a small percentage of cells[60]. KRAS downstream signaling molecules, including the ERKs were not activated when oncogenic *Kras* was expressed from its endogenous locus[61]. Accordingly, cell culture studies have shown that incubating PDAC cells in a serum-free medium failed to display activated ERK despite the presence of *KRAS* activating mutations in these cells. However, ERK activation could be induced by adding growth factors to the culture medium[62-64]. In mouse models, oncogenic *Kras* in adult mice was insufficient to induce PDAC, while concomitant induction of pancreatic inflammation (*e.g.*, by administration of the cholecystokinin analog cerulein) stimulated the formation of PanINs and cancers[65]. Our own studies have clearly demonstrated that an obesogenic diet accelerated early PanIN progression and PDAC development in KC mice, which was associated with metabolic disturbances (*e.g.*, hyperinsulinemia), increased pancreatic inflammation, and desmoplasia[55,56]. Taken together, the current evidence indicates that oncogenic *Kras* is indispensable but not sufficient to induce malignant pancreatic cells. Additional genetic or environmental factors (obesity, T2DM, inflammation) are required to elevate KRAS activity[52] and/or stimulate additional signaling pathways to promote PDAC formation[66].

Recent elegant gene-environment interaction studies have demonstrated that the increased risk of developing PDAC by environmental stimuli and conditions may be influenced by the presence of common genetic variations. A GWAS data analysis has found that genetic variations in inflammatory responses and insulin resistance may affect the risk of obesity- and diabetes-related pancreatic cancer[67]. It is apparent that a detailed understanding of the gene-regulatory networks that integrate signaling by KRAS and cooperating pathways to drive an oncogenic program in pancreatic cancer is of fundamental importance to design novel strategies to target this aggressive disease. Recent exciting studies from different laboratories indicate that the activity of the transcriptional regulators yes-associated Protein (YAP) and WW-domain-containing transcriptional co-activator with PDZ-binding motif (TAZ) play a critical role in the promotion and maintenance of PDAC. In what follows, we will review studies implicating YAP/TAZ in pancreatic cancer development and consider possible approaches to target these transcriptional regulators with emphasis in repurposing drugs that are currently in clinical use.

YAP/TAZ IN PANCREATIC CANCER

The Hippo pathway

The highly conserved Hippo pathway, originally identified and characterized as potent growth-suppressive pathway in *Drosophila*[68], is a key regulatory mechanism in development, organ-size, tissue regeneration and tumorigenesis[68,69]. Canonical Hippo signals are transmitted via the serine/threonine kinases mammalian Ste20-like kinases 1/2 (Mst1/2), in complex with the scaffold protein salvador homolog 1 (Sav1), phosphorylate and activate large tumor suppressor 1/2 (Lats1/2), in complex with its regulatory protein Mps One binder 1/2 (MOB1/2)[69]. As shown in Figure 1, Lats1/2 then phosphorylates the transcriptional co-activators YAP and TAZ which also can function as novel sensors of the mevalonate and glycolytic pathways[70-72].

The residues Ser^{127} and Ser^{397} of YAP are positioned within a consensus sequence (HXRXXS) phosphorylated by Lats1/2. The phosphorylation of YAP at these sites, restricts its cellular localization to the cytoplasm, reduces its stability, and inhibits its co-transcriptional activity. In addition to Lats1/2, YAP and TAZ can be phosphorylated by other protein kinases[68]. Although YAP and TAZ have very similar structural topologies, share nearly half of the overall amino acid sequence, and are thought to be largely redundant, they may differ in their regulation and downstream functions[73].

