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REVIEW

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Selective inhibitors for JNK signalling: a potential targeted therapy in cancer

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ABSTRACT

c-Jun N-terminal kinase (JNK) signalling regulates both cancer cell apoptosis and survival. Emerging evidence show that JNK promoted tumour progression is involved in various cancers, that include human pancreatic-, lung-, and breast cancer. The pro-survival JNK oncoprotein functions in a cell context- and cell type-specific manner to affect signal pathways that modulate tumour initiation, proliferation, and migration. JNK is therefore considered a potential oncogenic target for cancer therapy. Currently, designing effective and specific JNK inhibitors is an active area in the cancer treatment. Some ATP-competitive inhibitors of JNK, such as SP600125 and AS601245, are widely used *in vitro*; however, this type of inhibitor lacks specificity as they indiscriminately inhibit phosphorylation of all JNK substrates. Moreover, JNK has at least three isoforms with different functions in cancer development and identifying specific selective inhibitors is crucial for the development of targeted therapy in cancer. Some selective inhibitors of JNK are identified; however, their clinical studies in cancer are relatively less conducted. In this review, we first summarised the function of JNK signalling in cancer progression; there is a focus on the discussion of the novel selective JNK inhibitors as potential targeting therapy in cancer. Finally, we have offered a future perspective of the selective JNK inhibitors in the context of cancer therapies. We hope this review will help to further understand the role of JNK in cancer progression and provide insight into the design of novel selective JNK inhibitors in cancer treatment.

1. Introduction

c-Jun N-terminal kinase (JNK) is a subfamily of mitogen-activated protein kinases (MAPK), which regulates important cellular activities, including cell proliferation, differentiation, and apoptosis[1]. There are three differently spliced genes of JNK, namely, JNK1, JNK2, and JNK3. JNK1 and JNK2 are ubiquitously expressed in most tissues, whereas JNK3 expression is predominantly in brain, and, to a lesser extent, in the heart and testis[2]. JNK signalling plays important functions in neurodegenerative diseases, inflammation, and cancer progression. They can be activated by multiple and diverse stimuli leading to varied and seemingly contradictory cellular responses[3,4]. Currently, emerging evidence indicates that JNK can regulate both cancer cell apoptosis and survival[1,5]. Earlier researchers observed that sustained activation of JNK is associated with apoptosis, whereas acute and transient activation of JNK is involved in cell proliferation or survival pathways[6,7]. The different functions of JNK may be mediated by the specific substrate or related to temporal aspects[5].

JNK promotes tumour development in many cancers including human pancreatic cancer[8,9], lung cancer[10,11], breast cancer[12,13], and skin cancer[14]. JNK is also seen to have a pro-survival role in B-lymphoma and osteosarcoma[15,16]. The pro-survival function of JNK is related to its capacity to induce cancer cell proliferation[17], migration[18,19], and invasion[20]. JNK is also involved in tumour initiation, as demonstrated in non-small cell lung cancer (NSCLC) cells[11]. It is required for the tumour-initiating properties of the acquired chemoresistant cancer cell lines K562/A02 and KB/VCR[21]. JNK is therefore considered a potential target for cancer therapy. Data indicate that transiently activated JNK upregulates antiapoptotic gene expression and blocks caspase activation, thereby promoting cell survival[22]. Crosstalk between JNK and other pathways is critical for cancer programming. Nuclear factor kappa B (NF-κB), p38, and JNK share common upstream activators and may act synergistically to regulate cancer cell survival[23,24]. Certain signals suppress JNK-mediated apoptosis and induce the cell survival function of JNK[25]. The role of JNK in promoting cancer cell survival involves autophagy[26,27], as JNK can induce autophagy to counteract apoptosis[28]. Extensive evidence supports that JNK-mediated pro-survival autophagy promotes cancer cell resistance to chemotherapy[29,30] and recent studies suggest the involvement of tumour immune evasion in this process[31,32]. JNK is closely

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related to traditional immune evasion regulatory factors such as transforming growth factor-β (TGF-β) and interferon-γ (IFN-γ)[33,34]. In addition, a compensatory cell proliferation mechanism underlies the regulation of JNK-mediated cancer cell survival[35–37] .These studies highlight the complexity of the mechanisms by which JNK modulates cancer cell survival.

