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Title:

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Date:

2018-09-07

Citation:

Wang, K., Baldwin, G. S., Nikfarjam, M. & He, H. (2018). P21-activated kinase signalling in pancreatic cancer: New insights into tumour biology and immune modulation. World Journal of Gastroenterology, 24 (33), pp.3709-3723. <https://doi.org/10.3748/wjg.v24.i33.3709>.

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p21-activated kinase signalling in pancreatic cancer: New insights into tumour biology and immune modulation

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Author contributions: Wang K reviewed the literature and drafted the manuscript; He H, Baldwin GS and Nikfarjam M revised the manuscript; all authors approved the final version of this review.

Conflict-of-interest statement: No potential conflicts of interest.

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Manuscript source: Unsolicited manuscript

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Received: May 22, 2018

Peer-review started: May 23, 2018

First decision: June 11, 2018

Revised: June 22, 2018

Accepted: June 27, 2018

Article in press: June 27, 2018

Published online: September 7, 2018

Abstract

Pancreatic cancer is one of the most aggressive and

lethal malignancies worldwide, with a very poor prognosis and a five-year survival rate less than 8%. This dismal outcome is largely due to delayed diagnosis, early distant dissemination and resistance to conventional chemotherapies. Kras mutation is a well-defined hallmark of pancreatic cancer, with over 95% of cases harbouring Kras mutations that give rise to constitutively active forms of Kras. As important down-stream effectors of Kras, p21-activated kinases (PAKs) are involved in regulating cell proliferation, apoptosis, invasion/migration and chemo-resistance. Immunotherapy is now emerging as a promising treatment modality in the era of personalized anti-cancer therapeutics. In this review, basic knowledge of PAK structure and regulation is briefly summarised and the pivotal role of PAKs in Kras-driven pancreatic cancer is highlighted in terms of tumour biology and chemo-resistance. Finally, the involvement of PAKs in immune modulation in the tumour microenvironment is discussed and the potential advantages of targeting PAKs are explored.

Key words: Pancreatic cancer; Kras; p21-activated kinases; Cell signalling; Chemo-resistance; Immune response; Tumour microenvironment

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Core tip: Pancreatic cancer is still one of the most lethal malignancies, with a five-year survival of less than 8%. The dismal prognosis is largely the result of reprogramming of the tumour microenvironment, which leads to chemo-resistance and high aggressiveness. So far, combination chemotherapies can only marginally improve patients' survival, but with high toxicity. Therefore, alternative treatment targeting protein kinase signalling has been proposed. As downstream effectors of Kras signalling, p21-activated kinases (PAKs) are positioned at the nexus of multiple oncogenic signalling pathways. Here, the importance of PAKs as therapeutic targets in Kras signalling is discussed, and their essential

role in tumour biology and immune modulation within the tumour microenvironment is highlighted.

Wang K, Baldwin GS, Nikfarjam M, He H. p21-activated kinase signalling in pancreatic cancer: New insights into tumour biology and immune modulation. *World J Gastroenterol* 2018; 24(33): 3709-3723 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i33/3709.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i33.3709>

INTRODUCTION

Pancreatic cancer is a highly aggressive and lethal malignancy with a dismal prognosis. In contrast to the improvements in therapies and the consequent increasing long-term survival rate for most other cancers, few advances have been achieved in pancreatic cancer, for which the overall five-year survival rate is still less than 8%^[1]. The death rate from pancreatic cancer continues to increase by 0.3% per annum, and it is estimated that this malignancy will become the second most common cause of cancer-related death in the United States by 2030^[2].

Although surgery remains the only curative treatment, chemotherapy is still an important and indispensable treatment in maximizing the life span for both resectable and unresectable patients. Currently gemcitabine-based combination therapies and FOLFIRINOX (irinotecan, oxaliplatin, fluorouracil, and leucovorin) are the mainstream approaches for patients with local advanced and metastatic pancreatic cancer, with an increased survival compared to gemcitabine alone^[3-6]. However, the modest improvement in survival, the highly toxic side effects and chemo-resistance have become major challenges in the clinical setting. Therefore, there is an urgent need to develop more effective and less toxic therapeutic strategies to treat this malignancy.

Progression of pancreatic cancer is marked by an accumulation of multiple genetic mutations, of which mutation in the Kras oncogene is the most frequent, with over 95% of pancreatic cancers harbouring a Kras mutation^[7]. The presence of missense mutations at codons 12, 13 or 61 within the Kras gene disrupts the physiological inactivation cycle of the Kras protein, resulting in a constitutively activated state even in the presence of GTPase activating protein.

The Kras protein is notable for the absence of a well-defined drug-binding domain on its surface^[8]. So far, despite over thirty years of intensive biomedical research, no drug directly targeting the Kras protein has proved to be an effective cancer treatment in the clinic^[7,9]. While some exciting and promising results have appeared for treatments that targeted important downstream effectors of Kras such as PI3K, AKT and MEK, resistance developed rapidly in almost all cases, making these molecular targets less effective^[10]. In

order to overcome this challenge, approaches targeting novel downstream effectors of the Kras protein are urgently needed. Recently, the National Cancer Institute in the United States has proposed a new project to fight against Ras-driven cancers, with the stated aim that new therapeutic strategies interfering with Ras-dependent signalling pathways should be given priority in cancer research^[11]. One such family of novel effectors is the p21-activated kinases (PAKs), which are activated by Kras and by other small GTPases like Cdc42 and Rac by both direct and indirect mechanisms. PAKs are positioned at the nexus of multiple oncogenic signalling pathways that mediate a variety of hallmark processes in pancreatic cancer.

Pancreatic cancer has its own unique immune response during tumour development. The Kras oncogene can mediate the inflammatory process and establish within the tumour microenvironment an immune-privileged condition, which is responsible for the suppression of effector cells and the stimulation of immunosuppressive cells^[12]. Additionally, the extensive desmoplastic reaction in pancreatic cancer also functions as a physiological barrier against immune surveillance, leading to evasion of the anti-tumoural immune response and tumour progression^[13].

In this review, basic knowledge of PAK structure and regulation is briefly summarised, and the importance of PAKs as a therapeutic target in Kras signalling is highlighted. The essential role of PAKs in regulating tumour biology and stromal re-programming, especially of the immune response within the tumour microenvironment, is also discussed.

