

Myeloid cell leukemia 1 (MCL-1), an unexpected modulator of protein kinase signaling during invasion

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ABSTRACT

Myeloid cell leukemia-1 (MCL-1), closely related to B-cell lymphoma 2 (BCL-2), has a well-established role in cell survival and has emerged as an important target for cancer therapeutics. We have demonstrated that inhibiting MCL-1 is efficacious in suppressing tumour progression in pre-clinical models of breast cancer and revealed that in addition to its role in cell survival, MCL-1 modulated cellular invasion. Utilizing a MCL-1-specific genetic antagonist, we found two possible mechanisms; firstly MCL-1 directly binds to and alters the phosphorylation of the cytoskeletal remodeling protein, Cofilin, a protein important for cytoskeletal remodeling during invasion, and secondly MCL-1 modulates the levels SRC family kinases (SFKs) and their targets. These data provide evidence that MCL-1 activities are not limited to endpoints of extracellular and intracellular signaling culminating in cell survival as previously thought, but can directly modulate the output of SRC family kinases signaling during cellular invasion. Here we review the pleiotropic roles of MCL-1 and discuss the implications of this newly discovered effect on protein kinase signaling for the development of cancer therapeutics.

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Myeloid cell leukemia-1 (MCL-1), a unique pro-survival member or the BCL-2 family of proteins

Recently, work performed in our laboratory demonstrated that Myeloid cell leukemia-1 (MCL-1) antagonism suppressed tumour progression in pre-clinical models of breast cancer and revealed that in addition to its role in cell survival, MCL-1 modulated cellular invasion.¹ MCL-1 was first described as an immediate-early response gene in human myeloid leukaemia cells induced to differentiate with phorbol ester.² MCL-1 is best known as a pro-survival member of the BCL-2 family of proteins that regulates the intrinsic (mitochondrial) apoptotic cascade.³ MCL-1 is important for the survival of most normal and malignant tissues (reviewed in.⁴) The C-terminal region of MCL-1 shares homology with the BCL-2 family of proteins, which contain four BCL-2-homology (BH1–4)-domains that form a binding pocket for interaction with the pro-apoptotic BH3 only proteins and by doing so protect normal and malignant cells from cell death. The BCL-2 family members include two pro-apoptotic subgroups: the BH3-only sensor proteins (e.g. BIM, PUMA, NOXA, tBID etc), which trigger the intrinsic apoptotic cascade in response to cytotoxic insults or

cellular stresses and BAX and BAK, the apoptotic effectors (reviewed elsewhere³). The BH domain hydrophobic pocket dictates MCL-1 binding specificity for BIM, tBID, PUMA, NOXA and BAK thereby restraining cellular apoptotic activity.

MCL-1 is important for cancer cell survival and therapeutic resistance

MCL1 is one of the most common somatic copy number amplifications, observed in 11% of cancers across multiple tissue types, with the highest rates observed in breast (36% of cases) and lung (54% of cases).⁵ MCL-1 protein levels correlate with outcome, tumor grade and therapeutic resistance in many cancers including those of the hematopoietic system, breast, lung and pancreas.^{6–12} MCL-1 has been validated to participate in neoplastic progression of B-cell lymphomas¹³ as well as haematopoietic progenitor/stem cell tumours¹⁴ and accelerate Myc induced myeloid leukaemia.¹⁵ Several studies have also shown that MCL-1 is a barrier to therapeutic sensitivity, including those that target BCL-2 (reviewed in¹⁶). MCL-1 is responsible for

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therapeutic resistance in a range of cancers including oral cancers,¹⁷ lung cancer,¹⁸ pancreatic cancer,¹⁹ ovarian cancer, colon cancer²⁰ and triple negative breast cancer.²¹ MCL-1 also confers the survival of breast cancer cells *in vitro*²² and protects HER-2 positive breast cancers from hypoxia-induced death.²³ It is for the above reasons that there have been significant advances in the development of small molecule inhibitors that bind to and inhibit MCL-1, including the most recent and promising compounds A1210477 and S63845,^{24,25} with the later inhibitor having high affinity, efficacy at low doses, and low toxicity. Recent work has shown that the MCL-1 inhibitor S63845 could increase the sensitivity of patient derived xenografts to docetaxel and trastuzumab.²⁶ More work is to determine the genetic or proteomic biomarkers that would stratify patients to this type of therapy as a single agent or in combination with other therapies. Thus MCL-1 is a potent survival factor in hematopoietic and solid tumors and can be targeted with small molecule inhibitors to treat a wide range of cancers.