JNK signalling is apparently involved in cancer development and progression. Therefore, JNK is an attractive target for therapeutic intervention with small molecule kinase inhibitors. Actually some ATP-competitive (e.g. SP600125) and ATP-non-competitive inhibitors have been developed; however, some limitations are noted in these inhibitors. For example, cell toxicity and a lack of specificity are observed due to their indiscriminately inhibition of the phosphorylation of all JNK substrates[38,39]. During the last decade, some JNK inhibitors have been tested in many clinical trials. CC-401 is a seconded generation of ATP competitive inhibitors of JNK. This compound shows a high capacity in the inhibition of JNK and is also seen to show efficacy in renal injury models. However, a phase I clinical trial using CC-401 for acute myeloid leukaemia was discontinued[38]. Designing new selective JNK inhibitors is a very active area in the field of cancer therapies. Currently, some potential selective JNK inhibitors, including PYC98and PYC71N has been developed and are seen to show promising effect in the selective inhibition of one specific JNK isoform[40,41].

In this review, we primarily summarise the function of JNK in cancer cell survival; our main goal was to mainly discuss the development of JNK inhibitors and especially the selective JNK inhibitors. Finally, we also cast a future perspective of the selective JNK inhibitors in cancer treatment. We hope this review will help to further understand the function of JNK in cancer development and provide some new lights on the development of selective JNK inhibitors in the cancer therapy.

2. JNK signalling activation promotes cancer cell survival

Studies indicate that JNK is a mediator of cancer cell apoptosis and cell death. JNK activation promotes gastric cancer cell apoptosis[42,43]. TNF-α-mediated caspase-8 cleavage and apoptosis are dependent on JNK activation[44]. However, emerging evidence showed that JNK conducts an antiapoptotic role of in the regulation of cancer cell survival[22,29,45]. JNK inhibits the apoptosis of vestibular schwannoma-and lymphoma cells through limiting reactive oxygen species (ROS) accumulation[46,47]. JNK regulates leukemic cell survival in response to temperature-induced stress. At 37 °C, JNK is necessary for leukemic cell survival and drug resistance; however, JNK is also involved in cold stress-induced cell death, suggesting a dual role of JNK in cell survival[45].

JNK activation is involved in tumorigenesis in liver-, breast-, and skin cancers, brain tumours, leukaemia, multiple myeloma, and lymphoma[48]. JNK exerts a pro-survival effect by modulating cancer cell proliferation, migration, and invasion[49,50]. JNK promotes human pancreatic cancer cell proliferation by regulating microRNA-92a and GRP78[8,17]. Cancerous inhibitor of PP2A is an oncoprotein that activates MKK4/7-JNK signalling, thereby contributing to lung cancer cell proliferation[10]. Chemokine ligand-7 and CC chemokine receptor-3-correlated JNK activation are involved in the induction of metastasis in colon cancer cells[51]. In addition, the JNK/c-Jun pathway increases the invasiveness of triple negative breast cancer (TNBC) cells[20]. Activation of JNK/c-Jun is also required for epoxyeicosatrienoic acid-induced proliferation, survival, and angiogenesis in pulmonary artery endothelial cells[52]. JNK increases A549 and ovarian cancer cell migration and invasion

via the hypoxia-induced activation of the 37 kDa laminin receptor precursor and IL-33/ST2 axis[19,53]. JNK is also involved in IL-33-mediated colon cancer cell stemness and macrophage recruitment[54]. JNK/Slug signalling is regulated by juxtaposed with another zinc finger protein 1 to promote prostate cancer progression[55]. Also, JNK is emerging as a pivotal regulator of tumour initiation[50,56]. For example, ectopic JNK controls the tumour-initiating capacity of NSCLC cells[11]; JNK is specifically required for maintenance of the tumour-initiating population rather than for proliferation and survival of the entire cell population.

A unique pro-survival role of JNK was demonstrated in a B-lymphoma model. Blocking the JNK pathway inhibits the proliferation of murine and human B-lymphoma cells. JNK inhibition downregulates the early growth response gene-1 (Egr-1) protein and Egr-1 overexpression partially rescues lymphoma cell apoptosis[15]. JNK may act via Egr-1, which is important for B-lymphoma survival and growth. In diffuse large B cell lymphoma, dual specificity phosphatase 4 deficiency induces constitutively active JNK signalling and contributes to tumour cell survival[57].