STRUCTURE AND ACTIVATION OF PAKS

PAKs are a family of serine/threonine kinases that are the downstream effector proteins of Ras, and of other small GTPases such as Cdc42 and Rac. The six known members of the PAK family can be categorized by similarities in their sequence and structure into two groups: group I (PAK1-3) and group II (PAK4-6)^[14]. All PAKs are characterized by an N-terminal regulatory domain and a conserved C-terminal serine/threonine kinase domain with a single phosphorylation site (Figure 1), but the activation of group I and group II PAKs is regulated through completely different mechanisms^[15,16].

The group I PAKs share a high level of structural homology with over 88% identity in the GTPase-binding domain (GBD) that is responsible for binding Cdc42 or Rac, and more than 93% identity in the kinase domain^[14]. However, their tissue specific distribution is quite different from each other. PAK1 can be found in various organs including brain, mammary gland, muscle, and spleen; PAK2 is ubiquitously expressed; whereas PAK3 is only expressed in the nervous system^[17]. The N-terminal regulatory domain of group I PAKs contains an autoinhibitory domain (AID) that overlaps with the GBD. In the inactivated state, group

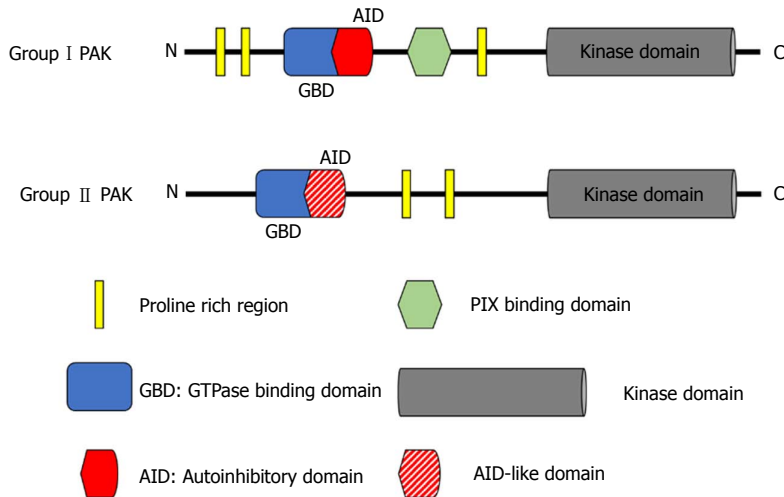


Figure 1 Structure of p21-activated kinases. The six members of the PAK family can be divided by sequence and structural differences into two groups: Group I (PAK1-3) and group II (PAK4-6). All PAKs have an N-terminal regulatory domain and a conserved C-terminal serine/threonine kinase domain. In group I PAKs, the regulatory domain contains an AID, whereas group II PAKs (with the possible exception of PAK5) do not have a well-defined AID, but instead an AID-like domain. PIX: PAK-interactive exchange factor; PAK: p21-activated kinases; AID: Autoinhibitory domain; GBD: GTPase-binding domain.

I PAKs form homodimers, with the AID domain of one PAK molecule binding to the kinase domain of its companion. When Cdc42/Rac binds to the GBD, binding of the AID to its partner PAK is disrupted. This critical process generates two PAK monomers, and allows the subsequent autophosphorylation at the Thr⁴²³ site, which is important for maintaining PAK1 activation^[18-21].

Group II PAKs have a quite different structure from group I PAKs, but the three members are still similar to each other. They share at least 60% identity in the N-terminal GBD and over 75% identity in the kinase domain. However, the identities between Group I and Group II PAKs are less than 40% in the GBD and only about 54% in the kinase domain^[14]. PAK4 is highly expressed throughout embryonic development, and ubiquitously expressed in all adult tissue at a low level^[22,23]. PAK5 is specifically expressed in the brain^[24]. PAK6 is not only found in the adult nervous system, but also in the male reproductive system (e.g., testes and prostate). This distribution correlates with its important role in the androgen receptor signalling pathway^[25,26]. Although group II PAKs (with the possible exception of PAK5) have no well-defined AID in the N-terminal domain, later studies have reported AID-like domains^[27,28]. Unlike group I PAKs, group II PAKs are monomers and are constitutively phosphorylated, even in their inactivated state^[15]. Although there is still much debate on the exact activation mechanism of group II PAKs, two different activation models have been proposed over the last decade. In the first model, the AID-like domain binds to the kinase domain of the same molecule, which results in an inactive conformation regardless of the constitutive autophosphorylation. When Cdc42 binds to the GBD, binding of the AID-like domain to the kinase domain is disrupted, leading to an active conformation^[15]. In the second model, an autoinhibitory pseudo-substrate domain, next to the GBD but distinct

from the AID, interacts with the kinase domain, reducing activity. The binding of Cdc42 to GBD translocates the group II PAK to a subcellular region where a Src homology 3 domain-containing protein binds to the autoinhibitory pseudo-substrate domain, preventing its interaction with the kinase domain and hence increasing activity^[28].

ROLE OF PAKS IN KRAS-DRIVEN ONCOGENIC PATHWAYS

Kras is the most frequently mutated isoform observed in all types of human cancer compared to NRas and Hras. Kras mutation is a key oncogenic driver in the development of pancreatic, colorectal and lung cancer^[29]. It acts as a regulatory switch in diverse sub-cellular signal transduction networks, which are responsible for stem-cell like features, cell survival, proliferation, invasion and migration^[30].