When the Hippo pathway is not functional, YAP localizes to the nucleus where it interacts with the TEA-domain DNA-binding transcription factors (TEAD 1-4). YAP/TEAD-regulated genes encode for proteins implicated many critical cellular processes, *e.g.*, autocrine/paracrine proliferation *via* EGFR (AREG) and G protein-coupled receptors (EDN2), and interact with other developmental pathways activated in PDAC, including Wnt, Notch, and Hedgehog[74]. YAP/TAZ also induces epithelial-

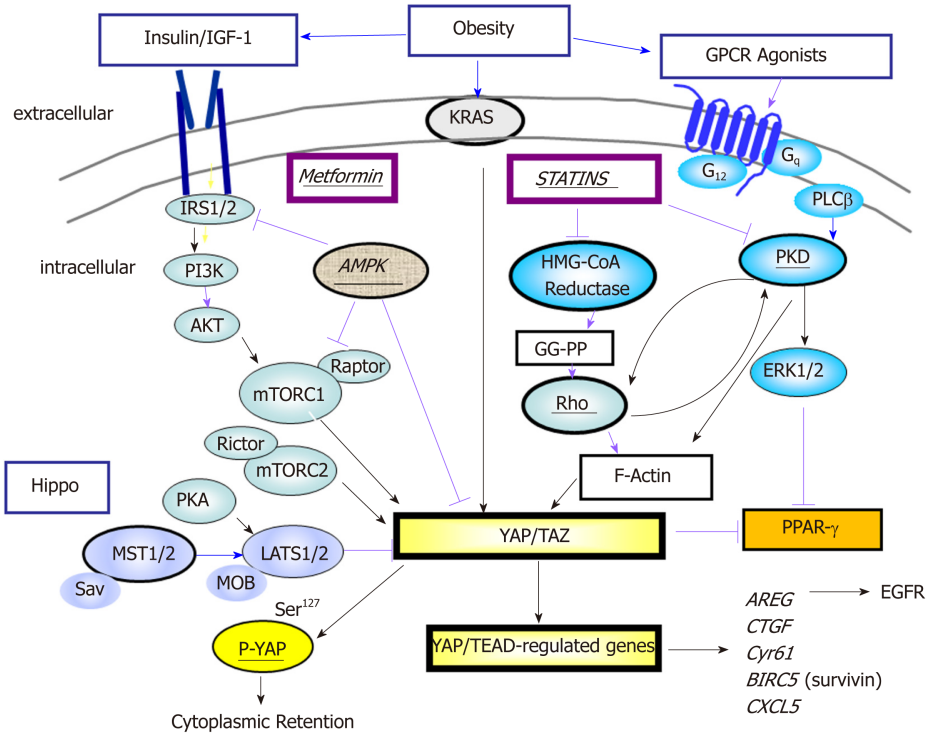

Figure 1 Yes-associated protein and WW-domain-containing transcriptional co-activator with PDZ-binding motif is a point of convergence in signaling pathways. A network that involves activated Ras, G protein-coupled receptors (GPCRs) and tyrosine kinase receptors positively regulates Yes-associated protein and WW-domain-containing transcriptional co-activator with PDZ-binding motif (YAP/TAZ) activity *via* Rho/PKD/organization of the actin cytoskeleton and PI3K/AKT/mTORC1. The interaction of mTORC1 and YAP is explained in the text. In addition, the localization and activity of YAP/TAZ is negatively impacted by the Hippo pathway which mediates phosphorylation of YAP and thereby its cytoplasmic sequestration. Metformin and statins inhibit YAP/TAZ activity at different sites in the network. Stimulatory effects are shown by black arrows whereas inhibitory effects are indicated by red arrows. YAP/TAZ: Yes-associated protein and WW-domain-containing transcriptional co-activator with PDZ-binding motif; GPCR: G protein-coupled receptor.

to-mesenchymal transition (EMT) and induces a more undifferentiated state to malignant cells. Accordingly, YAP/TAZ play an important role in pancreas development, which has implications for pancreatic regeneration, cancer, and diabetes[75]. It is accepted that YAP/TAZ acts as a potent oncogene in multiple cell types, including PDAC[76] and also contributes to the strong immunosuppressive microenvironment characteristic of mouse and human pancreatic cancer[77]. Recent findings indicate that YAP/TAZ opposes Ras-induced senescence by increasing the expression of the key enzymes involved in deoxyribonucleotide biosynthesis which are critical for DNA replication[78].

