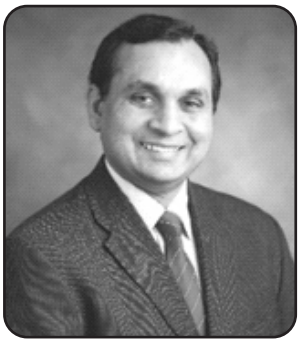
Shri R J Kinarivala Research Oration Award, Year - 2018



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Targeting Pancreatic Tumor Microenvironment for Effective Pancreatic Cancer Treatment

Pancreatic cancer (PanCa) management is exceptionally difficult due to the extremely poor response to available therapeutic modalities and lack of effective therapeutic strategies. Highly desmoplastic (excessive fibrosis and extracellular matrix deposition) microenvironment in pancreatic tumor causes suboptimal drug delivery and increases chemo-resistance. In addition to tumor cells, presence of stromal components such as tumor associated fibroblasts (TAFs), pancreatic stellate cells (PSCs), cancer stem cells (CSCs) and tumor associated macrophages (TAMs) also play a pivotal role in induction, progression and metastasis of PanCa. At the onset of cancer induction and progression various oncogenic signaling molecules such as Mucin 13 (MUC13), KRas, NF-κB, and Sonic Hedgehog (SHH) play critical roles. In response to aberrant expression of these oncogenic molecules, cancer cells and stromal cells secrete various growth factors which are involved in reciprocal cross-talk in between tumor and stromal cells. This creates desmoplastic tumor microenvironment (TME) to facilitate PanCaprogression and metastasis. Thus, targeting components of TME along with oncogenic signaling pathways by non-toxic agents/ drugs will be effective therapeutic approach to combat this lethal disease.

In this talk, we will discuss how components of pancreatic TME and oncogenic signaling pathways play an important role in PanCa progression and metastasis. We will also discuss new strategy and molecular mechanisms to suppress components of pancreatic TME by non-toxic nutraceuticals. Our lab has identified novel nutraceuticals (curcumin, α-Mangostin, and plumbagin) which inhibit expression of fibroblast cells marker (α-SMA, and CYGB) and oncogenic CXCL12/CXCR4/Shh signaling pathways in human TAFs and PanCa cells. Moreover, we have developed novel nano-formulations of these nutraceuticals which show high significant therapeutic and chemosensitization potential in orthotopic xenograft mouse model involving co-injection of PanCa cells along with TAFs. In, addition these agents also inhibit the growth of pancreatic CSCs via targeting CSCs marker (Nanog and CD44). These nutraceuticals could be a potential therapeutic modality in near future for the prevention and treatment of human PanCa.

" Persistence, perseverance, and continuous improvement are the ingredients for forming a successful person. "

Debasish Mridha