A study of a genetically engineered mouse model for pancreatic cancer, the KPC (LSL-Kras^{G12D}; LSL-Trp53^{R172H}; Pdx1-Cre) model, has revealed that expression of the Kras^{G12D} mutation is sufficient to induce pancreatic intraepithelial neoplasia (PanIN), followed by advanced carcinoma^[31]. Similarly, Ying and colleagues demonstrated that the Kras^{G12D} mutation was necessary for the maintenance of pancreatic cancer as Kras depletion resulted in rapid tumoural regression and stromal degeneration in an oncogenic Kras-induced tumour model^[32]. Mutated Kras can cause phosphorylation and activation of other p21 proteins such as Rac1 and Cdc42, through both canonical and alternative pathways^[33]. Then the interaction between Rac1/Cdc42 and PAKs can increase PAK activity, leading to persistent activation of downstream signalling pathways such as the RAF/MEK/ERK and PI3K/PDK1/

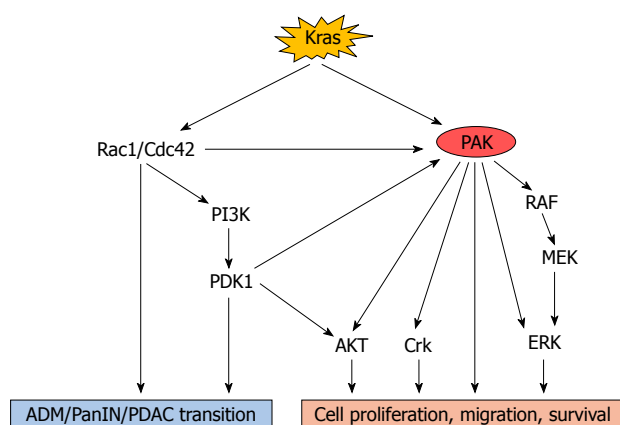


Figure 2 Role of p21-activated kinases in Kras-driven oncogenic signalling pathways. Rac1 is the 4th best validated effector in Kras signalling and is a well-defined upstream protein of PAKs. Rac1 plays an important role in the ADM/PanIN/PDAC transition. In addition, Rac1/Cdc42 mediates this pathological process via the PI3K-PDK1 signalling pathway. PDK1 can also interact with PAK1, leading to its phosphorylation. The Kras oncogene activates PAKs through direct and indirect pathways. Activated PAKs can increase cancer cell proliferation, migration and survival through activation of AKT, Crk and RAF-MEK-ERK pathways. PAK: p21-activated kinases; ADM: Acinar-ductal metaplasia; PDAC: Pancreatic ductal adenocarcinoma; PDK1: Phosphoinositide-dependent kinase-1.

AKT pathways^[34-37] (Figure 2).

A recent study of non-small cell lung cancer reported that Kras-mutated tumours expressed more Thr⁴²³-phosphorylated PAK1 than Kras-wild type tumours, and that the Kras/PAK1/Crk axis played an essential role in the oncogenesis of Kras-mutated lung cancer^[38]. Activation of PAK1 could also be mediated by multiple Kras-dependent pathways via different cell surface receptors. Dominant-negative Ras, Rac, and Cdc42 suppressed PAK1 activation whereas activated Rac1 and Cdc42 were able to stimulate PAK1 even in the absence of any agonists^[39]. As a potent activator of PAK1, Rac1 is the 4th best validated effector in the Kras-driven cell signalling cascade^[40]. In an early study, Rac1 was found to be associated with pancreatic acinar plasticity and Rac1 inhibition reduced acinar cell damage induced by pathological inflammation^[41]. The important role of Rac1 in early metaplasia and neoplasia-related actin rearrangements has been revealed in a Kras-driven mouse model of pancreatic cancer^[42]. Rac1 ablation in this model reduced the incidence of acinar-ductal metaplasia (ADM), PanIN and tumour formation and significantly improved animal survival. Interestingly, this study also found that Rac1 was not indispensable in pancreas development^[42]. Similarly, Zheng *et al.*^[43] reported that Rac1 and Cdc42 could mediate the activation of PI3K by interacting with its 85-kDa regulatory domain. Another study documented that PI3K together with PDK1 acted as critical downstream effectors of oncogenic Kras signalling in mediating ADM and formation of pancreatic cancer^[44]. PDK1 was also reported to interact with PAK1 both *in vitro* and *in vivo*, leading to increased phosphorylation at the Thr⁴²³ site

and hence activation of PAK1^[45].

There is increasing evidence for a key role of PAK1 in regulating Kras-dependent signalling pathways. PAK1 can phosphorylate c-RAF at Ser³³⁸ in NIH3T3 cells (murine fibroblast cell line), and inhibition of group I PAK kinase activity significantly reduced the phosphorylation of MEK1 at Ser²⁹⁸ and the activation of ERK in response to different growth factors (e.g., platelet-derived growth factor or epidermal growth factor) in NIH3T3 and HeLa cells (human cervical cancer cell line)^[46]. Huynh *et al.*^[47] demonstrated that PAK1 stimulates colon cancer cell proliferation, migration/invasion, and survival via ERK- and AKT-dependent pathways. Inhibition of PAK1 effectively inhibits both ERK and AKT, to an extent which cannot be achieved by inhibition of either alone. Another study also showed that genetic deletion of PAK1, followed by decreased ERK and AKT activity, suppressed tumourigenesis and progression in a Kras-mediated skin cancer model^[48]. In contrast, Tabusa and colleagues found that knockdown of PAK1 or PAK4 inhibited the proliferation of Kras-mutated colorectal cancer cells via non-canonical pathways independent of RAF/MEK/ERK and PI3K/AKT signalling^[49].

A relationship between PAK4 and Kras has been identified through genetic analysis of human pancreatic cancer cell lines and patients' samples^[50]. By sequencing the Kras gene in PAK4-amplified tumour samples, mutations in codon 12 were observed in 4 out of the 5 samples. Furthermore, genomic amplification and overexpression of Kras occurred in 3 samples. Interestingly, no mutations were detected in Kras or PAK4 in the fifth sample, but the observation of increased PAK4 expression suggests that PAK4 could be up-regulated and activated through some Kras-independent pathways. Taken together, the above evidence suggests that PAKs play an important role in interacting with and transmitting Kras-driven oncogenic signals in different kinds of human cancer.