As indicated above, YAP and TAZ do not bind directly to DNA but act by enhancing the activity of transcription factors or other proteins that interact with DNA. Although TEAD family members are the major DNA-binding partners, YAP/TAZ can also bind to other transcription factors, *e.g.*, RUNXs, p73, Smad1, Klf4, AP-1 to elicit context-specific functions[74,79,80]. It is important to point out that YAP and TAZ not only act as co-activators of transcription factors that bind to promoter sites contiguous to the gene that they control but exert regulatory effects via distant enhancer elements[81,82]. Furthermore, recent studies indicate that YAP/TAZ-bound to enhancers mediate the recruitment of the general coactivator bromodomain-containing protein 4 (BRD4) and RNA polymerase II at promoters regulated by YAP/TAZ, thereby enhancing expression of multiple growth-regulating genes[83]. It is evident that YAP and TAZ control gene-regulatory programs through a variety of mechanism, further supporting their fundamental role in cell signaling.

Regulation of YAP/TAZ in PDAC

Recent studies demonstrated that YAP is required for acinar-to-ductal metaplasia (ADM), an early event that precedes PanIN progression into PDAC in genetically engineered mouse models[84,85]. In addition, YAP is a major mediator of pro-oncogenic mutant p53[86] and p53 deficiency promotes YAP signaling trough Ptpn14[87]. Also, YAP confers resistance to RAF/MEK inhibitors[88] and chemotherapy in PDAC[89]. While initially thought to be primarily an effector of the tumor-suppressive Hippo pathway, more recent studies revealed that YAP/TAZ subcellular localization and co-transcriptional activity is regulated by multiple upstream signals including those

mediated by various G protein-coupled receptors (GPCRs), tyrosine kinase receptors (EGFR, MET, Insulin/IGF-1 receptor), integrins, PI3K, mTOR, PKC, PKD, RHO and actin cytoskeleton, all of which stimulate YAP/TAZ transcriptional co-activator activity[66,69,76,90-92]. Recently, Src kinases, downstream of KRAS, have been shown to inhibit the Hippo pathway by directly phosphorylating Lats1 thereby activating YAP[93]. Interestingly, some of the tumor suppressive effects of wild type p53 appear to be exerted via inhibition of YAP1 function[87].

In human PDAC cells, YAP functions as a downstream effector of the crosstalk between insulin/IGF-1 receptor and GPCR systems[94] (Figure 1). We have demonstrated that stimulation with insulin and the GPCR agonist neurotensin induced rapid YAP nuclear import and markedly augmented the mRNA levels of YAP/TEAD-regulated genes, including CTGF and Cyr61. The growth-promoting agonists regulated YAP activity via PI3K and PKD in PANC-1 and MiaPaCa-2[94], human cell lines that correspond to the squamous/quasi mesenchymal/ basal-like sub-type of PDAC. In other cell types, several studies have also been shown that PI3K activation inhibits the Hippo pathway[95,96] thereby promoting YAP activity, and PKD mediates YAP nuclear localization and activation of YAP/TEAD-regulated gene expression[90]. Overall, YAP has emerged as a central node of transcriptional convergence in growth-promoting signaling in PDAC cells (Figure 1). In addition to rapid regulation *via* phosphorylation and sub-cellular localization, additional pathways and epigenetic stimuli modulate YAP/TAZ protein expression. In this context, it has been shown that the RAS pathway, independently of the Hippo cascade, enhances YAP1 stability through downregulation of the ubiquitin ligase complex substrate recognition factors SOCS5/6[97]. Moreover, the eukaryotic translation initiation factor 5A (eIF5A), which is up-regulated by KRAS in PDAC, interacts with the tyrosine kinase PEAK1 leading to enhanced YAP expression[98].

The nutrient sensor mTORC1, a central downstream component of the PI3K/AKT and RAF/MEK/ERK pathways, is implicated in the development of multiple types of cancer, including PDAC[99]. Interestingly, YAP and mTORC1 form a positive feedback loop that leads to enhanced YAP protein expression. Specifically, YAP stimulates mTORC1 *via* increasing the activity of the PI3K pathway[100] and augmented amino acid transport[101,102]. In turn, mTORC1 activation leads to YAP accumulation at least in part, via decreased autophagy[103]. Importantly, amplification and overexpression of YAP has been shown to bypass the need of mutant *Kras* in murine PDAC[104] and other cancer cell types[105] though the mechanism(s) differ(s), probably reflecting cell-context factors[106]. These finding indicates that YAP not only acts downstream of KRAS but also that YAP can sidestep the need of KRAS mutant expression in PDAC[107].

