Oncogene functions in human cancer

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Abstract

I delineated the functions of Signal Transducer and Activator of Transcription (STAT)-5A and STAT5B in human mammary carcinoma cells. Overexpression of a constitutively active (CA) variant of STAT5A (CA STAT5A) enhanced survival and anchorage-independent growth of human mammary carcinoma cells but concordantly suppressed cell motility as revealed in colony scattering, cell migration, and invasion assays. Over-expression of CA STAT5B exhibited lower potency than CA STAT5A in enhancing survival and anchorage-independent growth of mammary carcinoma cells but exerted no effects on cell motility. Differential expression of genes that regulate cellular survival and motility was concomitantly observed on overexpression of CA STAT5A or CA STAT5B. Small interfering RNA (siRNA)-mediated depletion of either STAT5A or STAT5B and xenograft analyses provided confirmatory results. Therefore, STAT5A and STAT5B differentially regulate behaviour of human mammary carcinoma cells.

I also demonstrated that Artemin (ARTN), one of the glial-cell-line-derived neurotrophic factor (GDNF) family of ligands, promotes progression of human non-small cell lung carcinoma (NSCLC). Information retrieved from Oncomine database indicates that expression of components of ARTN signalling pathway are increased in neoplastic compared to normal lung tissues; increased expression of ARTN also predicted metastasis to lymph nodes and a higher grade in certain NSCLC subtypes. Overexpression of ARTN stimulated survival, anchorage-independent, Matrigel and xenograft growth of NSCLC cell lines. ARTN increased BCL2 expression by transcriptional upregulation and inhibition of BCL2 abrogated the oncogenic properties of ARTN in NSCLC cells. Forced expression of ARTN also enhanced migration and invasion of NSCLC cells. Concordantly, either siRNA-mediated depletion or functional inhibition of endogenous ARTN with antibodies reduced oncogenicity and invasiveness of NSCLC cells. ARTN, therefore, mediates progression of NSCLC and may be a potential therapeutic target for NSCLC.

I additionally demonstrated an oncogenic role of STAT3α (the full-length STAT3 isoform), which also mediates the human growth hormone (hGH)-stimulated oncogenicity, in human endometrial carcinoma (EC) cells. Autocrine hGH stimulated Y705 phosphorylation of STAT3 and STAT3-mediated transcriptional activity in a SRC and JAK2 dependent manner. Overexpression of a constitutively active variant of STAT3α increased proliferation, anchorage-independent, Matrigel and xenograft growth of EC cells; and promoted epithelial-mesenchymal transition, migration and invasion of these cells. Conversely, JSI-124, a specific inhibitor of STAT3, abrogated the oncogenic capacities of EC cells and the enhancement in the oncogenicities stimulated by hGH. STAT3α may therefore be a common mediator of oncogenic signalling pathways stimulating progression of EC.

This thesis is dedicated to Dr. Rui Tong Liu and the innocent others suffering with cancer.

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°C	degree Centrigrade
3D	three dimensional
AKT	v-akt murine thymona viral oncogene homolog 1
APS	Ammonium persulfate
ARTN	artemin
ATCC	American Type Culture Collection
BAX	Bcl2-associated protein X
BCL2	B-cell lymphoma 2
bp	base pair
BrdU	5-Bromo-2'-deoxyuridine
BSA	bovine serum albumin
C/EBP	CCAAT/enhancer binding protein
CA	constitutively active
CDX2	caudal type omeobox 2
cDNA	complementary deoxyribonucleic acid
c-MET(MET)	Mesenchymal-epithelial transition factor
CNS	central nervous system
DAPI	4 ,6-diamidino-2-phenylindole
DEPC	diethylpyrocarbonate
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DNAse	deoxyribonuclease
dNTP	deoxynucleotide-triphosphate
DTT	dithiothreitol
e.g.	for example
EC	Endometrial carcinoma
EDTA	ethylenediaminetetra-acetic acid
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
ER	estrogen receptor
FBS	fetal Bovine Serum
FM	10% FBS medium
g	gram
g	gravitational constant
GDNF	Glial cell line-derived neurotrophic factor
GFL	Glial cell line-derived neurotrophic factor family of ligands
GFR	GDNF family ligands receptor
GH	growth hormone
GHR	growth hormone receptor
HCl	hydrochloric acid
HER	human epidermal growth factor
hGH	human growth hormone
IGF	Insulin-like growth factor

JAK	Janus kinase
KCl	Potassium Chloride
kDa	kilodalton(s)
HOX	Homeobox
IL	Interleukin
m	metre
M	molar
mA	milliampere
MAPK	Mitogen-activated protein kinase
MEF	mouse embryonic fibroblast
mg	milligram(s)
$MgCl_2$	Magnesium Chloride
$MgSO_4$	Magnesium Sulphate
miRNA	micro-ribonucleic acid
mm	millimetre(s)
ml	millilitre
mM	millimolar
mRNA	messenger ribonucleic acid
MTT	dimethylthiazoldiphenyltetrazoliumbromide
Na_2HPO_4	disodium hydrogen phosphate dodecahydrate
NaH_2PO_4	Sodium dihydrogen phosphate
NaOH	Sodium Hydroxide
NCAM	neural cell adhesion molecule
NCBI	National Center for Biotechnology Information
nm	nano meter
NRTN	Neurturin
l	liter
LIF	leukemia inhibitory factor
PBS	phosphate buffered saline
PCR	polymerase chain reaction
PDGF	platelet-derived growth factor
pH	potential hydrogen
PI	propidium iodide
PI3K	phosphoinositol 3'-kinase
PIAS	protein inhibitors of activated STAT
PPAR	peroxisome proliferator-activated receptor
PR	progesterone receptor
PRL	prolactin
PRLR	prolactin receptor
PSPN	Persephin
PVDF	polyvinylidene difluoride
NSCLC	non small cell lung carcinoma
RNA	ribonucleic acid
RNAse	Ribonuclease
RPM	revolutions per minute
RT-PCR	reverse transcriptase PCR

SCCHN	squamous cell carcinoma of the head and neck
SCLC	small cell lung carcinoma
SDS	sodium dodecyl sulphate
SDS-PAGE	SDS-polyacrylamide gel electrophoresis
SFM	serum free medium
SOCS	suppressor of cytokine signaling
siRNA	small interfering RNA
STAT	signal transducer and activator of transcription
TBS	Tris Buffered Saline
TBST	Tris Buffered Saline containing Tween 20
TDLU	terminal ductal lobular unit
TEB	terminal end bud
TEMED	N,N,N,N -Tetramethyl-Ethylenediamine
TERT	telomerase reverse transcriptase
TGF	transforming growth factor
Tris	2-amino-2-hydroxymethylpropane-1, 3-diol
TUNEL	terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling
UK	United Kingdom
USA	United States of America
µg	microgram
µl	microlitre
µm	micrometer
µM	micromolar
UV	ultra-violet
V	volt
v/v	volume per volume
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
w/v	weight per volume
WCL	whole cell lysate