Supplementary Materials: RKIP: A Key Regulator in Tumor Metastasis Initiation and Resistance to Apoptosis: Therapeutic Targeting and Impact

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Table S1. Reported signaling modules whose modification by RKIP contributes to inhibition of metastasis initiation in various cancer types. PF, Preliminary Findings; CSC, Cancer Stem Cells; PDAC, Pancreatic Adenocarcinoma; GCA, Gastric Cardia Adenocarcinoma; HCC, Hepatocellular Carcinoma; CRC, Colorectal Adenocarcinoma; NSCLL, Non-Small Cell Lung Cancer; LN, Lymph Node; NPC, Nasopharyngeal Carcinoma; IDC, Invasive Ductal Carcinoma; TNBC, Triple Negative Breast Cancer; TAM, Tumor Associated Macrophages; OVCA, Ovarian Carcinoma; LAC, Lung Adenocarcinoma.

Signaling Module	Cancer Type	Mechanism	Effect	References
MAPK/Myc/Lin28/let-7	Breast	↓ Let-7 targets	↓ Invasion Intravasation Bone metastasis	[18,105–107]
Lin28 (MAPK-independent)	Esophageal	GRK-2, MMP-14	Invasion LN metastasis	[147]
MAPK/let-7/HMGA2	Breast	↓ CDC2, LOX, OPN, miR-29, miR-200, Snail, Slug, Twist,	↓ EMT, invasion	[14,18,106,110, 113,114,109]
	Breast	↑ TET1, HOXA	Invasion/Intravasation Extravasation	[14,112]
Let-7/BACH1	Breast	↓ CXCR4, MMP-1	Bone metastasis	[63,106,111]
Let-7 independent modules				
MAPK/HMGA2	Glioma	MMP-2, MMP-9	Invasion, Migration	[152]
	TNBC	TAM recruitment CCL5, TNFR2, PRGN	Invasion, Intravasation	[101,160]
miR-98/HMGA2	Glioma	HMGA2 targets	Invasion	[115]

miR-185/HMGA2	Breast	HMGA2 targets	Invasion	[116]
Raf-1/MEK/ERK1/2	PDAC	↓ ERK1/2 targets	↓ Migration, invasion	[84]
	NPC		Invasion	[46]
	CRC			[19,21,202]
	HCC			[127,226]
	OVCA			[230]
Raf-1/MEK/ERK2	Breast	MMP-13	Invasion	[102]
Raf-1MEK/ERK2/AP-1	Breast	MMP-1	Invasion	[151]
	Melanoma	AP1-targets	Invasion	[58]
NF-κB	Breast	↓ MMPs	↓ Invasion	[19,125]
	CRC			
	Melanoma			
	HCC		Invasion, Migration	[127]
	Melanoma	MDA-9/ c-Src/FAK	Invasion, Metastasis	[129]
	GCA	↑ T-cell response	LN metastasis	[163]
NF-κB/Snail,Twist	Prostate	↓ EMT markers	↓ EMT	[15,52,62,120,123, 128,130,131,243]
	Breast	Epithelial markers	Migration	
			Invasion	
	CRC	↓ CSC markers	EMT	[21,140]
		EMT markers	Invasion, Migration	
NF-kB/YY1/Snail	Prostate	↓ EMT	↓ EMT	PF, [134–138]
	Breast	Invasion markers	Invasion	
c-Src /STAT3	Prostate	↓ Muc1, CXCR4, VEGF	↓ Angiogenesis	[97]
	Breast		Migration, Invasion	
	Gastric	?	LN metastasis	[98]