Several studies in different cell types demonstrated that an increase in the intracellular level of cAMP inhibits YAP activation, at least in part through activation of protein kinases of the Hippo pathway[108,109]. Interestingly, concomitant expression of mutated (R201C) GNAS, which encodes for stimulatory G-protein alpha subunit that increases cAMP synthesis, with oncogenic Kras in mice, induced the formation of pancreatic cystic neoplasms, resembling human intraductal papillary mucinous neoplasms (IPMN), a less aggressive histological subtype of pancreatic tumors, by inhibiting YAP signaling[110]. These recent findings underscore the importance of YAP activation in the development of specifically PDAC. In this regard, it is of great interest that YAP function has been associated with the squamous/quasi mesenchymal/basal-like sub-type of PDAC (discussed above), considered the most clinically aggressive form. The significance of YAP expression in human PDAC is discussed in the next section.

An important feature of human and murine PDAC is an extensive desmoplastic stroma[111] that increases the stiffness of the extracellular matrix (ECM) surrounding the epithelial cancer cells[42]. The Hippo/YAP pathway has been recognized to play a critical role in mechano-transduction[112,113] and in sensing ECM stiffness[114] but the mechanisms involved are not fully understood. Recently, the Ras-related GTPase RAP2 has been identified as a major sensor of mechanical cues from the ECM. At low stiffness, RAP2 activates the Hippo kinases Lats1/2 thereby inhibiting YAP/TAZ activity[115]. Therefore, high stiffness leads to inhibition of the Hippo tumor suppressive pathway, thus enhancing the co-activator activity of YAP and TAZ. Reciprocally, increased expression of a number of YAP/TEAD-regulated genes, including CTGF, Cyr61 and CXCL5 contribute to shaping the stroma of PDAC, thus establishing an important amplification loop involving the tumor microenvironment leading to the stimulation of PDAC development.

YAP and human PDAC

Several studies reported that YAP and TAZ are over-expressed and over-active in human PDAC[104,116,117] and identified YAP expression as an independent prognostic marker for survival of PDAC[118]. We have examined the prognostic value not only of

YAP but also of upstream and downstream components of the YAP-driven network in pancreatic cancer[119]. We confirmed that higher expression of YAP is significantly associated with unfavorable prognosis (survival) in PDAC[120]. Indeed, none of the patients of the population with higher levels of YAP mRNA expression survived for 5 years while 32% of the subset with the lower levels of YAP mRNA survived for 5 years or more. In addition, multiple genes regulated by YAP/TEAD, including *AJUBA*, ANLN, *AREG*, *ARHGAP19*, *ARHGAP29*, *AURKA*, *BUB1*, *CCND1*, *CDK6*, *CXCL5*, *DKK1*, *JAG1*, *NOTCH2* and *RHAMM* were significantly associated with unfavorable prognosis in PDAC[120]. In a further analysis of the data, we verified that the expression of each of these genes was positively and significantly correlated with the expression of YAP in PDAC. In contrast, genes in pathways, *e.g*., LKB/AMPK and cAMP/PKA, that oppose YAP action, including *STRAD*, *MARK1*, *PKA*, are associated with favorable prognosis in PDAC patients[120]. Similar results were obtained using other web-based tools, such as Gene Expression Profiling Interactive Analysis[121].

YAP and obesity

Besides its recognized role in the regulation of growth and development, recent studies show that Hippo kinases and YAP/TAZ transcriptional coactivators, are regulated by metabolism and conversely that the Hippo/YAP pathway controls metabolic processes in physiological and pathologic conditions, including obesity and T2DM[122,123]. In fact, cellular metabolites and metabolic pathways, *e.g*., glucose and free fatty acids, regulate the Hippo pathway. Glucose metabolism through the glycolytic pathway activates phosphofructokinase 1 (PFK1), a key rate-limiting enzyme of glycolysis. In turn, PFK1 interacts with TEAD, thereby regulating YAP/TEAD complex formation and expression of YAP/TEAD-regulated genes[70]. Furthermore, O-linked β-N-acetylglucosamine (O-GlcNAc) is another post-translational mechanism by which a sugar is attached to serine residues of nuclear or cytoplasmic proteins and modifies protein activity[124]. Indeed, the attachment of O-GlcNAc to Ser^{109} of YAP stimulates its transcriptional co-activator activity by interfering with the interaction of YAP with Lats1/2, thus protecting YAP from inhibitory phosphorylation and providing a novel mechanism linking glucose availability to YAP activity[125]. This multilayered regulation of YAP activity by glucose metabolism is potentially important in the obese state, which often is accompanied by insulin resistance and elevated glucose levels.

