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Palmatine suppresses glutamine-mediated interaction between pancreatic cancer and stellate cells through simultaneous inhibition of survivin and COL1A1

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ABSTRACT

Reciprocal interaction between pancreatic stellate cells (PSCs) and cancer cells (PCCs) in the tumor microenvironment (TME) promotes tumor cell survival and progression to lethal, therapeutically resistant pancreatic cancer. The goal of this study was to test the ability of Palmatine (PMT) to disrupt this reciprocal interaction *in vitro* and examine the underlying mechanism of interaction. We show that PSCs secrete glutamine into the extracellular environment under nutrient deprivation. PMT suppresses glutamine-mediated changes in GLI signaling in PCCs resulting in the inhibition of growth and migration while inducing apoptosis by inhibition of survivin. PMT-mediated inhibition of (glioma-associated oncogene 1) GLI activity in stellate cells leads to suppression (collagen type 1 alpha 1) COL1A1 activation. Remarkably, PMT potentiated gemcitabine's growth inhibitory activity in PSCs, PCCs and inherently gemcitabine-resistant pancreatic cancer cells. This is the first study that shows the ability of PMT to inhibit growth of PSCs and PCCs either alone or in combination with gemcitabine. These studies warrant additional investigations using preclinical models to develop PMT as an agent for clinical management of pancreatic cancer.

1. Introduction

Late stage diagnosis and lack of early detection markers contribute to the near equal rates of pancreatic cancer incidence and mortality. 20% patients are eligible for surgical resection and 3–4% remain disease-free following surgical resection while about 80% will relapse and die of the disease [1]. Gemcitabine (GEM)-monotherapy has been the standard of care for advanced pancreatic ductal adenocarcinoma (PDAC) for more than a decade although overall survival of patients on GEM is an average of 6 months. Therapeutic approaches based on combination of GEM with additional chemotherapy agents such as oxaliplatin, irinotecan, leucovorin and 5-FU (FOLFIRINOX) have provided modest survival benefit with significant toxicity, and is reserved for a select group of patients [2]. Therefore, there is a critical need for new agents that can effectively manage PDAC.

Uniquely, a dense stroma or desmoplastic reaction (DR) in the tumor microenvironment (TME) plays a critical role in tumor maintenance and in limiting therapeutic efficacy by decreasing drug delivery [3,4]. This constitutes about 90% of the tumor area and is comprised of a variety of cells including stellate cells (PSCs), fibroblasts, endothelial cells, myeloid cells, and extracellular matrix (ECM) components such as collagens [5]. PSCs, considered to be the driver of pancreatic fibrosis, are usually quiescent in the normal

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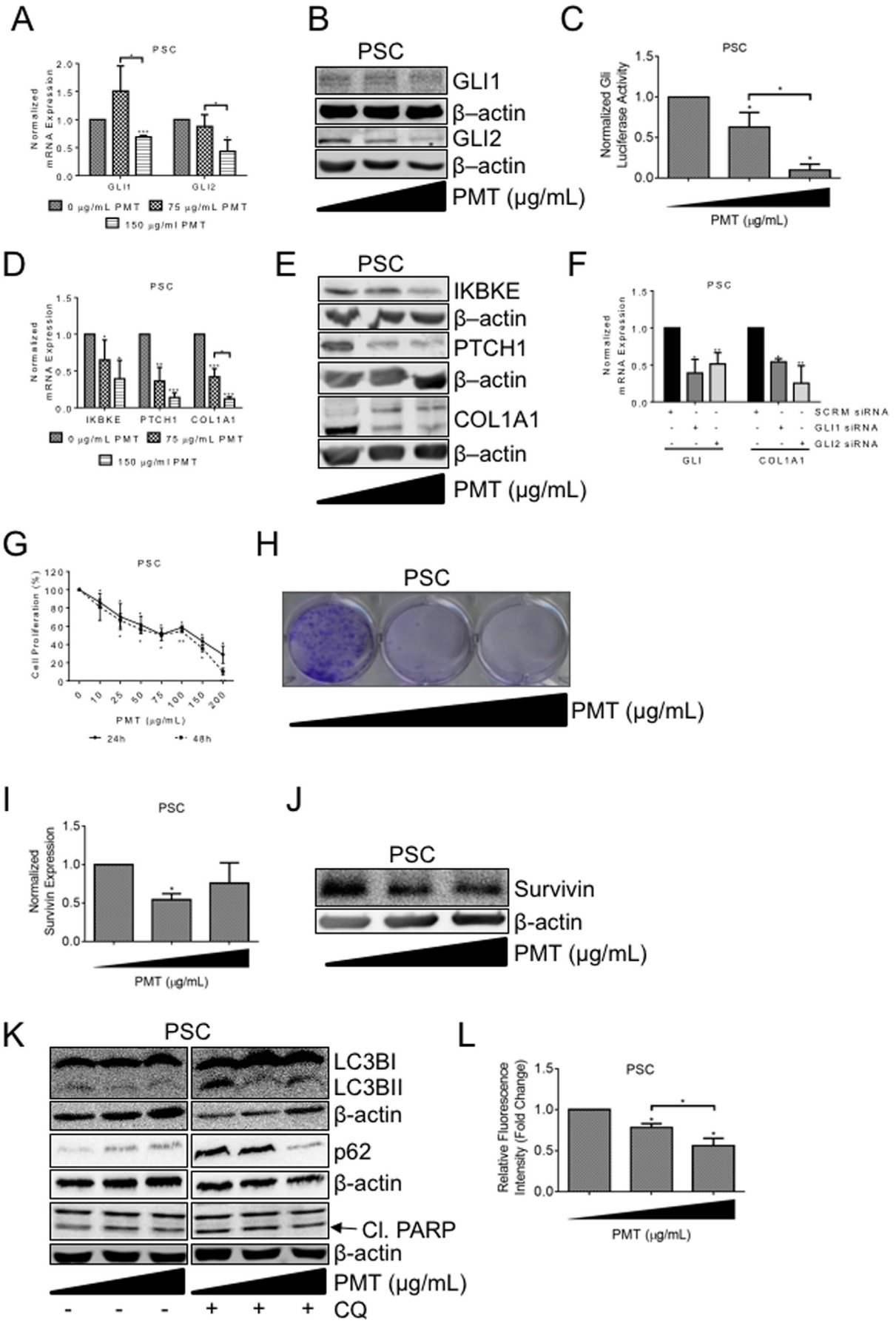
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PSC
Normalized mRNA Expression
GLI1
GLI2
0 μg/mL PMT
75 μg/mL PMT
150 μg/ml PMT
B
PSC
GLI1
β–actin
GLI2
β–actin
PMT (μg/mL)
C
PSC
Normalized Gli Luciferase Activity
PMT (μg/mL)
D
PSC
Normalized mRNA Expression
IKBKE
PTCH1
COL1A1
0 μg/mL PMT
75 μg/mL PMT
150 μg/ml PMT
E
PSC
IKBKE
β–actin
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β–actin
COL1A1
β–actin
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Normalized mRNA Expression
SCRM siRNA
GLI1 siRNA
GLI2 siRNA
GLI
COL1A1
G
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Cell Proliferation (%)
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48h
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