PAK SIGNALLING IN PANCREATIC CANCER

Amplification of the PAK1 gene within chromosomal region 11q13 was reported to be linked to both tumourigenesis and poor prognosis of different human cancers^[51,52]. Amplification of the PAK4 gene within chromosomal region 19q13.2 was also identified in a variety of human malignancies, especially pancreatic, breast, and ovarian cancer^[50,53,54]. By using fluorescent *in situ* hybridization on tumour microarrays, Kimmelman *et al.*^[55] found PAK4 amplification occurred in 14 of 63 (22%) pancreatic cancer samples. In addition, RT-qPCR and Western blots showed increased PAK4 expression in multiple pancreatic cancer cell lines regardless of gene amplification, implying different underlying mechanisms mediating PAK4 expression. Interestingly, the observation that the CCND1 (Cyclin D1) and CCNE1 (Cyclin E1)

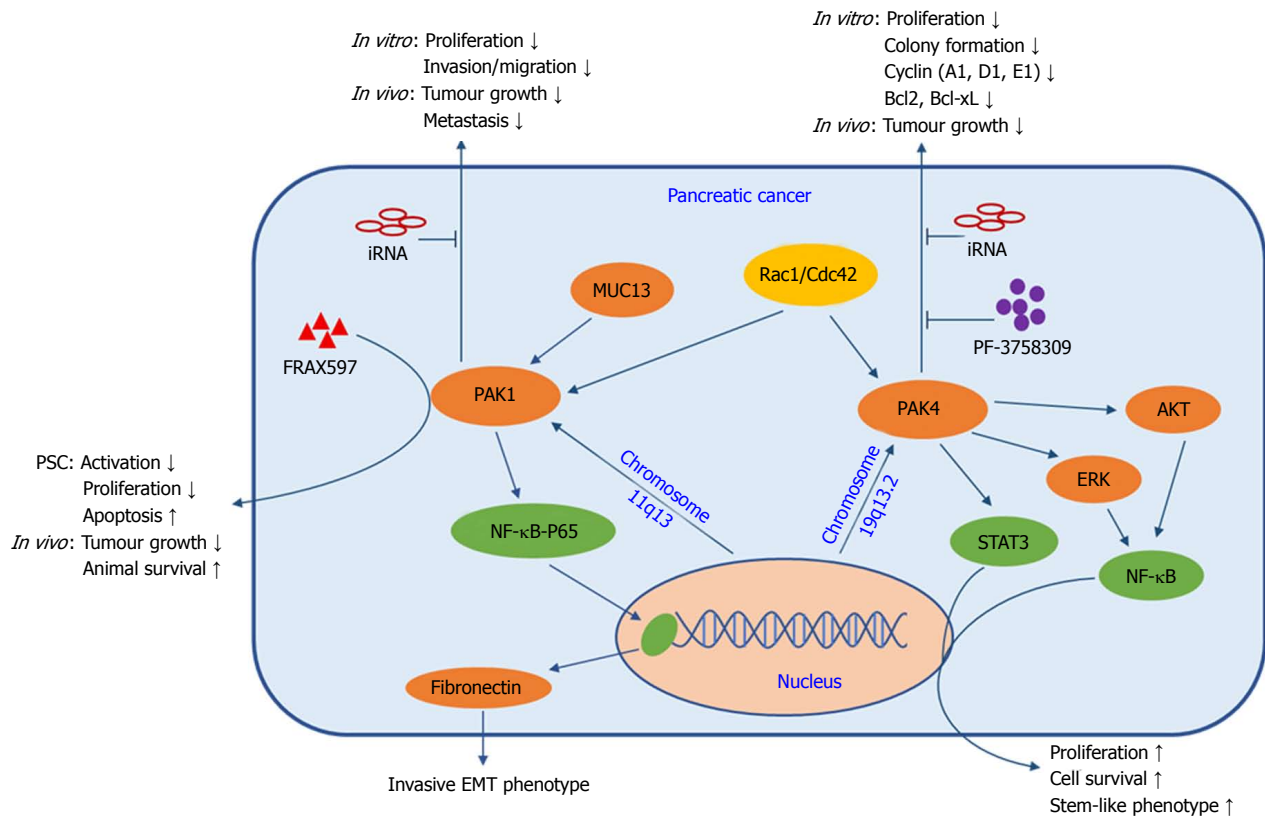


Figure 3 p21-activated kinases signalling in the development of pancreatic cancer. PAK signalling is involved in several pathobiological processes in pancreatic cancer, including proliferation, migration/invasion, apoptosis and maintenance of stem cell-like properties. Amplification of the PAK1 and PAK4 genes, present within the chromosomal regions 11q13 and 19q13.2, respectively, has been observed. Activated PAK1 regulates cell transformation and the invasive EMT phenotype of pancreatic cancer cells via the NF-κB-p65-fibronectin axis. Additionally, MUC13 promotes cancer cell growth and invasion/migration, and reduces animal survival, by up-regulating expression and phosphorylation of PAK1. Furthermore, PAK4 modulates proliferation and survival by mediating the activity of NF-κB via AKT- and ERK-dependent pathways, and cancer stem cell-like properties via STAT3 signalling. Pharmacological or genetic inhibition of PAK1 or PAK4 leads to decreased cancer cell proliferation, invasion/migration and PSC activation *in vitro*, and reduced tumour growth and metastasis, and increased animal survival *in vivo*. PAK: p21-activated kinases; PSC: Pancreatic stellate cells.

genes were co-amplified within the same chromosomal region as PAK1 and PAK4, respectively^[16,56], suggests that co-amplification of PAK1 with CCND1 and PAK4 with CCNE1 may have synergistic effects on the initiation and progression of pancreatic cancer.

Role of PAK1 in tumour proliferation, migration and tumour-stroma interaction

A study of 304 human primary pancreatic cancer samples found that 262 (86%) cases were positive for cytoplasmic PAK1 staining, and approximately one-third of all samples showed moderate (2+) to strong (3+) intensity in the malignant cells and nuclear localization of PAK1^[57]. Two more recent studies have also shown increased PAK1 expression in resected human pancreatic cancer tissues and cell lines, when compared to the adjacent normal pancreas and an immortalized normal pancreatic ductal epithelial cell line, respectively^[58,59]. A PAK1 knock-down pancreatic cancer cell line failed to develop tumours in nude mice^[58] and showed markedly reduced proliferation^[59]. Furthermore, Jagadeeshan and colleagues demonstrated that fibronectin was a transcriptional target of PAK1 signalling via the NF-κB-p65-fibronectin axis, which modulates cell transformation

and the invasive EMT phenotype of pancreatic cancer cells (Figure 3). Early studies also showed the localization of activated PAK1 to the cell nucleus^[60] and its involvement in the activation of NF-κB, by demonstrating that active Ras or Rac1 stimulated NF-κB in a PAK1-dependent manner and that active PAK1 itself could stimulate NF-κB as well^[61]. An important transmembrane mucin (MUC13) was also reported to be involved in PAK1 signalling in the development of pancreatic cancer^[62]. Overexpression of MUC13 promoted cancer cell proliferation, invasion/migration and anchorage-dependent or -independent colony formation *in vitro* and led to increased xenograft tumour growth and decreased animal survival *in vivo*. These tumourigenic properties were closely associated with the up-regulated expression and phosphorylation of PAK1, ERK and AKT, and suppression of p53. Wei *et al.*^[57] screened a panel of pancreatic cancer cell lines and characterized PAK1 as a key downstream effector of cell motility triggered by multiple growth factors. In their study, PAK1 inhibition not only restored sensitivity to a hepatocyte growth factor/Met antagonist (onartuzumab) in the presence of exogenous growth factors or PAK1-amplification *in vitro*, but also suppressed tumour growth and metastasis *in vivo*.