JNK1 acts synergistically with Bcl-2 to promote prolonged cell survival in the absence of IL-3 or in response to different stresses[58]. The anticancer drug bortezomib activates JNK signalling leading to Bcl-2 phosphorylation and autophagy[47]. JNK and autophagy activation play a pro-survival role in this context and their inhibition increases the cytotoxic effects of bortezomib in PEL cells. JNK-mediated survival signalling also involves the transcription factor JunD[59], as the JNK/JunD pathway collaborates with NF-κB to upregulate the expression of the antiapoptotic gene *cIAP-2*. In the absence of activated NF-κB, the JNK pathway promotes an apoptotic response[60].

Together, JNK activation can promote cancer cell survival and plays an important role in cancer cell proliferation, migration, and invasion. JNK associates with other regulators, including MKK, c-Jun, Slug, and Egr-1 and this interaction promotes cancer cell survival. JNK is therefore a potential oncogenic target for cancer treatment. However, these findings are mostly based on *in vitro* studies and additional *in vivo* studies using animal cancer models are necessary to clarify the function of JNK. In summary, the tumour suppressive or oncogenic role of JNK is likely to depend on cancer/cell type-specific differences, the tumour microenvironment, and crosstalk with other signalling pathways. The molecular profiles associated with the role of JNK in promoting cancer cell survival are shown in Figure 1.

3. A "break the brake" model of JNK in cancer cell survival

Earlier studies indicate that the cancer cell survival or death function of JNK depends on functional time. In 2002, Lin[61] proposed that a potential mechanism underlying JNK-mediated cell survival is the time course of JNK activation. Normally, transient JNK activation is important for mediating a survival response in TNF-treated cells, whereas chronic JNK activation contributes to apoptotic responses[59,61,62]. Tang et al.[63] further showed that activation of JNK by TNF-α is transient in TNF-α-insensitive cells, whereas it is sustained in sensitive cells (apoptosis). Conversion of JNK activation from prolonged to transient suppresses TNF-α-induced apoptosis (survival)[63]. Ventura et al.[6] also showed that the time course of JNK signalling can influence the biological response to JNK activation. These authors demonstrated that the early transient phase of JNK activation (<1 h) promotes cell survival, whereas the later and more sustained phase of JNK activation (1–6 h) mediates proapoptotic signalling. The dependency of the survival response on
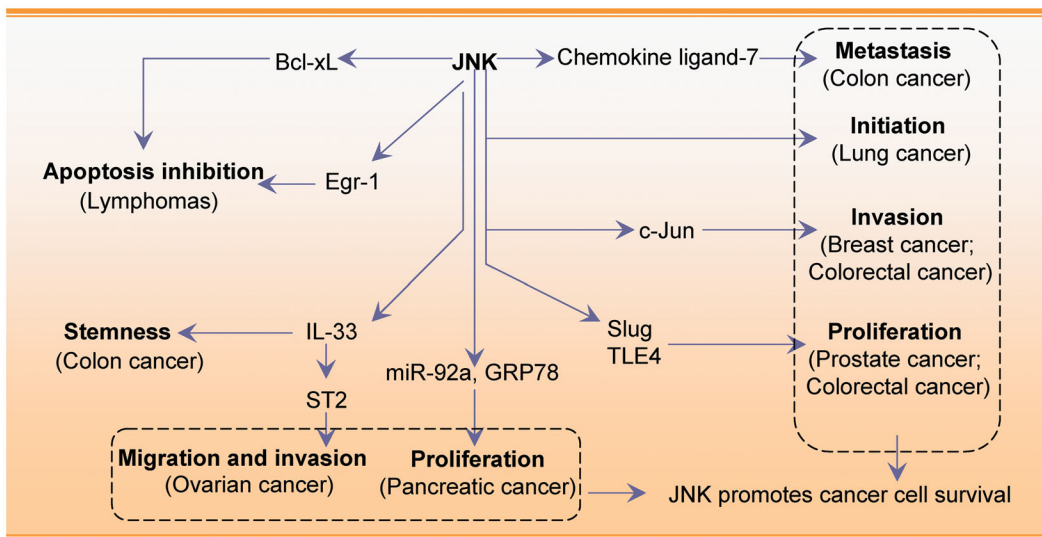
Figure 1. JNK promotes cancer cell survival by modulating cancer cell initiation, invasion, proliferation, and migration.
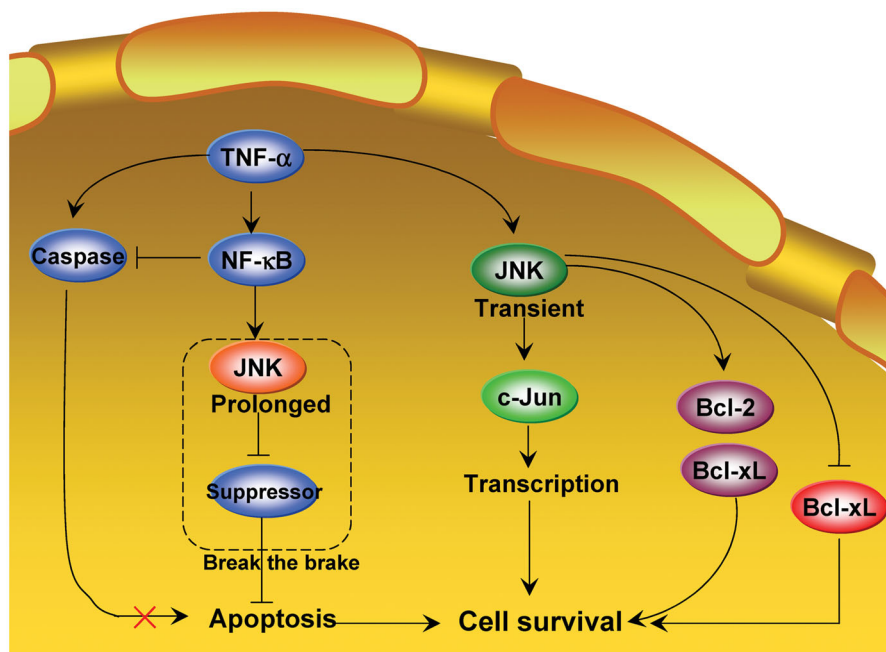