A characteristic and defining feature of obesity is the enlargement of adipose tissue depots, which is often accompanied by adipose tissue (AT) inflammation[126]. Dysfunctional adipose tissue with alterations of adipokine production, ectopic fat storage, and AT inflammation are thought to be critical, pathophysiological processes underlying the development of insulin resistance. Adipocytes and adipose tissue macrophages are central cellular players of AT inflammation[127-132]. The Hippo pathway has been shown to modulate adipocyte proliferation and differentiation, with YAP/TAZ nuclear localization stimulating proliferation and suppressing adipogenesis[133-136]. As depicted in Figure 1, nuclear YAP/TAZ interacts with and inhibits PPAR-γ, a major pro-adipogenic transcription factor, thereby suppressing adipocyte differentiation[133,137]. In that context, hyperglycemia and advanced glycation end products impair adipogenesis by upregulating and activating YAP[138].

There are few studies investigating the importance of YAP/TAZ in macrophage polarization[139]. It has been shown that the cell shape, independent of cytokines present in the micromilieu, has a profound influence on macrophage polarization via the actin cytoskeleton[140], which strongly suggests an important role of YAP/TAZ in this process due to the critical function or YAP/TAZ as mechano-sensors and mechano-transducers[112,113]. In addition, adipose tissue in obese subjects is characterized by peri-adipocyte fibrosis with elevated levels of CTGF (connective tissue growth factor)[141], a recognized product of YAP/TEAD transcriptional activity. Our own studies have shown that YAP is overexpressed in mesenteric adipose tissue of obese KC mice (unpublished). Taken together, an important role of YAP/TAZ in adipose tissue inflammation during obesity emerges, which might have important implications in the PDAC promoting effects of obesity[142,143].

Strategies to inhibit YAP/TAZ in pancreatic cancer

As indicated above, YAP hyper-activation can evade the need of KRAS mutant expression in PDAC[107]. Thus, even if Ras could be effectively inhibited by new therapies, YAP amplification could provide a potential pathway to tumor recurrence. Given that YAP is as a key element not only downstream of Ras but also an alternative route to bypass the need of this oncogene for tumor relapse, YAP is emerging as a fundamental target in PDAC. Although targeting transcription factors or their co-activators has proven difficult, recent studies suggest novel approaches to inhibit YAP/TAZ activity with drugs in clinical use, including statins and metformin

in PDAC and other malignancies.

Statins

Several studies demonstrated activation of the pathway leading to mevalonate biosynthesis in epithelial cancers through mutant p53[144-146] and AKT/mTORC1[146]. Statins, which have been used to treat dyslipidemia and prevent heart diseases, selectively inhibit 3-hydroxy-methylglutaryl (HMG) CoA reductase[147], the rate-limiting enzyme in the generation of mevalonate (Figure 2). Mevalonate is a precursor for the generation of important lipids and lipid intermediates, including farnesyl pyrophosphate (FPP), geranylgeranyl pyrophosphate (GG-PP) and cholesterol. The function and activity of small GTPases of the Rho family, including Rho A and C, depend on the transfer of the geranylgeranyl moiety of GG-PP to a cysteine in their COOH-terminal region. Active Rho plays a critical role in YAP/TAZ activation through actin remodeling in several cell populations[69] (Figure 2). Accordingly, increased expression of RHOA and RHOC is associated with unfavorable prognosis in patients with PDAC.