In recent years, the interaction between pancreatic cancer cells and pancreatic stellate cells (PSCs) has become the focus of pancreatic cancer research. Activation of PSCs by cancer cells is predominately responsible for fibrosis and stromal remodelling. The role of PAK1 in modulating EMT markers (*e.g.*, fibronectin, E-cadherin, and vimentin) has been established in early studies^[63]. A recent study revealed the role of PAK1 in PSC modulation for the first time by showing that inhibition of PAK1 by FRAX597 (a potent group I PAK inhibitor) reduced the activation and proliferation of PSC and increased apoptosis *in vitro*. In an orthotopic pancreatic cancer mouse model, survival in the PAK1 knockout group was significantly increased compared to the PAK1 wildtype group, and depletion of PAK1 in the pancreatic stroma also reduced PAK1 expression and activity in the tumour^[64]. Similarly, survival was prolonged in the group treated with FRAX597 plus gemcitabine in the same orthotopic pancreatic cancer model^[59]. These results pave the way to a detailed investigation of the role of PAK1 in tumour-stroma interactions in order to improve therapeutic response by using targeted inhibitors.

Role of PAK4 in tumour proliferation, migration, survival and stemness maintenance

PAK4 expression is reported to be correlated with pancreatic cancer pathology. Tyagi *et al.*^[65] found 54 out of 56 tumour samples from patients with pancreatic cancer had positive PAK4 staining, with no PAK4 positive staining in normal pancreatic tissue. Furthermore, PAK4 promoted cancer cell proliferation and survival by stimulating the nuclear accumulation and transcriptional activity of NF- κ B *via* AKT- and ERK-dependent pathways (Figure 3). PAK4 knockdown in pancreatic cancer cells caused suppression of growth and colony formation associated with reduced expression of cell-cycle (cyclin A1, D1, E1) and anti-apoptosis (Bcl2, Bcl-xL) proteins. Similarly, inhibition of PAK4 by PF-3758309 (a potent pan-PAK inhibitor) suppressed cancer cell proliferation and migration both *in vitro* and *in vivo*^[66]. Kimmelman *et al.*^[55] identified Rio Kinase 3 and PAK4 as amplified genes in highly recurrent and focal amplifications in pancreatic cancer. Rio Kinase 3 can activate the small GTPase protein Rac, which can subsequently promote cell motility and invasion *via* PAK4-mediated signalling. In addition, overexpression of activated PAK4 resulted in increased invasion/migration in a gain-of-function experiment, while PAK4 knockdown by shRNA significantly reduced anchorage independent growth in a loss-of-function experiment. Recently, PAK4 has been shown to modulate STAT3 signalling in the maintenance of pancreatic cancer stem cells, which are considered to be responsible for high aggressiveness and chemo-resistance. Pancreatic cancer stem-like cells (CD24⁺/CD44⁺/EpCAM⁺) showed higher PAK4 expression as compared to triple negative cells (CD24⁻/CD44⁻/EpCAM⁻). PAK4 expression enhanced the expression of stem cell-

associated transcription factors (Oct4/Nanog/Sox2 and KLF4), whereas PAK4 silencing caused reduced nuclear accumulation and transcriptional activity of STAT3 and loss of stem cell phenotypes^[67,68]. The accumulated evidence, which suggests that PAKs are positioned at the convergence point of numerous oncogenic pathways, highlights their potential as promising therapeutic targets in the treatment of pancreatic cancer.

PAKS AND CHEMO-RESISTANCE IN PANCREATIC CANCER

Currently, surgical resection is the only curative treatment for pancreatic cancer. However, due to the lack of biomarkers for early diagnosis, low surgical resectability (only 15%-20% of patients are considered to be eligible candidates)^[69], and high recurrence rate (up to 60%), the overall median survival is still less than 20 mo in patients undergoing resection of pancreatic cancer with curative intent^[70]. Therefore, chemotherapy remains a crucial alternative or adjuvant treatment for patients with resectable or unresectable tumours^[71].

Two decades ago, gemcitabine emerged as the standard of care for pancreatic cancer patients^[72]. So far, gemcitabine + nab-paclitaxel and FOLFIRINOX have been approved by the United States Food and Drug Administration as first-line therapies, especially for patients with locally advanced and metastatic pancreatic cancer^[3,6]. Although previous clinical studies reported several advantages of gemcitabine over 5-FU, including prolonged median survival, improved tumour-related symptoms and lower systemic toxicity^[73-75], the results were still unsatisfactory, with effective responses in less than 10% of patients. Therefore, various modifications of gemcitabine treatment have been designed to overcome resistance and increase drug delivery into the tumour. These modifications include CO-101^[76] (a lipid-conjugated gemcitabine, which can be transported into tumour cells independently of the human equilibrative nucleoside transporter, and Acelarin^[77] (an aryloxy phosphoramidate derivative of gemcitabine with greater lipophilicity, which accumulates in cancer cells by passive diffusion independently of the nucleoside transporter). However, intrinsic and acquired gemcitabine resistance occurs in most patients, and its underlying molecular mechanism is still not fully understood.