Figure 2. The "break the brake" hypothesis of JNK during regulation of cancer cell survival.

early JNK activation is attributed to antiapoptotic gene expression at an early period. Indeed, transient JNK1 activation (<2 h) cross-talks with STAT3 to upregulate the antiapoptotic genes Bcl-2 and Bcl-xL, and inhibit the proapoptotic gene Bax, thereby promoting RAW264.7 cell survival[64].

Lin[61] further hypothesised that prolonged JNK activation may "break the brake" on apoptosis. In this model (Figure 2), JNK may be a modulator rather than an intrinsic component of the apoptotic machinery. JNK activation thus facilitates, but does not induce, apoptosis. Prolonged JNK activation may inhibit apoptotic pathway suppressors in the presence of TNF-α, thereby allowing apoptotic cells to fulfil their death wish[22]. TNF-α induces apoptosis in TNF-α-sensitive cells[63]. While caspase activation initiates and executes apoptosis, prolonged JNK activation promotes apoptosis by inactivating suppressors of the mitochondrial-dependent death pathway. Activation of NF-κB by TNF-α blocks caspase activation

and prevents prolonged JNK activation, thereby inhibiting TNF-α-induced apoptosis[63]. However, additional evidence is necessary to prove this hypothesis, as the "break the brake" model has not been tested since its proposal 15 years ago.

4. JNK inhibitors in the treatment of cancer

Due to the important role of JNK in the cancer development, designing effective and specific JNK inhibitors is a very active filed of research in different academic and industrial laboratories in the world. Currently, the clinical success of selective kinase inhibitors, such as imatinib and erlotinib, as therapeutic agents for several human cancers has prompted substantial interest in the development and clinical testing of such inhibitors for a wide variety of malignancies[65,66]. Protein kinase inhibitors are widely used as

therapeutic agents in many cancers; however, they have potential off-target effects associated with the highly conserved protein kinase family[65,67].

