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Targeting cancer at the nuclear pore complex

Asfar S Azmi
Wayne State University, USA

Eukaryotes shuttle proteins and RNAs in and out of the cell nucleus using highly complex gated machinery. The movement of most of the proteins and RNAs require active transport that is mediated by specialized carriers in a strictly controlled manner. Such energy dependent trafficking occurs through the nuclear pore complex (NPC) that is embedded in the nuclear membrane. This is functionally critical for tumor suppressor proteins (TSPs) and transcription factors (TFs) that require nuclear retention and sequence specific DNA alignment to modulate their target gene expression or conduct genome surveillance activity. Indeed, cancer cells have evolved methods to disturb the nuclear traffic by abnormal expression of the nuclear exporters particularly exportin 1 (Xpo1) that leads to a cascade of de-regulations favoring uncontrolled growth and loss of surveillance within the cells. Major cancer hallmarks have been shown to be influenced by Xpo1 de-regulation directly or indirectly. Recently, specific inhibitors of nuclear export (SINE) have been developed as a broad form of therapy targeting global re-alignment of multiple TSPs in the correct cellular compartment through inhibition of Xpo1 to rein in cancer. Our new findings highlight a novel role of nuclear exporter XPO1 in microRNA biology. We have demonstrated the activity of SINE across a spectrum of solid tumors and hematological malignancies. Based on these studies SINE compounds are under extensive Phase I and Phase II clinical evaluation for various tumor indications

azmia@karmanos.org