Mechanisms involved in chemo-resistance of cancer cells

In a prospective randomized clinical study, the human equilibrative nucleoside transporter 1 (hENT1), which is the principal cellular transporter of gemcitabine, was found to be a valuable predictive marker of gemcitabine sensitivity in patients with resected pancreatic cancer^[78]. In addition, a comparative study also indicated that decreased hENT1 expression was associated with gemcitabine resistance and poorer overall survival in

patients with pancreatic cancer^[79]. However, an early study reported that up-regulated hENT1 expression was also observed in some gemcitabine-resistant pancreatic cancer cell lines^[80]. This evidence implicated hENT1 as the predominant, but not the only, metabolic protein mediating resistance. To some extent, hENT2 and the human concentrative nucleoside transporters hCNT1 and hCNT3 may also contribute to the development of acquired and intrinsic gemcitabine resistance^[81,82]. Moon and colleagues have shown that gemcitabine-resistant cell lines express more PAK4 and less hENT1. PAK4 knockdown in gemcitabine-resistant cell lines induces the up-regulation of hENT1 and restoration of sensitivity to gemcitabine^[83]. In contrast, one recent retrospective clinical study, which analyzed 160 resected human pancreatic cancer samples by immunohistochemistry, reported that higher expression of PAK4 was correlated with higher expression of hENT1^[84]. Therefore, the controversial role of PAK4 in regulating hENT1 should be further explored.

Furthermore, Jagadeeshan *et al.*^[85] revealed that PAK1 plays a pivotal role in mediating gemcitabine resistance by altering apoptosis and survival signals, and suppressing DNA damage *via* the NF- κ B pathway. Phosphorylation of PAK1 and ribonucleotide reductase M1 was elevated in patient samples when compared with normal tissue. Combination treatment with a PAK1 inhibitor synergistically improved gemcitabine efficacy and led to tumour regression in animal models. In agreement with this finding, inhibition of PAK1 or/and PAK4 by shRNA knockdown or PAK inhibitors enhanced gemcitabine sensitivity both *in vitro* and *in vivo*^[59,66].

Other potential PAK-associated signalling pathways also contribute to chemo-resistance. Higher expression of HIF-1 α was observed in gemcitabine-resistant pancreatic cancer cell lines^[86] and inhibition of HIF-1 α can sensitize cancer cells to gemcitabine treatment^[87]. The increased activity of HIF-1 α was associated with inhibition of the transcription of hENT1 and hENT2, leading to reduced expression of transporter proteins followed by decreased gemcitabine uptake^[88,89]. The critical role of PAKs in regulating HIF-1 α has been demonstrated in our previous studies, which showed that PAK1 could enhance cancer cell survival by up-regulation of HIF-1 α and that inhibition of PAK1 caused decreased expression of HIF-1 α and tumour growth^[59,90]. Another recent study also found that PAK4 inhibition reduced expression of HIF-1 α *via* the AKT-mTOR-4E-BP1 axis^[91].

Additionally, the important transcription factor NF- κ B is also a critical regulator closely associated with gemcitabine resistance in pancreatic cancer. As discussed above, localization of active PAK1 to the nucleus is involved in activation of NF- κ B^[60,61], and both PAK1 and PAK4 contribute to cell transformation, proliferation and survival *via* NF- κ B-dependent signalling pathways in pancreatic cancer^[58,65]. Over a decade ago, Arlt and colleagues revealed that resistant cell lines (BxPC-3, Capan-1 and PancTu-1) showed higher expression of NF- κ B, comparing to sensitive cell lines

(PT45-P1 and T3M4). Treatment of these five pancreatic cancer cell lines with gemcitabine induced NF- κ B activity in a dose-dependent manner^[92]. Inhibition of the p65 subunit of NF- κ B by siRNA can improve gemcitabine sensitivity to suppress proliferation and induce apoptosis both *in vitro* and *in vivo*^[93]. In agreement with this conclusion, Skrypek *et al.*^[94] also showed that decreased activation of NF- κ B pathway was correlated with an alteration of hCNT1 expression and increased gemcitabine sensitivity in MUC4-knockdown pancreatic cancer cell lines.

Furthermore, both expression and activity of PAK4 have also been reported to be up-regulated in cisplatin-resistant cancer cells as compared with parental cells. Inhibition of PAK4 diminished cisplatin resistance *via* PI3K/AKT and MEK/ERK-dependent signalling pathways^[95].

Stromal remodelling

The extensive desmoplastic reaction, which is a hallmark of pancreatic cancer, is reported to result in a dense stroma, deficient vascularization and inefficient drug delivery, eventually leading to chemo-resistance^[96,97]. As mentioned above, PAK1 is responsible for PSC activation, leading to stromal fibrosis^[64] in pancreatic cancer similar to its pivotal role in liver fibrogenic pathways^[98].

The importance of Hedgehog (Hh) signalling in tumorigenesis and desmoplasia has been well established. Hh can modify the extracellular matrix component *via* regulation of the differentiation and motility of PSCs and fibroblasts^[99,100]. The observation, in an early global genomic analysis of 24 human pancreatic cancers, that Hh signalling was one of the core set of 12 most commonly altered cellular signalling pathways and was present in 100% of cases suggests a significant contribution of Hh signalling to the development of pancreatic cancer^[101]. A number of previous studies also demonstrated that depletion of the Hh signalling pathway could partly diminish desmoplasia-associated resistance and synergistically enhance gemcitabine efficacy both *in vitro* and *in vivo*^[102-104]. Hiroshi *et al.*^[105] found that activation of NF- κ B resulted in the aberrant activation of Hh signalling *via* up-regulation of sonic Hh (a ligand of Hh signalling) in pancreatic cancer.

Interaction of the C-X-C motif chemokine 12 (CXCL12), which is also known as stromal cell-derived factor 1, with its receptor, the C-X-C motif chemokine receptor 4 (CXCR4), can induce activation of downstream signalling pathways related to tumour progression and metastasis^[106]. Singh *et al.*^[107] have identified the essential role of the CXCL12/CXCR4 axis in stimulation of Hh signalling in a dose- and time-dependent manner. CXCL12-induced Hh up-regulation is due to the increased nuclear accumulation and activation of NF- κ B mediated by AKT and ERK signalling pathways. The involvement of PAK1 and PAK4 in NF- κ B signalling in pancreatic cancer has been clearly identified^[58,61,65]. Although the interaction between PAKs and Hh-mediated chemo-resistance is still not clear, the above findings indicate that PAKs might

regulate Hh signalling in a NF- κ B-dependent manner and further investigation is needed.

