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Therapeutic Targeting at Fusion Genes in Human Cancers

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Chromosome mutations and rearrangements are some of the hallmarks of human malignancies. Chromosomal rearrangement is frequent in human cancers. One of the consequences of chromosomal rearrangement is gene fusions in the cancer genome. We have identified a panel of fusion genes in aggressive prostate cancers. In the present study, we found that these fusion genes are present in 7 different types of human malignancies with variable frequencies. Among them, CCNH-C5orf30 and TRMT11-GRIK2 gene fusions were found in breast cancer, colon cancer, non-small cell lung cancer, esophageal adenocarcinoma, glioblastoma multiforme, ovarian cancer and liver cancer, with frequencies ranging from 12.9% to 85%. In contrast, four other gene fusions (mTOR-TP53BP1, TMEM135-CCDC67, KDM4-AC011523.2 and LRRC59-FLJ60017) are less frequent. Both TRMT11-GRIK2 and CCNH-C5orf30 are also frequently present in lymph node metastatic cancer samples from the breast, colon and ovary. Thus, detecting these fusion transcripts may have significant biological and clinical implications in cancer patient management. One of these fusion genes called MAN2A1-FER generated a constitutively activated tyrosine protein kinase. The fusion translocates FER kinase from the cytoplasm to Golgi apparatus. The fusion protein ectopically phosphorylates the N-terminal domain of EGFR and activates the EGFR signaling pathway in the absence of a ligand. MAN2A1-FER has been found in a variety of human malignancies. It transforms immortalized cell lines into highly aggressive cancer cells. Expression of MAN2A1-FER produces spontaneous liver cancer in animals. Cancer cells positive for MAN2A1-FER are highly sensitive to several tyrosine kinase inhibitors and can be targeted by genome therapy intervention. Thus, targeting at MAN2A1-FER or other oncogenic fusion genes may hold promise to treat human cancer effectively.

Biography:

Dr. Luo has been studying molecular pathology related to human malignancies in the last 28 years. Currently, he is a Professor of Pathology and Director of High Throughput Genome Center at University of Pittsburgh. In the last 17 years, Dr. Luo has been largely focusing on the genetic and molecular mechanism of human prostate and hepatocellular carcinomas. In this period, his group has identified and characterized several genes that are related to prostate cancer and hepatocellular carcinoma, including SAPC, myopodin, CSR1, GPx3, ITGA7, MCM7, MCM8, MT1h and GPC3. He has characterized several signaling pathways that play critical role in prostate cancer development, including Myopodin-ILK-MCM7 inhibitory signaling, myopodin-zyxin motility inhibition pathway, CSR1-CPSF3, CSR1-SF3A3 and CSR1-XIAP apoptotic pathways, MT1h-EHMT1 epigenomic signaling, ITGA7-HtrA2 tumor suppression pathway, GPx3-PIG3 cell death pathway, AR-MCM7, MCM7-SF3B3 and MCM8-cyclin D1 oncogenic pathways. He proposed prostate cancer field effect in 2002. He is one of the pioneers in utilizing high throughput gene expression and genome analyses to analyze field effects in prostate cancer and liver cancer. He is also the first in using methylation array and whole genome methylation sequencing to analyze prostate cancer. Recently, his group discovered several novel fusion transcripts and their association with aggressive prostate cancer. One of the fusion genes called MAN2A1-FER, was found present in 6 different types of human cancers. He later defined a critical MAN2A1-FER/EGFR signaling pathway that is essential for MAN2A1-FER mediated transformation activity. His group also developed a genome intervention strategy targeting at the chromosomal breakpoint of fusion gene to treat cancers. Overall, these findings advance our understanding of how cancer develops and behaves and lay down the foundation for better future diagnosis and treatment of human malignancies.