JAK/STAT3	NSCLC	?	Invasion	[99]
	NPC	EMT-markers	EMT/Invasion/Migration	[145]
AMPK/mTORC1/STAT3	Prostate	ANXA7/ ANXA7 GTPase	Metastasis	[144]
Notc1/NICD	Cervical Stomach	↓ Snail, EMT markers	↓ EMT	[153–156]
GSK3β/Snail	CRC	↓ β-catenin, Snail, Slug	↓ EMT	[92]
PI3K/Akt (with or without PTEN involvement)	Melanoma	↓ Snail, YY1, MMPs	↓ Migration	PF, [40]
	Prostate		Invasion	PF, [137]
	Neuroblastoma	CD31, N-myc, vimentin	Angiogenesis	[242]
Unidentified modules	Gastric	↓ MMP-1, MMP-2	↓ Angiogenesis	[57]
	IDC		Invasion	[35]
	TNBC		Migration	[10]
	Prostate		Vascular Invasion	[17]
	PDAC		EMT	[232]
	LAC	miR-27a	EMT	[68]

Table S2. Reported signaling modules whose modification by RKIP contributes to inhibition of therapeutic resistance in various cancer types. PF, Preliminary Findings; IS, Immunosurveillance; IT, Immunotherapy; MTIs, Microtubule Inhibitors; PDT, Photodynamic Therapy; CSC, Cancer Stem Cells; MDR, Multi-Drug Resistance; B-NHL, B-cell Non-Hodgkins Lymphoma; HCC, Hepatocellular Carcinoma; CRC, Colorectal Adenocarcinoma; NPC, Nasopharyngeal Carcinoma; LAC, Lung Adenocarcinoma; GCA, Gastric Cardia Adenocarcinoma; NSCLL, Non-Small Cell Lung Cancer.

Signaling Module	**Cancer Type**	**Mechanism**	**Effect**	**Ref.**
NF-κB (direct effect)	Prostate	↑ PARP, caspase 8, FLIP	↓ Chemo-resistance	[27]
	Breast Prostate	↓ anti-apoptotic proteins	Chemo-resistance	[22,34,123,
		↑ pro-apoptotic proteins	TRAIL-resistance	124,138]
	GCA	T-cell responses	Resistance to host IS	[163]

NF-kB/Snail	Prostate	↓ Bcl-xL, XIAP, cyt-C, ↑ caspases-8 /9,	↓ Chemo-resistance TRAIL-resistance Resistance to PDT	[22,34,123,124 165,29] [177]
	CRC	↓ CSC markers, MDR1, ABCG2, anti-apoptotic proteins	TRAIL resistance Chemo-resistance	[140]
NF-κB/ϒϒ1	B-NHL prostate	↓ Snail, Bcl-2/Bcl-xL, Mcl-1 ↑ DR5, Fas	↓ Chemo-resistance TRAIL/FasL-resistance	[22,28–30,33,34,124,138,139,172,173,183,184,189]
NF-κB…/PTEN	B-NHL	↓ Snail, pAkt	TRAIL-resistance Chemoresistance	[74,215]
Raf-1/MEK/ERK1/2	Prostate	↓ AP-1 anti-apoptotic targets	↓ Chemo-resistance	[27]
	Breast HCC	ERK-anti-apoptotic targets	Chemoresistance	[58,200]
	CRC		Chemo-resistance	[202]
	NPC		Radio-resistance	[164,201]
	B-NHL	Bcl-xL	Chemo-resistance	[32]
	Melanoma	↑ T-cell response genes	Resistance to DC IT	[162]
PI3K/Akt	NPC neuroblastoma	↓ Akt-anti-apoptotic targets Bcl-2, cyclin D1, CDK4	↓ Radio-resistance Resistance to apoptosis	[201] [242]
Shh/Gli1	NSCLC	↓ Snail CSC markers and function	↓ Radio-resistance	[168,169]
c-Src/IL-6/ or Jak1/2-activated STAT3	Breast Prostate	↑ Stathmin ↓ MT stabilization	↓ Resistance to MTIs	[4,97]
Unidentified modules	LAC	↓ miR-27a anti-apoptotic targets	↓ Chemo-resistance	[68]

	Cervical	Bcl-2	↓ Resistance to apoptosis	[241]