EMERGING ROLE OF PAKS IN IMMUNE MODULATION IN THE TUMOUR MICROENVIRONMENT

As an important component of the stromal micro-environment, infiltrating immune cells (IICs) have been characterized as valuable markers in predicting prognosis. Generally, IICs exhibit both pro-tumour and anti-tumour effects. The former class of IICs include regulatory T cells, myeloid-derived suppressor cells (MDSC), and tumour-associated macrophages (TAM) which suppress anti-tumour immunity and promote tumour growth, whereas the latter class include CD8⁺ T cells, Th1-type CD4⁺ T cells, and natural killer cells^[108,109]. Immunosuppressive cells can ward off the host immune defence, prevent tumour cells from being recognized and further lead to immune evasion, even in pre-cancerous lesions such as PanINs and intraductal papillary mucinous neoplasm (IPMN)^[110]. Therefore, a great deal of attention has been paid to targeting the aberrant immune regulation of the tumour microenvironment, with the intention of reversing the suppression of active anti-tumour immunity. A good example is the conversion of pancreatic cancer from “a non-immunogenic malignancy” into “an immunogenic malignancy” by treatment with a novel immunomodulatory vaccine, which blocked the immune checkpoint (PD-1/PD-L1, CTLA-4) and made therapy more effective in vaccine-treated patients than in untreated patients^[111].

Myeloid-derived suppressor cells

MDSCs, which include both granulocytic and monocytic subsets, are a heterogeneous mixture of activated immature myeloid cells, which can stimulate angiogenesis, promote tumour invasion and migration, and suppress T-cell activation^[112]. Both circulating and tumour-infiltrating MDSCs, of the granulocytic subset (Lin-HLA-DR-CD33⁺CD11b⁺CD15⁺), but not the monocytic subset (Lin-HLA-DR-CD14⁺), are markedly elevated in patients with pancreatic cancer compared to the healthy population. Moreover, MDSCs can also serve as an independent prognostic factor for patients' survival as one unit increase in MDSC percentage leads to a 22% greater risk of mortality^[113,114]. The report by Thomas *et al.*^[115] of a non-canonical role of the mammalian target of rapamycin (mTOR) protein in recruiting tumourigenic MDSC suggests that cancer cells can stimulate intra-tumoural MDSC accumulation by promoting granulocyte colony-stimulating factor (G-CSF) production *via* an mTOR-dependent pathway. He and colleagues demonstrated the critical role of PAK4 in regulating mTOR signalling through the PI3K/AKT axis in breast cancer^[116]. In addition, PAK1 can be activated by the mTOR/p70 S6 kinase pathway, and treatment with rapamycin, a mTOR inhibitor, leads

to reduced PAK1 expression^[117]. Interestingly, an early study on vascular smooth muscle cells indicated that G-CSF was involved in activation of the GTPase Rac1, a potent upstream activator of PAK1, and inhibition of Rac1 suppressed G-CSF-driven migration of vascular smooth muscle cells^[118]. Previous studies also found that pancreatic cancer cells or stellate cells can attract and transform peripheral blood monocytes into MDSCs *via* STAT3 activation, which in turn will increase the stem-cell properties and mesenchymal features of tumour cells^[119,120]. The role of PAK1 and PAK4 in regulating STAT3 signalling in pancreatic cancer cells has been clearly identified^[67,121]. Although there is as yet little direct evidence linking PAK to MDSC modulation, the above findings indicate that PAK might orchestrate multiple signalling pathways to mediate MDSC recruitment and activation.

Tumour-associated macrophages

TAMs can be divided into two subtypes: M1 (pro-inflammatory macrophages) and M2 (anti-inflammatory macrophages). Like MDSCs, the majority of TAMs are derived from circulating monocytes^[122]. M1 TAMs can suppress tumour development by stimulating a T-cell-mediated anti-tumour response, whereas the crosstalk of M2 TAMs with tumour and stellate cells can stimulate secretion of various anti-inflammatory cytokines, and reprogram immune surveillance within the tumour microenvironment to facilitate tumour progression^[123].

Stephen *et al.*^[124] have identified a role of PAK1 in regulating macrophage spreading and lamellipodial dynamics through the activation of ERK1/2. However, they also found that PAK1 knockout had no impact on migration or chemotaxis of macrophages, whereas another study reported that absence of Rac1 or Rac2 could promote macrophage migration^[125]. These observations suggest either that PAK2 might compensate for the lack of PAK1, or that other Rac down-stream effectors are involved in regulating cell migration^[126]. In addition, Gringel *et al.*^[127] found that PAK4 functioned as a physiological regulator of podosomes, which are involved in the migration of human macrophages. Up-regulated expression and activity of PAK4 and its regulator α -PIX (PAK-interacting exchange factor) enhanced the number and size of macrophage podosomes.

There are some additional potential mechanisms linking PAKs to macrophage migration and chemotaxis. The interaction between PAK and HIF-1 α has been well established from previous studies^[59,90,91]. Recently, HIF-1 α was reported to be involved in the recruitment of TAMs in pancreatic cancer through promoting C-C motif chemokine ligand 2 (CCL2) secretion, which stimulated monocyte infiltration into the tumour microenvironment by binding to its receptor CCR2^[128]. In agreement with this report, Sanford *et al.*^[129] revealed an important role of CCL2/CCR2 in TAM recruitment by showing that a CCR2 antagonist (PF-04136309) was able to block the migration of circulating CCR2⁺ monocytes toward

the tumour with a consequent depletion of TAMs in a mouse model of pancreatic cancer. Their clinical data also indicated that pancreatic cancer patients with a higher level of CCL2 expression and greater infiltration of immunosuppressive CCR2⁺ TAMs were significantly more likely to have decreased survival. Additionally, Allen and colleagues revealed the importance of Rho family proteins in regulating actin organization and cell adhesion in macrophages^[130]. Using a colony-stimulating factor-1-dependent murine macrophage cell line (Bac1.2F5), they demonstrated that constitutively activated Rac1 or Cdc42, which are both well-defined up-stream activators of PAKs, could stimulate formation of lamellipodia or filopodia, whereas dominant negative Rac1 or Cdc42 inhibited colony-stimulating factor-1-induced formation of lamellipodia or filopodia.