Protein kinase signalling control of MCL-1 activity

Unlike other members of the BCL-2 family, MCL-1 contains a unique 150 amino acid N-terminus consisting of PEST-like sequences (rich in proline (P), glutamic acid (E), serine (S), and threonine (T)) implicated in the control of protein stability and activity. Degradation of MCL-1 is thought to be primarily controlled primarily by ubiquitylation via 13 different lysine residues, and modulated by phosphorylation, targeting it to the proteasome.²⁷ E3 ubiquitin-protein ligases known to regulate MCL-1 stability include HUWE1/MULE,^{28,29} SCF F-box containing proteins F-box/WD repeat-containing protein 7 (Fbw7,^{20,30}) and F-box/WD repeat-containing protein 1A (β TrCP) and the deubiquitinase Ubiquitin Specific Peptidase 9 (USPX,³¹). As a result MCL-1 has a short half-life of approximately 3 hours.³² MCL-1 expression and activity is also controlled by a variety of stress, growth factor, hormone, cytokine and signals culminating in receptor tyrosine kinase signalling involved in the stimulation of differentiation of myeloid lineage cells or in response to stress to enhance cell survival.^{7,33} A summary of the various signalling pathways and kinases responsible for the regulation of MCL-1 is provided in Table 1 and illustrated in Fig. 1. Best known in the regulation of MCL-1, is output of the PI3K/AKT, MAPK/ERK and JAK/STAT pathways that can be activated by a variety of receptor tyrosine kinases that including EGFR. The interleukin (IL) family of cytokines, which have roles in differentiation, growth and

survival,³⁴ also induce MCL-1 transcription. These include IL3,^{35,36} IL5,³⁷ IL6,^{38,39} IL7⁴⁰ and IL15.⁴¹ Signalling downstream of the interleukin family predominantly occurs via the JAK/STAT pathway,^{37,39,41} with a STAT binding site present in the *MCL-1* promoter.³⁸ Consequently STAT5 has been shown to induce *MCL-1* transcription.⁴² *MCL-1* transcription is also activated after endoplasmic reticulum stress⁴³ and hypoxia⁴⁴ resulting in the death of diseased cells. Intracellular kinases (eg GSK3 β , CDK1 and CDK2) downstream of these signalling pathways also control MCL-1 activity resulting via phosphorylation on nine potential phosphosites influencing the stability, activity, degradation and even localisation (summarised in Table 2). Thus MCL-1 is a critical cell survival factor in normal and malignant tissues that is induced and activated in response to a variety of extracellular and intracellular cues via protein kinase signalling.

MCL-1 is not just a mediator of cell survival

In addition to its role in cell survival, MCL-1 has been shown to possess multiple functions in different cellular compartments. Deletion of MCL-1 in mice resulted in peri-implantation lethality an effect that was independent of apoptosis.⁴⁵ Additionally, MCL-1 and STAT3 have been shown to interact during embryonic implantation, which resulted in the expression of epithelial to mesenchymal markers, increased apoptosis and decreased invasion.⁴⁶ MCL-1 is highly expressed in both human and mouse embryonic stem cells (ESCs), with the loss of MCL-1 through siRNA or up-regulation of NOXA by CDK1 inhibitor treatment leading to significant induction of cell death, pointing to MCL-1 playing an active role in ESC homeostasis.⁴⁷

The divergent roles of MCL-1 are dependent on its post-translational modification and protein-protein interactions. Proteolytically cleaved amino-truncated MCL-1 can localise to the inner mitochondrial membrane and is important for mitochondrial structure and physiology.^{48,49} Furthermore, cell cycle progression by MCL-1 is also mediated through the direct recruitment and inhibition of CDK1, due a reduced capacity of CDK1 to bind to Cyclin 1B.⁵⁰ In this manner MCL-1 binding may subvert the interaction of other target proteins thereby restricting kinase activity eg by binding to CDK1 and preventing cell cycle progression. MCL-1 has also been shown to directly interact with other proteins such as CDK1, PCNA and CHK1 in the nucleus, where it similarly regulates cell cycle progression and DNA damage.⁵¹ In the nervous system, MCL-1 is important for neural precursor cell survival⁵² but also for cell cycle progression in

Table 1. Extracellular and intracellular regulation of MCL-1 function. The effects of extracellular and intracellular signalling (signalling pathways) on MCL-1 transcription in various cellular contexts.