Numerous epidemiological studies have concluded that statin use is correlated with beneficial effects in PDAC[148-156], especially in men[151,152]. A large study demonstrated that statins were associated with a significantly reduced PDAC risk (by 34%) with a stronger effect in males[151]. The beneficial effects of statins depend on the type of statins used, with several reports showing positive associations with lipophilic (and not hydrophilic) statins and reduced cancer risk[157-160]. However, a recent study, in which statin use was self-reported and the type of statins was not documented in early cohorts, failed to detect an effect of statins in lowering PDAC risk[161]. The same authors published a follow up study of the same dataset, in which they reported an increased survival in PDAC patients with regular pre-diagnosis use of statins[162]. Recently, a meta-analysis of PDAC risk that included more than 3 million participants and 170000 pancreatic cancer patients has been published[163]. This study indicates a significant decrease in pancreatic cancer risk with statin use, thus reinforcing the conclusion that statin administration is associated with beneficial effects in PDAC patients. In addition to their potential efficacy in primary prevention and interception, statins may improve the outcome of patients after surgical removal of their primary PDAC[148,149,164], indicating a possible role of statins in the prevention of PDAC recurrence.

In preclinical studies[165,166], statins delayed progression of PDAC in mice harboring *Kras*^{G12D}. Statins were identified as potential YAP inhibitors by screens of molecules that changed the nuclear/cytoplasmic distribution of YAP[167]. Our own experiments using PDAC cells also indicated that lipophilic statins induce cytoplasmic localization of YAP and markedly inhibited YAP/TEAD-regulated genes, proliferation, and colony formation by PDAC cells (submitted for publication). Taken together, converging evidence from epidemiological and preclinical studies indicates a protective effect of statins in PDAC.

Metformin

1,1-dimethylbiguanide hydrochloride (metformin) is the most widely administered drug for the treatment of T2DM worldwide[168,169]. The anti-diabetic, *i.e*., lowering the blood glucose levels, actions of metformin are mediated systemically by a reduction of hepatic glucose production and output into the circulation and improvement of insulin sensitivity *via* increasing cellular uptake of glucose in skeletal muscles and adipose tissue[170]. In addition to lowering blood glucose levels, metformin decreased the levels of insulin and IGF-1 in both diabetic and non-diabetic patients[171,172]. Multiple epidemiological studies showed an association of metformin with reduced incidence, recurrence and mortality of cancer in patients with T2DM[173-182]. However, a therapeutic efficacy of metformin has not been observed in all studies[183], in particular in late-stage, advanced cases of cancer. In that context, recent meta-analyses supported the notion that the beneficial effects of metformin depend on the stage of the tumor, with a substantially enhanced survival in patients with local, non-metastatic, disease[178,184]. Further reports indicated that metformin administered to T2DM patients could be also beneficial in secondary chemoprevention, i.e. after surgical resection of the cancer in the pancreas[185,186].

The mechanism of action of metformin remains incompletely understood. Besides its systemic (glucose lowering) effects, at the cellular level metformin indirectly activates AMP-activated protein kinase (AMPK)[187], though other AMPK-independent mechanisms are also operational[188,189]. AMPK is activated by phosphorylation by the tumor suppressor LKB-1/STK11 in the activation loop[190] when cellular ATP levels decrease and 5′-AMP and ADP concentrations increase[169]. It generally thought that metformin leads to AMPK activation by directly inhibiting complex I of the mitochondrial respiratory chain[191,192], which leads to a decrease in ATP synthesis