SP600125that belongs to the ATP-competitive inhibitor, is the most commonly used JNK inhibitor in many *in vitro* and *in vivo* studies[68,69]. This compound has remarkable antitumor potential in different cancers, including stomach cancer, oral squamous cell carcinoma, lung adenocarcinoma, cholangiocarcinoma, colon carcinoma, pancreatic cancer, and glioblastoma[65,70]. AS601245 is a cell-permeable JNK inhibitor that shows promising anticancer effects in colon cancer and T cell acute lymphoblastic leukaemia[71,72]. Another promising JNK inhibitor is JNK-IN-8, which can sensitise TNBC cells to lapatinib by upregulating p65 and Nrf2. Combination treatment significantly increased the survival of mice bearing MDA-MB-231 human TNBC xenografts[73,74]. Mice treated with SP600125 or JNK-IN-8 showed significantly increased survival rates after invasive fungal infections, particularly with Candida albicans[75]. AS602801 is cytotoxic against CSCs derived from human pancreatic cancer, NSCLC, ovarian cancer, and glioblastoma[76]. AS602801 also inhibits the self-renewal and tumour-initiating capacity of CSCs. *In vivo*, AS602801 inhibits CSCs in established xenograft tumours when administered at a dose and schedule that does not adversely affect the health of tumour-bearing mice[76]. However, as is known, these inhibitors have varying toxicity and lacks specificity as they indiscriminately inhibit phosphorylation of all JNK substrates[38].

Hepatic ischemia/reperfusion (I/R), which is characterised by severe inflammation and cell death, causes significant liver damage and hepatic cancer[77]. Ginsenoside Rg1 (20 mg/kg/day), which inhibits JNK signalling, significantly promotes hepatic function and suppresses liver necrosis and inflammatory responses[78]. An aza-quinolone analog168 and N-alkyl (propyl and butyl)-bearing pyrazoloanthrone scaffolds show promise as therapeutic inhibitors of JNK[79]. Angell et al.[80] and Jang et al.[81] further showed that N-(3-cyano-4,5,6,7-tetrahydro-1-benzothien-2-yl)amides acts as an ATP-binding site-targeting inhibitor of JNK2 and JNK3. The mechanism was further studied, and the authors showed that this inhibitor can cause apoptotic DNA fragmentation in parallel with G2/M arrest, phosphorylation of Bcl-2, Mcl-1, and Bim and activation of Bak and the caspase cascade, suggesting its anticancer potential[81].

However, JNK has at least three isoforms (JNK1–3) with different functions in cancer development. These inhibitors lack specificity and selectivity for the different JNK isoforms[65]. Suppressing total JNK activity is not an appropriate strategy because different JNK isoforms have distinct functions in cancer, asthma, diabetes, or Parkinson's disease[82]. Apparently, the identification and development of selective JNK inhibitors should be a valuable strategy for the treatment of cancer.

Several peptide inhibitors have been developed, such as JNKi-1[83], which has been successfully used in mouse models, for example, HCC or Bi-78D3, which inhibits JNK activity by interfering with binding to the JNK-interacting protein 1 scaffold[84]. However, these novel compounds are not selective inhibitors of JNK1–3 and isoform-specific JNK inhibitors are rarely reported. Among few isoform-specific JNK inhibitors identified, the isoquinolone derivative methylsulfonyl exhibits potent inhibitory activity against JNK1 and acts as a JNK1 selective and ATP competitive inhibitor[85]. Moreover, this inhibitor significantly inhibits cardiac hypertrophy in a rat pressure-overload model without affecting blood pressure. Yao et al.[86] reported that 7–(6-N-phenylaminohexyl)amino-2H-anthra[1,9-cd]pyrazol-6-one (AV-7) has selective inhibitory activity against JNK1, but not JNK2/3. The novel inhibitory peptides

PYC98, PYC71N, and adamantyl azaquinolone selectively inhibit JNK1 activity towards c-Jun[40,41]. Currently, many researchers and laboratories are focussing on the selective inhibition of JNK3, because this isoform is mainly expression in the brain and is an attractive target of neurodegenerative disease[38]. Pyrimidinyl-substituted benzazole-acetonitriles specifically target JNK3, showing inhibitory activity in the double-digit nanomolar range[87]. A specific JNK3 inhibitor derived from triazolone variants showed >10-fold higher selectivity than JNK1[88]. In addition, 6-anilinoindazoles[89], 20-anilino-4,40-bipyridines[90], isoxazole derivatives[17], XG-102[91], and pyridopyrimidinone derivatives[92] were identified as selective inhibitors of JNK3. XG-102 shows potential for the treatment of patients with inflammatory bowel disease[93]. The chemical structures of these selective inhibitors are shown in Figure 3.