	Signal	Pathway	Transcription Factors	Cell context	Outcome	References	
Activation of Transcription	Cytokines	IL3	PI3K/AKT	CREB Complex	Haematopoietic progenitor cell line	Increased survival when challenged with PD98059, LY294002, wortmannin and DMSO.	[35]
			p38MAPK	PU.1 Complex	Haematopoietic progenitor cell line	Survival outcome unknown.	[36]
		IL7			Mouse derived RAG-2 deficient thymocytes	Increased survival was observed in unchallenged cells treated with IL7.	[40]
		IL6	JAK	STAT3		Cholangiocarcinoma cell lines	Addition of STAT3 inhibitor, AG490, or IL-6 antisera led to a downstream loss of MCL-1 expression and sensitized cells to apoptosis induced by tumor necrosis factor related apoptosis inducing ligand (TRAIL).
	Isolated human macrophages					Sodium salicylate treatment resulted in loss of STAT3 signaling, and downstream loss of MCL-1 expression reduced survival. Overexpression of constitutively active STAT3 rescued this loss of viability.	[39]
	IL15	JAK PI3K/AKT	STAT5		Isolated mouse T-cells	Survival outcome unknown.	[41]
	IL5	JAK	STAT5		Haematopoietic progenitor cell lines	Increased survival was observed in unchallenged cells treated with IL5.	[37]
	SCF	AKT/PKB			Haematopoietic progenitor cell lines	Increased survival was observed in unchallenged cells treated with SCF.	[37]
					MAPK	TCF-SRF	HeLa ovarian cell lines
		ML-1 Myeloblastic cell line				Activated in response to TPA (12-O-tetradecanoylphorbol 13-acetate), colchicine and vinblastine resulting in reduced apoptosis.	[88]
Chronic myeloid leukaemia cell lines						Reduced apoptosis in response to imatinib treatment.	[42]
Fusion Proteins Stress Signalling	ER Stress	MAPK		Humans melanoma cell lines	Reduced loss of survival in response to ER stress stimulators thapsigargin and tunicamycin.	[43]	
	Hypoxia	IRE1 α /ATF6	HIF1 α	Heptoma cell lines	Reduced apoptosis induced by tert-Butyl Hydroperoxide.	[44]	
					Integrated stress response	EIF2 α	Cholangiocarcinoma cell lines, Pancreatic Cancer cell lines and Ovarian Cancer cell lines
Inhibition of Transcription							

embryonic neural precursor cells. Furthermore, MCL-1 expression correlates with the levels of VEGF (vascular endothelial growth factor),⁵³ and although this expression pattern is important for the survival of endothelial cells, it is also important for vessel sprouting and invasion.^{54,55}

MCL-1 has also been implicated in the migration and invasion of normal and malignant tissues, for example MCL-1 has shown to be important for neuronal progenitor cell migration from the ventricular zone into the cortical plate during cortical neurogenesis.⁵⁶ MCL-1 has further been demonstrated to play a role in

the migration and invasion of colorectal⁵⁷ and gastric⁵⁸ cancer cell lines, whereby siRNA knockdown led to a loss of motility in wound healing and trans-well assays. Furthermore forced expression of MIR26a, which targets MCL-1 in breast cancer cell lines led to the loss of migration in wound healing assays.⁵⁹ MIR26a does have other targets such as MTDH and EZH2 therefore it is still unclear whether this effect is solely dependent on the activities of MCL-1. These data suggest that MCL-1 possesses functions beyond merely its role in cell survival, including roles in mitochondrial physiology, cell cycle progression, DNA damage and possibly