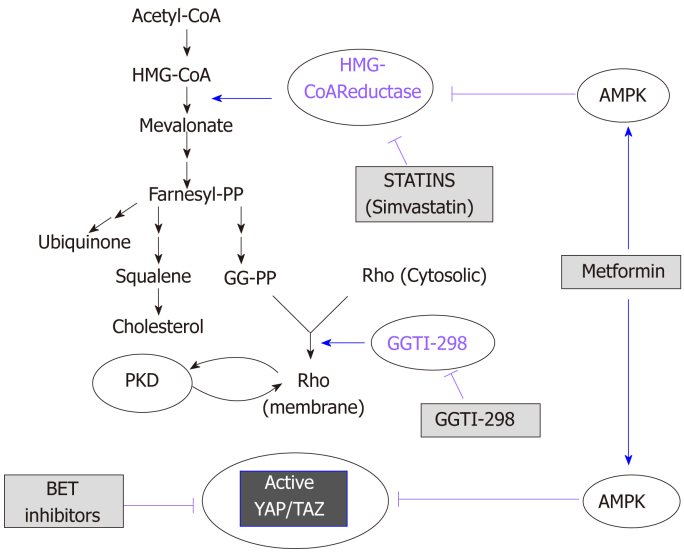

Figure 2 Schematic overview of the mevalonate pathway. The scheme illustrates the site of action of statins, metformin and bromodomain and extra-terminal domain inhibitors (see text for details). BET: Bromodomain and extra-terminal domain; AMPK: AMP-activated protein kinase; GG-PP: Geranylgeranyl pyrophosphate.

resulting in increased AMP and ADP thereby leading to AMPK activation. AMPK suppresses cellular proliferation by inhibiting the function of mTORC1 through several mechanisms. AMPK activates TSC2 by phosphorylation on Ser^{1345}[193-195], which leads to an accumulation of inactive Rheb-GDP thereby inhibiting mTORC1. AMPK can also inhibit mTORC1 function by phosphorylation of Raptor, which disrupts its complex with mTOR[196]. In addition, mTORC1 activation induced by insulin/IGF-1 signaling is also inhibited *via* phosphorylation of IRS-1 on Ser^{794} by AMPK, a phosphorylation that impedes PI3K activation[197,198]. We demonstrated that metformin, at low concentrations, activates AMPK in PDAC cells[199,200] and inhibits mTORC1, ERK and DNA synthesis *via* AMPK[199-201]. Metformin also reduced the rate of growth of PDAC xenografts[202,203]. Furthermore, we recently reported that oral administration of metformin strikingly prevented the increase in PDAC incidence in KC mice with diet-induced obesity[204]. This effect was associated with an increase in pancreatic AMPK activity (as measured by ACC Ser^{79} phosphorylation), and decrease in phospho MEK1/2 ($Ser^{217/221}$), phospho S6 ($Ser^{235/236}$), and phospho ERK1/2 (Thr^{202}, Tyr^{204})[204]. In that context, berberine, a natural compound that activates AMPK and inhibits ATP production, also inhibited mTORC1, ERK, DNA synthesis and proliferation of pancreatic cancer cells and reduced the growth of PDAC xenografts[201].

Recent evidence indicates that AMPK also opposes YAP activity via multiple mechanisms, including direct YAP phosphorylation on Ser^{94}[205,206], a residue that is important for the interaction of YAP with TEAD. In addition, AMPK has been shown to phosphorylate HMG-CoA reductase (Ser^{872}), thereby inhibiting its activity and reducing mevalonic acid synthesis[207]. Furthermore, AMPK phosphorylates and activates upstream regulators of the Hippo pathway[208]. The inhibitory effects of AMPK on the YAP/TAZ pathway is illustrated in Figure 2. These studies suggest an important direct link among adenine nucleotide levels, AMPK and YAP/TAZ activity. In studies from our laboratories, we found recently that diet-induced obesity markedly increased pancreatic TAZ expression in KC mice and that oral metformin prevented the increase in YAP/TAZ[204]. Given that statins and metformin inhibit YAP activation through different mechanisms, it is logical to speculate that administration of a combination of these FDA-approved drugs will suppress YAP/TAZ activity and exerts PDAC-protective activity. The scheme presented in Figure 1 dramatizes this notion by showing that statins and metformin reach YAP through different pathways.

Inhibitors of BRD4: A new approach for targeting YAP/TAZ

BRD4, which interacts with acetyl-lysine, acts as a critical regulator of the expression of selected subsets of genes. Bromodomain and extra-terminal domain (BET) inhibitors interfere with the proliferation of PDAC cells, raising the possibility that BET proteins may be new targets for PDAC therapy[209]. A recent elegant study demonstrated a direct physical interaction between YAP or TAZ and BRD4, as revealed by co-immunoprecipitation experiments. The data imply that YAP, TEAD and BRET-containing proteins (*e.g.*, BRD4, BRD2) form a multi-molecular complex in

the nucleus[83]. Consistent with the notion that BRD4 plays a critical role in YAP/TAZ function, the BET cell-permeable inhibitor JQ1[210] downregulates the expression of YAP/TAZ-regulated genes[83]. Considerable efforts are being made to develop new inhibitors of BRD proteins and thus this field will develop rapidly[211]. These new findings suggest a novel approach to target YAP/TAZ that remains to be tested experimentally *in vivo*, using models of PDAC. As suggested by Figure 2, the possibility of using BET inhibitors in combination with statins and/or metformin is attractive and warrants further experimental work.