The studies summarised above indicate that selective JNK inhibitors are important for the treatment of cancer. However, compared with other pathway inhibitors, there are relatively less JNK inhibitors for clinical application. This could be partly attributed to our poor understanding of the complex functions of JNK, as JNK not only functions in cancer development, but also contributes to cancer cell death and is involved in many physiological processes[39]. Nevertheless, some inhibitors of JNK have been tested in the clinical study. For example, CC-401, a second-generation ATP-competitive inhibitor, shows antineoplastic activity. However, it is a pity that a Phase I clinical study of CC-401 in the acute myeloid leukaemia was discontinued and the development of CC-401 was stopped. The clinical trials of other JNK inhibitors, including CC-930, were terminated by the sponsor due to the lack of support[94]. PGL5001 (AS601245) is another ATP-completive inhibitor and is currently being evaluated in a Phase II clinical trial[38]. It should be noted that the context of tissue-dependent expression was not considered in the clinical trials of JNK inhibitors. The lack of efficacy and the side effects are highly possible, at least in part, due to the lack of selecting and identifying of a subset of patients who would respond positively to anti-JNK therapies[38].

The role of JNK as a target for cancer treatment needs to be further explored to develop substrate-specific inhibitors, this may contribute to the alleviation of different types of cancer[48,95]. Moreover, future clinical studies should mainly consider the context of tissue-dependency too. The potential of JNK inhibitors for the treatment of cancer and other clinical applications is summarised in Table 1.