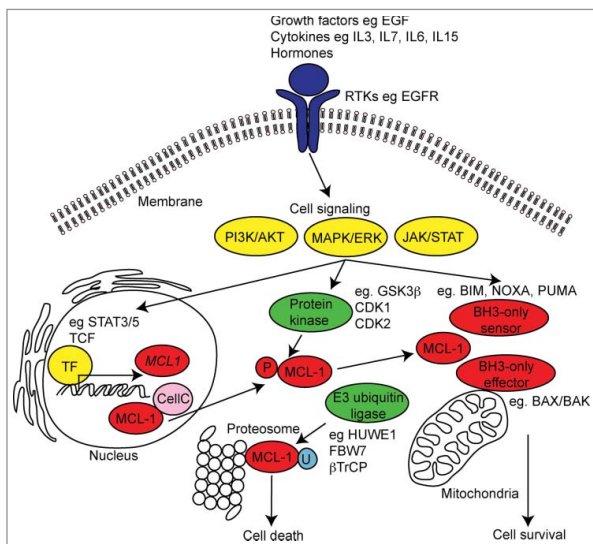


Figure 1. Schematic diagram of MCL-1 regulation and function. MCL-1 is induced by a variety of extracellular receptor tyrosine kinases (RTKs) (purple), growth factors, stress induced cytokines and hormones resulting in the activation of intracellular signals (yellow) and inducing the transcription of MCL-1 mRNA by target transcription factors (TF). MCL-1 activity and stability is regulated by E3 ubiquitin-ligase and protein kinase induced phosphorylation (P) during post-translational processing. The best recognized function of MCL-1 is its role in maintaining cell survival via interaction with the intrinsic apoptotic machinery at the mitochondria. MCL-1 can also participate in the regulation of mitochondrial structure and function, cell cycle (CellC) and DNA damage mechanisms. In diseased and damaged cells, MCL-1 can be ubiquitinated (U) and targeted for degradation at the proteasome resulting in cell death.

invasion but it has been difficult to discriminate these cellular functions from apoptosis as they are intrinsically linked to cellular viability.

MCL-1 is a new regulator of protein kinase signalling during invasion

We investigated the consequences of inhibiting MCL-1 in triple negative breast cancer cells,¹ a subtype of breast cancer with limited treatment options and some of the poorest outcomes.⁶⁰ We inhibited MCL-1 using a genetic approach via inducible expression of a modified form (L62A/F69A double mutant) of the short isoform of BIM (BIMs2A).⁶¹ This approach mimics that of small molecules (BH3-mimetics) targeting MCL-1 and was chosen as it was highly specific for MCL-1 and previously validated permitting an investigation of MCL-1 in a tumor cell autonomous manner.⁶² Expression of BIMs2A increased cell death in basal-like MDA-MB-468 cells but did not induce apoptosis in highly invasive claudin-low MDA-MB-231 cells when cultured on plastic. When seeded on contracted collagen I matrices that more accurately recapitulated key aspects of the *in vivo*

microenvironment,⁶³ MCL-1 antagonism suppressed invasion, an effect that was independent on its effect on apoptosis.¹ Furthermore inhibition of MCL-1 significantly suppressed both the size and number of lung metastases in the lungs of mice bearing both MDA-MB-468 and MDA-MB-231 mammary intraductal xenografts, indicating that MCL-1 was essential for metastatic progression in both models. This specific model of antagonism provided definitive proof that MCL-1 controls invasive capacity of cancer cells, as what had been suggested previously using wound healing assays.⁵⁹

To invade, cancer cells form specialised membrane protrusions termed invadopodia⁶⁴ rich in filamentous (F)-actin filaments initiated by a kinase signalling cascade (often involving the SRC family kinases cSRC, FYN and YES and others).⁶⁵ This signalling cascade results in the phosphorylation and activation of cytoskeletal remodelling proteins that include Dynamin, Cortactin, Cofilin, Talin, N-Wasp and ARP2/3 complex, augmented by the activity of GTPases CDC42 and RAC⁶⁶ and the co-ordinated assembly of adhesion proteins (eg FAK) and those that promote F-Actin stabilisation (eg Paxillin, Vimentin).⁶⁷