Macrophage polarization is induced by different stimuli *via* interferon-regulatory factor/signal transducer and activator of transcription (IRF/STAT) signalling pathways, NF- κ B pathways and HIF stabilization. IRF/STAT factors (IRF3, IRF5, STAT1 and STAT5), HIF-1 and the active NF- κ B heterodimer (p50-p65) contribute to M1 polarization, while IRF/STAT factors (IRF4, STAT3 and STAT6), HIF-2 and the inhibitory NF- κ B heterodimer (p50-p50) trigger an M2 response^[131]. The involvement of PAK1 in macrophage polarization has recently been characterized by Zhang and colleagues, who reported that pharmacological or genetic inhibition of PAK1 diminished M1 macrophage polarization. This observation suggested that the up-regulation of PAK1 induced by inflammatory stimuli may contribute to M1 polarization *via* NF- κ B-mediated transcriptional activation. PAK1 was also observed to play a key role in suppressing M2 macrophage polarization^[132]. Blockade of the M2 response is an important approach to treatment involving TAM reprogramming. As mentioned above, STAT3 and STAT6 have been reported to be important regulators of M2 polarization. Pharmacological inhibition of STAT3 and STAT6 with specific inhibitors resulted in suppression of M2 polarization, increased production of pro-inflammatory cytokines and stimulated a T cell response^[133-135]. Since PAK1 and PAK4 are closely associated with the STAT3 and NF- κ B signalling pathway^[67,121], it is likely that PAK may interact with STAT3 or NF- κ B signalling pathways to block M2 polarization.

Tumour-infiltrating lymphocytes

Tumour-infiltrating lymphocytes (TILs), including CD4⁺ T cells, CD8⁺ T cells, regulatory T cells, B cells and natural killer cells, are another class of immune cells, which are critical in modulating the tumour microenvironment in pancreatic cancer^[136]. Although CD8⁺ T cells are also referred to as cytotoxic T cells, with the capability of recognizing and killing tumour cells, infiltration of CD8⁺ T cells into the tumour microenvironment is very rare. In contrast, a large number of CD4⁺ T cells, which can promote the development of PanINs *via* inhibition of the anti-tumour response, are observed in the stromal

compartment^[108,137]. Indeed, an increasing number of studies have revealed the predictive value of stromal TILs in patients with resectable pancreatic cancer. Two of the latest studies have demonstrated that negative stromal TIL patients had larger tumour at a more advanced stage and showed worse overall survival and liver metastasis^[138], and that an increased number of tumour-infiltrated CD8⁺ lymphocytes were significantly and independently related to improved disease-free survival and overall survival^[139]. Recently, it was reported that pharmacological or genetic depletion of PAK1 up-regulated the immune response to tumours in a colorectal mouse model (APC^{14/+} mouse)^[140]. Similarly, the role of PAK in regulating the tumour-associated immune response was investigated in an murine orthotopic pancreatic cancer model^[66]. In agreement with the colorectal model, removal of PAK1 by knock-out or inhibition of PAK1 by PF-3758309 not only suppressed tumour growth *in vivo*, but also stimulated the immune response by increasing the numbers of splenic CD3⁺ and CD8⁺ T lymphocytes as well as by promoting tumour-infiltrating CD3⁺ T lymphocytes. In contrast, gemcitabine did not significantly change the tumour-associated immune response. Furthermore, it has been reported that granulocyte-macrophage colony-stimulating factor (GM-CSF) secreted by tumour cells can recruit and stimulate the development of stromal myeloid cells (Gr-1⁺ CD11b⁺ cells), which can suppress the anti-tumour effect of CD8⁺ T cells^[141]. So far, the mechanism by which PAK regulates the production of GM-CSF has not been fully elucidated. However, Kras activation is found to be positively associated with GM-CSF expression in cancer patients when compared to normal controls^[142], and this observation is consistent with an early study indicating that oncogenic Kras-dependent secretion of GM-CSF can promote the development of pancreatic neoplasia *via* immunosuppression mediated by Gr-1⁺ CD11b⁺ myeloid cells^[143]. As Kras is the most important oncogenic mutation in pancreatic cancer and a potent up-stream regulator of PAK, these studies provided possible evidence implicating the involvement of PAK in a pathway linking aberrantly activated Kras to GM-CSF-induced immuno-evasion. The mechanisms underlying the connection between PAKs and GM-CSF should be investigated further.

CONCLUSION

More than a decade ago, an expert consensus proposed precise targeting of protein kinase signalling pathways as a potential weapon against cancers^[144,145]. As an important down-stream effector of Kras, PAK is overexpressed and hyperactivated in different types of cancer, especially pancreas, colorectal and lung cancer. This review highlights the key role of PAK in Kras signalling pathways in pancreatic cancer, and summarizes that PAK mediates the biological behaviour

of pancreatic cancer cells by orchestrating multiple oncogenic pathways, such as NF- κ B, STAT3, RAF/MEK/ERK, PI3K/PDK1/AKT *etc.*, PAK inhibition (FRAX597, PF-3758309 *etc.*), not only suppresses tumour growth and synergistically improves chemotherapeutic efficacy, but also plays a critical role in mediating tumour-stroma crosstalk. More importantly, immunotherapy is now emerging as a promising approach for cancer treatment and immune modulation within the tumour microenvironment has become a hot spot in pancreatic cancer research. The potential role of PAK in the anti-tumour immune response has been unveiled by showing that pharmacological and genetic depletion of PAK leads to an increased number of tumour infiltrated T cells in pancreatic and colorectal cancer. In this regard, PAK may become a novel target for reprogramming the tumour microenvironment.

Pancreatic cancer is still one of most lethal malignancies and, in contrast to other types of cancers (*e.g.*, melanoma, breast cancer, prostate cancer *etc.*), the poor survival of pancreatic cancer patients has been only marginally improved over past decades. Therapeutic breakthroughs in pancreatic cancer still require a more comprehensive understanding of its biology and of the intrinsic mechanisms involved in tumour progression. Further study of PAKs holds the promise of developing more effective and less toxic treatments for this devastating malignancy.

ACKNOWLEDGMENTS

The authors would like to acknowledge Pancare Foundation (<https://www.pancare.org.au>) for supporting the pancreatic cancer research program in the Department of Surgery, University of Melbourne. Kai Wang was supported by Melbourne International Fee Remission Scholarship (MIFRS), Melbourne International Research Scholarship (MIRS) and the Moshe Sambor Scholarship (Pancare Foundation).

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ISSN 1007-9327