5. Future perspectives of selective JNK inhibitors in cancer therapy

Development of selective JNK inhibitors that target specific JNK-mediated cellular events is challenging. Currently, numerous selective pathway inhibitors have entered the clinical and market stages as anticancer therapies. For example, STAT3 inhibitors OPB-31121 and OPB-51602 have completed Phase I and II studies for treatment of various cancers, including advanced solid tumours, non-Hodgkin's lymphoma, and liver cancer[103,104]. Two inhibitors of the PI3K/AKT/mTOR pathway (SF1126 and GDC-0980) are in Phase I and II clinical trials, respectively[105,106]. The FDA has approved the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib for treatment of chronic lymphocyte leukaemia; this prompted researchers to conduct "me too/me better" investigations[107]. However, the complex roles of the JNK pathway during tumorigenesis remain unclear. To date, the exact mechanism by which JNK regulates cancer development and which isoforms play the major role in this context, are unclear. The pro-survival and
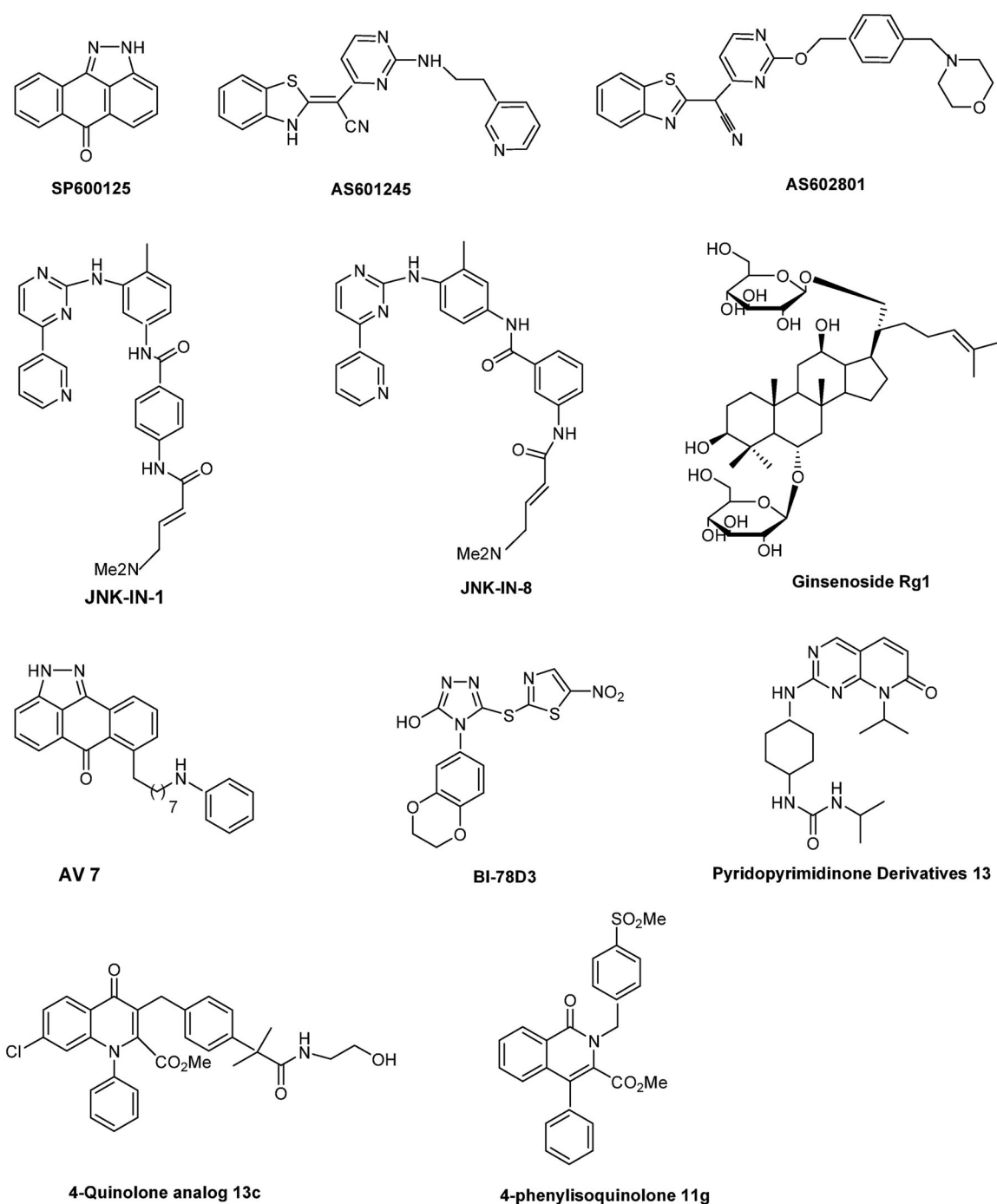
Figure 3. Chemical structures of selective JNK inhibitors.

apoptosis functions of JNK are not fully understood. The effects of JNK signalling on tumour cell growth are not static; the function of JNK may change according to time or cell cycle stage. Therefore, development of selective JNK inhibitors should take into account the functional time and the function of different JNK isoforms also.

Currently, an ideal JNK-specific inhibitor has not been identified yet, and many reported JNK inhibitors lack specificity for JNK with different conformations. Highly specific JNK inhibitors can be developed by chemical synthesis, by screening natural products that specifically inhibit the JNK pathways or by chemically modifying these natural products. Of course, development of JNK inhibitors for cancer therapy requires a systemic approach that requires consideration of metabolism, toxicity, drug resistance, side effects,

and price. Development of substrate- or isoform-specific inhibitors and their clinical application may represent an innovative therapeutic approach to prevention and treatment of some cancers.

Development of novel JNK inhibitors specific for different tumour types should be encouraged. However, considering the dual roles of JNK in cancer, treatment with a JNK inhibitor during chemotherapy would require careful planning. It is very possible that the mechanism underlying JNK-mediated cell survival and even chemoresistance is not the same for different cancers. We think that, as a first step, we may do not need to clarify all JNK-mediated resistance mechanisms for all cancers. Rather, we can try to develop a single specific JNK inhibitor for one or some, typical cancers once we understand the JNK-mediated mechanisms relevant to that cancer. This process will make development of

Table 1. Anticancer and other potential clinical applications of JNK inhibitors.

