Extended Abstract

Journal of Pharmacology and Medicinal Chemistry

2019
Vol. 3, Iss. 1

Redox-dependent targeting of mutant RAS driven cancers

Shazib Pervaiz

National University of Singapore, Singapore National University Cancer Institute - NUHS, Singapore.

RAS family of GTPases is frequently mutated in human cancers. The current therapeutic strategies to target mutant RAS driven cancers rely mostly on inhibitors that either block the farnesylation/geranylation of RAS or inactivate effectors downstream of activated RAS, such as AKT, MEK and ERK. Despite these endeavors, the clinical outcome of patients harboring mutant RAS expressing cancers remain less than optimal. Our recent work highlights a novel strategy to overcome RAS addiction in human colorectal, pancreatic and non-small cell lung cancer that frequently carry RAS mutations. Exploiting the RAS specific activity of a novel small molecule compound, we provide evidence that hyper-activation of mutant KRAS-and not its inhibition-results in massive redox catastrophe culminating in mitochondrial short circuiting and death execution. We also provide evidence to implicate activation of Akt/PKB, downstream of mutant active KRAS, in triggering oxidative stress and autophagy associated cell death. These data and their potential implications for the design of novel therapeutic strategies to target mutant RAS driven cancers will be discussed. Recent Publications 1. Wong C H, Iskandar K B, Yadav S K, Hirpara J L, Loh T Pervaiz S (2016) Simultaneous induction of non- canonical autophagy and apoptosis in cancer cells by ROS-dependent ERK and JNK activation. PLoS One. 5(4):e9996. 2. Iskandar K, Rezlan M, Yadav S, Foo Chuan Han J, Sethi G, Qiang Y, Bellot G, Pervaiz S (2016) Synthetic lethality of a novel small molecule against mutant KRAS expressing cancer cells involves Akt dependent ROS production. Antioxid. Redox. Signal. 24(14):781-94.

Biography:

Shazib Pervaiz holds a Full Professorship in the Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore. Over the years, he has held various leadership positions at the YLL School of Medicine, such as Vice Dean (Research and Graduate Education) and is a Distinguished Visiting Fellow at the Faculty of Health Sciences, Curtin University, Perth, Australia. He is spearheading a group investigating cellular redox status and its impact on cancer cell fate decisions with an overall objective of identifying novel targets for therapeutic intervention. He has authored more than 145 research papers and book chapters and his research work is highly cited in the field, as indicated by over 12000 citations and an H-index of 52 (by Google Scholar). He has been an invited speaker at several international and regional conferences and is serving on the editorial boards of several international peer-reviewed journals. He was elected to the European Cell Death Organization (ECDO) Academy in 2013. Being a Clinician Scientist, he also has an extensive understanding of working with the healthcare sector as well as with the biotechnology and pharmaceutical industries.