Additional work in our laboratory provided a potential mechanism for the effects of MCL-1 during cancer cell invasion and suggested that MCL-1 may modulate cytoskeletal remodelling during invasion. Kinomic profiling data revealed that MCL-1 inhibition altered a large number of proteins important for invasion and regulated by SRC family kinases.¹ These included increased CSK levels (cSRC tyrosine kinase), a negative regulator of SRC family kinases,⁶⁸ decreased total levels of the SRC family kinase, FYN, and the cSRC target, ABL. The cSRC target and adhesion protein FAK was also decreased as was the phosphorylation of Paxillin and Vimentin. Serine 3 phosphorylation of Cofilin 1 and 2 was increased, an effect that suppresses actin remodelling during invasion. All of these targets are regulated by SRC family kinase activity.^{69,70} Western blotting confirmed the observed decrease in total FAK and an increase in E-Cadherin (data not shown), suggestive of a more epithelial and less invasive state.⁷¹ MCL-1 antagonism also decreased the auto-phosphorylation site Y1148 in EGFR indicating suppression of invasion activity, perhaps due to loss of cSRC activation.⁷² Mass spectrometry and proximity ligation assays showed for the first time that MCL-1 was in direct contact with Cofilin, which perhaps is similar to what has been observed for MCL-1 and CDK1,⁵¹ may be important for restricting activity,¹ via preventing the binding of its inhibitory partner Cortactin.^{73,74} Our data possibly places MCL-1 in complexes in direct contact with F-Actin signalling apparatus important for dynamic cytoskeletal changes during invasion

Table 2. Protein kinase regulation of MCL-1. The effects of protein kinase phosphorylation on target residues of MCL-1 by protein kinases in various cellular contexts.

	MCL-1 target residue	Kinase	Cell context	Function	References
Stability and Activity	Serine 64	JNK, CDK1, CDK2, CDK1/Cyclin 1B, CDK2/Cyclin E, CDK2/Cyclin A	Cholangiocarcinoma, cervical and various cancer cell lines	Phospho-negative mutants had no effect on MCL-1 protein turnover, but increased interactions with BIM, NOXA and BAK have been observed. Phosphorylation is thought to occur during G2/M cell cycle progression and NOXA up-regulation enhanced phosphorylation.	[90-93]
	Serine 121-Threonine 163	JNK	Epithelial cell line HEK293 <i>in vivo</i> liver injury mouse model	Phosphorylation occurs downstream of stress. Phosphomimetic mutants increased MCL-1 half-life and anti-apoptotic activity.	[94,95]
	Threonine 92 and 163	ERK CDK2/Cyclin E	Breast Cancer cell lines Lymphocytic Leukaemia cell line	Phosphorylation increased the half-life of the MCL-1 protein, and enhanced interaction with PIN-1.	[90,96]
	Threonine 163	GSK3 β ERK GSK3 β	Burkitt Lymphoma cell line Breast Cancer cell lines	Phosphomimetics increased MCL-1 protein stability and led to chemoresistance. Phospho-negative mutants doubled the half-life of wild type MCL-1 and resulted in chemoresistance in MCF7 cells.	[97,98] [31]
Degradation	Serine 155 and 159Threonine 163	CDK1/Cyclin 1B	Cervical Cancer cell line	Phosphorylation occurred during mitosis and targeted MCL-1 for degradation.	[91,99]
	Serine 64-Threonine 92	GSK3 β	Oral Cancer cell line Cervical Cancer cell line	Phosphorylation occurred as a result of cellular stress and has been demonstrated to be regulated by SGK1, and targeted MCL-1 for degradation.	[100] [101-103]
	Serine 159	JNK	IL-3 dependent mouse cell lines Fibroblast cell lines		
Localisation	Neuronal cell lines Serine 162		Cervical Cancer and epithelial cell lines	Located in the mitochondrial targeting motif of MCL-1, phospho-negative mutants are localised at the nucleus.	[100]
Unknown	Threonine 70, 86, 156	CDK1/Cyclin 1B	Cervical Cancer cell lines	Unknown	[100]

(Fig. 2A). Although additional experimentation is required to confirm this hypothesis, these results suggest that MCL-1 may play a critical role in invasion via the modulation of SRC family kinase signalling.

MCL-1 regulation of SRC family kinase signalling; implications for cancer therapeutics

Our findings have significant implications for the treatment of cancers that rely on MCL-1 and SRC family kinase signalling for survival and metastatic progression. SRC family kinases are important in the development, maintenance, progression and the metastatic spread of several malignancies leading to extensive research into the development of agents that target this family. Examples of these agents include dasatinib (targeting ABL, cSRC and c-KIT), saracatinib (targeting cYES, FYN, LYN, BLK, FGR and LCK) and bosutinib (targeting SRC and ABR).⁶⁵ Dasatinib has shown profound improvements in tumor and metastatic outcomes in pancreatic xenograft pre-clinical models in mice^{75,76} but despite this Phase II clinical trials of SFK inhibitors alone and/or in combination with gemcitabine have failed to show any

improvement in progression free or overall survival in patients with advanced pancreatic adenocarcinoma.⁷⁷⁻⁷⁹ In breast cancer, FYN activation plays an important role in breast cancer cell motility and drug resistance *in vitro*,⁸⁰ but so far trials of saracatinib targeting FYN have not succeeded.⁸¹