Inhibitor	Target	IC$_{50}$	Clinical potentials	References
SP600125	JNKs	JNK1/2 = 40 nM; JNK3 = 90 nM	Anticancer potential for stomach cancer, oral squamous carcinoma, lung adenocarcinoma, cholangiocarcinoma, and colon carcinoma.	[65]
AS601245	JNKs	JNK1 = 150 nM; JNK2 = 220 nM; JNK3 = 70 nM	Anticancer potential for colon cancer and T cell acute lymphoblastic leukaemia.	[71,72]
AS602801	JNKs	JNK1 = 80 nM; JNK2 = 90 nM; JNK3 = 230 nM	Induces apoptosis of cancer stem cells.	[76]
JNK-IN-1	JNKs	JNKs = 2.31 nM	Anticancer potential for skin cancer and attenuation of chronic colitis.	[93,96]
BI-78D3	JNKs	JNKs = 280 nM	Anticancer potential for osteosarcoma.	[97]
JNK-IN-8	JNKs		Sensitizes triple-negative breast cancer cells to lapatinib.	[73]
Bi-78D3	JNKs		Blocks JNK-dependent Con A-induced liver damage; restores insulin sensitivity in mouse models of type 2 diabetes.	[84]
Ginsenoside Rg1	JNKs		Protects against ischemia/reperfusion-induced liver damage.	[98]
4-fluorophenyl isoxazoles	JNKs	JNK1 = 13 nM; JNK3 = 16 nM	A structure-activity relationship study was performed; however, the cellular potency and *in vivo* properties need to be improved.	[17]
XG-102 (D-JNKI-1)	JNKs		31-D-amino-acid peptide; it is safe for the treatment of patients with post-surgery or post-trauma intraocular inflammation; protects against TNBS-induced colitis.	[99,100]
4-quinolone analogues	JNKs	JNK1 = 62 nM; JNK2 = 170 nM	This compound shows excellent kinase selectivity and impressive efficacy in a rodent asthma model.	[101]
CC-930	JNKs	JNK1 = 61 nM; JNK2 = 7 nM; JNK3 = 6 nM	Does not inhibit CYP450 enzymes significantly; it shows low toxicity, is well tolerated, and exposure is dose-proportional.	[94]
Quinazoline	JNK3	JNK3 = 40 nM	Shows good brain penetration and pharmacokinetic (PK) properties and is a candidate for *in vivo* evaluation in the central nervous system (CNS)efficacy models.	[102]
Triazolothione 1	JNK3	JNK3 = 1.07 nM	It has CNS properties.	[88]
Pyridopyrimidinone Derivatives	JNK3	JNK3 = 15 nM	Clean CYP-450 inhibition profile; good microsomal stability; and good oral bioavailability.	[92]
AV7	JNK1		It has the potential to treat of diabetes.	[86]
D-PYC98	JNK1		A novel retro-inverso peptide; inhibits p38, and c-Jun Ser63 phosphorylation during hyperosmotic stress.	[41]
Isoquinolone derivatives	JNK1	JNK1 = 86 nM	They can be novel therapeutic agents for heart failure without affecting blood pressure.	[85]

(*continued*)

Table 1. Continued.

Inhibitor	Target	IC$_{50}$	Clinical potentials	References
JNK inhibitor IX (JNKi)	JNK2/3		Induce DNA fragmentation and apoptotic cell death in human Jurkat T cells.	[81]

JNK inhibitors much faster and we believe that more specific JNK inhibitors will be tested in many clinical studies in the near future.

6. Conclusion

JNK signalling is a crucial oncogenic target that raises many researcher's interest. Uncovering highly efficient selective JNK inhibitors is a hot topic of the last decade. Currently, some selective JNK inhibitors have been developed; however, more clinical studies of these inhibitors should be tested. Moreover, clinical studies of JNK inhibitors should determine which JNK inhibitor is most effective against cancer therapy. We should make further efforts to understand which JNK proteins are beneficial targets and should also uncover the potential mechanisms of the inhibitors on the various physiological process. The particular use of JNK inhibitors should be considered as the genetic background and the precise signalling pathway that directs the carcinogenic properties of the cells for a given cancer type needs to be noted. In conclusion, we believe that there is a bright future of JNK inhibitors and their use in cancer therapies should be tested in more clinical trials.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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