Feedback loops and effect of pathway inhibitors

Most signaling pathways are subjected to potent feedback loops that adjust the activity and function of the signaling network. There is evidence that besides their stimulating effects on mitogenic signaling the mTORC1/S6K and RAF/MEK/ERK pathways also mediate robust negative feedback loops that restrict the activity of insulin/IGF-1, EGFR, and other tyrosine kinase receptors[99]. In that context, the mTORC1/S6K pathway inhibits the function of IRS-1 by phosphorylating several residues ($Ser^{636/639}$ by mTORC1 and $Ser^{307/636/1001}$ by S6K)[212]. Inhibitors of mTORC1/S6K or MEK/ERK suppress these feedback loops, which in turn causes a compensatory activation of upstream signaling molecules, *e.g.*, PI3K, AKT, and ERK that as a consequence strongly counteract the anti-proliferative actions of these inhibitors[99,200,213]. The up-regulation of these pathways conceivably can promote YAP activity leading to drug resistance. Therefore, a detailed understanding of feedback mechanisms that regulate upstream signaling is critical and will enable the identification of rational drug combinations that will circumvent drug resistance produced by unleashing the activity of alternative pathways.

CONCLUSION

Despite major advances in defining the molecular mutations driving PDAC, this disease remains universally lethal with an overall 5-year survival rate of only about 7%-8%. More efficacious therapeutic strategies are clearly needed but given the late presentation and early dissemination of the disease, substantial efforts should be concentrated on prevention and interception. Hereby, detailed knowledge of the molecular mechanisms underlying risk-factor promoted PDAC will surely facilitate and enable the discovery of novel molecular targets and agents for primary or secondary prevention. Epidemiological studies convincingly demonstrate that obesity is a risk factor for PDAC development, the importance of which takes an added level given the epidemic proportions of metabolic diseases. It is also recognized that almost all PDACs harbor an oncogenic *KRAS* mutation, which seems necessary but not sufficient for complete PDAC formation. Besides additional mutations, which greatly accelerate PDAC progression in mice, environmental conditions, including obesity, T2DM, and inflammation, have been shown to also promote PDAC in murine models. As illustrated in Figure 1, we propose that PI3K/mTORC1 and PKD/ERK are critical nodes in the network activated by GPCRs, EGFR and insulin/IGF-1 receptor in PDAC. These signaling modules are responsive to obesogenic signals and reinforce KRAS signaling. In turn, oncogenic *KRAS* mutations potentiate the intensity of signaling network emanating from GPCRs, EGFR, and insulin/IGF-1 receptors by activating PI3K/AKT and Raf/MEK/ERK, the most prominent downstream pathways of oncogenic KRAS.

We also postulate that YAP/TAZ transcriptional co-activators are central and critical players in this amplification network, further intensifying positive feedback loops. GPCRs, EGFR, and insulin/IGF-1 receptor signaling rapidly stimulate nuclear import and transcriptional co-activator activity of YAP/TAZ, while oncogenic KRAS increases the levels of YAP protein. In turn, YAP stimulates signaling *via* autocrine/paracrine stimulation of EGFR *via* increased production of EGFR ligands (*e.g.*, amphiregulin), thereby further propagating and enhancing KRAS activity, as well as creating an immunosuppressive microenvironment. We hypothesize that oncogenic *KRAS* potentiates a signaling network that is stimulated and sustained by environmental factors. As YAP/TAZ play a central role in the signaling network, targeting this network at different sites with FDA-approved drugs, including statins and metformin (Figure 2), is therefore a compelling approach, especially in obese patients at higher risk of developing PDAC.

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