Conversely, Phase II clinical trials of single agent dasatinib have shown durable and objective clinical responses in a small proportion (5%) of patients with locally advanced and metastatic triple negative breast cancer.⁸² Combination trials have shown improved outcomes in patients with breast cancer, for example Phase I clinical trials of dasatinib with Capecitabine show clinical response rates of 56% in unselected patients.⁸³ Other trials combining dasatinib with paclitaxel⁸⁴ and bosutinib with exemestane⁸⁵ are currently underway in patients with advanced metastatic breast cancer and are showing improved responses compared to single agents alone. These preliminary results suggest that the efficacy of SFK inhibitors will likely be improved by combining these drugs with others that increase potency or have parallel cytotoxic activity.

As MCL-1 modulated the output of SFK signalling, we then examined whether MCL-1 antagonism could be one

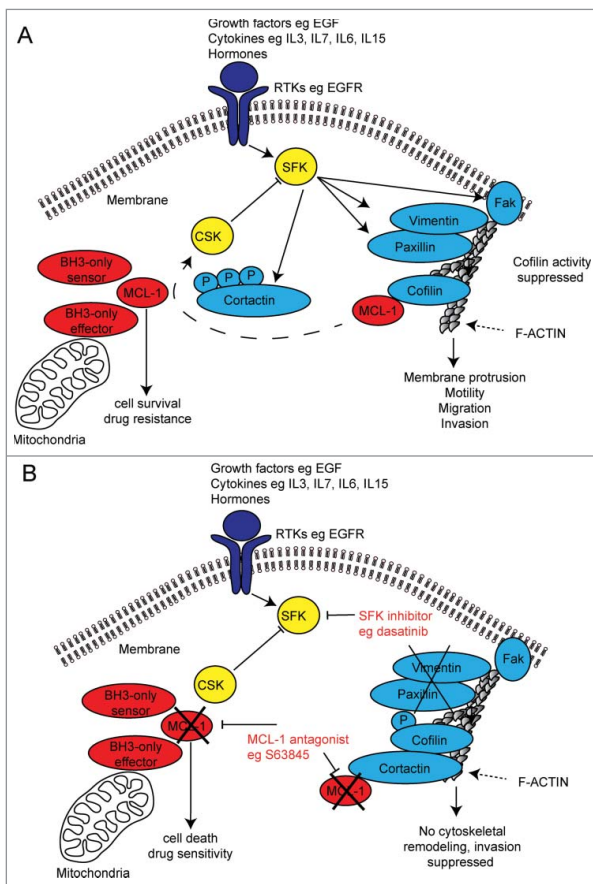


Figure 2. Schematic diagram of a putative mechanism for MCL-1 regulation of SRC family kinase signalling in invasive cancer cells and dual therapeutic strategy. (A) Receptor tyrosine kinase (RTK) activation induces SRC family kinase (SFK) signalling and its targets important for cytoskeletal invasion by cancer cells. MCL-1 binds and prevents serine 3 phosphorylation of Cofilin, which may prevent Cortactin inhibition of Cofilin, permitting cytoskeletal (F-actin) remodelling and cellular invasion. MCL-1 modulates the output of the SRC family kinases (eg Vimentin, Paxillin, FAK and CSK) via an unknown mechanism promotes cellular invasion. (B) MCL-1 antagonism using pharmaceutical inhibition (eg S63845) may allow Cortactin inhibition of Cofilin activity thereby preventing its cytoskeletal remodelling function and also alters the output of the SRC family kinases. When combined with SRC family kinase inhibitors (eg dasatinib, saracatinib and bosutinib), MCL-1 inhibition suppresses invasion while simultaneously induce cell death and increasing drug sensitivity.

way to increase the efficacy of these SFK inhibitors. Encouragingly, MCL-1 inhibition greatly enhanced the anti-invasive potential of dasatinib in 3D organotypic assays in vitro and suppressed tumour progression in pre-clinical models of breast cancer.¹ The next logical step is to investigate whether this effect extends to other inhibitors of SRC family and their targets (eg saracatinib, bosutinib and others), as recently achieved for other highly metastatic cancers,⁸⁶ and examine efficacy of this new dual targeting therapeutic strategy in clinical trials

for metastatic disease (Fig. 2B). Importantly the advantage of using an MCL-1 antagonist to improve potency of anti-metastatic agents is the simultaneous suppression of cell survival and increased therapeutic sensitivity that may result in a substantial improvement in patient survival.

