Piperlongumine nanoformulation attenuates pancreatic tumor desmoplasia and alter tumor immune responses

Vivek Kumar Kashyap
The University of Texas Rio Grande Valley

Neeraj Chauhan
The University of Texas Rio Grande Valley

Mohammed Sikander
The University of Texas Rio Grande Valley

Eswara N. H. K. Ghali
The University of Texas Rio Grande Valley

Bilal Hafeez
The University of Texas Rio Grande Valley

See next page for additional authors

Presenter Information (List ALL Authors)
Vivek Kumar Kashyap, Neeraj Chauhan, Mohammed Sikander, Eswara N. H. K. Ghali, Bilal Hafeez, Murali M. Yallapu, Meena Jaggi, and Subhash C. Chauhan

Piperlongumine nanoformulation attenuates pancreatic tumor desmoplasia and alter tumor immune responses

Vivek K Kashyap, Neeraj Chauhan, Mohammed Sikander, Eswara Naga Hanuma Kumar Ghali, Bilal Bin Hafeez, Murali M. Yallapu, Meena Jaggi, Subhash C. Chauhan

South Texas Center of Excellent in Cancer Research, Medicine and Oncology Unit, School of Medicine, University Texas Rio Grande Valley, McAllen, Texas, USA

Abstract:
Pancreatic cancer (PanCa) is characterized by lack of early diagnosis, poor response to available therapeutic modalities and chemoresistance. Gemcitabine (GEM) is currently considered the most effective therapy for PanCa; however, it shows only a marginal survival benefit of 6 months. This poor drug response has been attributed to desmoplasia, causes suboptimal drug delivery, alters tumor microenvironment (TME), which includes tumor surrounding blood vessels, fibroblasts, immune cells, extracellular matrix, and other signaling molecules and induces chemo-resistance in tumors. To overcome these existing issues associated with chemotherapy, identification and development of novel therapeutic modalities are a pressing need. Piperlongumine (PL) is a natural alkaloid isolated from the long pepper, Piper longum L., and has shown substantial cancer-preventive and therapeutic efficacy against a variety of cancers. However, delivering its effective concentration in pancreatic tumors has been challenging. We have recently engineered a multi-layered Pluronic F127 and polyvinyl alcohol stabilized, and poly-L-lysine coated piperlongumine loaded poly(lactic-co-glycolic acid) nanoparticle formulation (PLGA-PL), which effectively inhibits the growth of PanCa cells. In this study, we demonstrate that PLGA-PL effectively sensitizes tumor cells to GEM *via* decreased desmoplasia, altered TME, SHH/CXCL12/CXCR4 and immune surveillance. Our finding show that PLGA-PL synergizes with GEM in inhibiting PanCa cell (HPAF-II and Panc-1) growth, migration, and invasion compared to free PL. Mechanistically, PLGA-PL targets the TME via inhibition of sonic hedgehog (SHH) pathway and oncogenic CXCR4/CXCL12 signaling axis that inhibits bidirectional tumor-stromal cells interaction. We have also found that PLGA-PL alone and in combination with GEM targets cancer stem cells by inhibiting pluripotency maintaining stemness factors (Nanog, Sox2, c-Myc, CD133, and Oct-4) as determined by qRT-PCR, Western blotting, and immunofluorescence analysis, and further confirmed by restricting tumor sphere formation. Furthermore, PLGA-PL also effectively targets tumor-associated macrophages (TAM) by repolarizing M2 into M1 phenotype via inhibiting expression of M2 markers and an increase in M1 markers in mouse macrophage cell line RAW264.7. M2 polarization of RAW264.7 cells were induced by culture with IL-4 (20 ng/mL) in presence of PLGA-PL or vehicle control. In addition, PLGA-PL effectively increases phagocytic capacity in murine macrophages as determined by phagocytosis assay (Vybrant Phagocytosis Assay Kit). In conclusion, we observed that PLGA-PL effectively targets TME, facilitates GEM uptake by inhibiting the activation of CXCR4/CXCL12/SHH signaling, and reprograming the tumor immune surveillance. This study suggests that PLGA-PL has great potential for future clinical use in management of PanCa.

Keywords: Pancreatic cancer, Gemcitabine, nanoformulation, tumor-associated macrophages