Concluding remarks

MCL-1 is an important regulator of normal and cancer cell viability but there is increasing evidence that MCL-1 has additional roles in mitochondrial structure and function, cell cycle regulation, DNA damage response and cellular invasion. Receptor tyrosine kinase signalling upstream of MCL-1 is important for its effects but our new evidence suggests that MCL-1 can also feed back to directly modulate protein kinase invasion signalling during metastasis (Fig. 2). Although more work is needed to understand to fully understand the mechanisms underlying these effects, the regulation of the cytoskeletal machinery by MCL-1 regulation via modulation of protein kinase signalling provides a valuable opportunity to increase the potency of drugs that antagonise these networks. For those SRC family kinase inhibitors that have largely disappointed in clinical trials, it may now be prudent to consider pharmaceutical inhibitors of MCL-1 (eg S63845^{24,25}) in combination with these to improve clinical response.

Abbreviations

ABL	Abelson murine leukaemia viral oncogene homolog 1
AKT/PKB	Protein kinase B
BAX/BCL2L4	Bcl-2 associated X protein/Bcl-2-like protein 4
BAK/BCL2L7	Bcl-2 homologous antagonist killer/Bcl-2-like protein 7
BCL-2	B-cell lymphoma 2
BIM/BCL2L11	Bcl-2-like protein 11
BH	BCL-2 homology
BLK	Tyrosine-protein kinase Blk
β TrCP	F-box/WD repeat-containing protein 1A
CDC42	Cell division control protein 42 homolog
CDK1	Cyclin dependent kinase 1
CDK2	Cyclin dependent kinase 2
CHK1/CHEK1	Checkpoint kinase 1
CSK	cSRC tyrosine kinase
cKIT/CD117	Tyrosine-protein kinase Kit
cSRC	Tyrosine kinase Src
cYES	Tyrosine-protein kinase Yes

EGFR/HER1	Epidermal growth factor receptor
ERK	Extracellular signal-related kinases
ESC	Embryonic stem cell
EZH2	Enhancer of zeste homolog 2
FAK/PTK2	Focal adhesion kinase/protein tyrosine kinase 2
FBW7	SCF F-box containing proteins F-box/WD repeat-containing protein 7
FGR/SRC2	Gardner-Rasheed feline sarcoma viral
FYN	Tyrosine-protein kinase Fyn
GSK3 β	Glycogen synthase kinase-3 beta
HUWE1/MULE	E3 ubiquitin ligase HUWE1/MCL-1 ubiquitin ligase E3
JAK	Janus kinase
JNK	c-Jun N-terminal kinases
LCK	Tyrosine-protein kinase Lck
LYN	Tyrosine protein kinase Lyn
MAPK	Mitogen-activated protein kinases
MCL-1	Myeloid cell leukemia-1
MIR26a	microRNA 26a
MTDH/AEG1	Metadherin/Astrocyte elevated gene-1
MYC	Avian myelocytomatosis viral oncogene homolog
NOXA/PMAIP1	Phorbol-12-myristate-13-acetate-induced protein 1
N-Wasp	Neural Wiskott-Aldrich syndrome protein
PCNA	Proliferating cell nuclear antigen
PI3K	Phosphoinositide 3-kinase
PUMA/BBC3	p53 upregulated modulator of apoptosis/BCL-2 binding component 3
RAC	Ras-related C3 botulinum toxin substrate 1
SFK	SRC family kinase
STAT	Signal transducer and activator of transcription
STAT3	Signal transducer and activator of transcription 3
STAT5	Signal transducer and activator of transcription 5
tBID	truncated BH3- interacting-domain death agonist
USPX	Ubiquitin Specific Peptidase 9
YES	Tyrosine-protein kinase Yes

Disclosure statement


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