

## Redox-sensitive inhibition of Hsp90 disrupts the super-chaperone complex and attenuates pancreatic adenocarcinoma

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Pancreatic cancer is almost always fatal, in part because of its delayed diagnosis, poor prognosis, rapid progression and chemoresistance. Oncogenic proteins are stabilized by the heat shock protein 90 (Hsp90), making it a potential therapeutic target. We investigated the oxidative stress-mediated dysfunction of Hsp90 along with direct hindrance of its chaperonic activity by a carbazole alkaloid (CM-5), as a strategic therapeutic in pancreatic cancer. CM-5 exhibited anti-proliferative activity against several pancreatic cancer cells through apoptosis. It induced early accumulation of reactive oxygen species (ROS) leading to thiol oxidation, aggregation and dysfunction of Hsp90 in MIAPaCa-2 cell line. N-acetyl-L-cysteine prevented CM-5-induced ROS accumulation, aggregation of Hsp90, degradation of client proteins and cell death. CM-5 may possibly disrupted Hsp90-Cdc37 chaperone complex in MIAPaCa-2 in addition to inducing ROS generation. Client proteins were restored by MG132, suggesting a possible role of ubiquitinated protein degradation pathway. Surface plasmon resonance study gave the dissociation constant (KD) of Hsp90-CM-5 as 4.99  $\mu$ M, which is in (a) good agreement with the dynamic simulation value (3.16  $\mu$ M). CM-5 formed hydrogen bonds with Gln47 and Asn51 of Hsp90 and exhibited hydrophobic interactions with several amino acids in the Hsp90-Cdc37 interface. However, CM-5 did not impede the ATP binding pocket of Hsp90. CM-5 also reduced in vitro migration and tube formation in cancer cells. Further, it inhibited orthotopic pancreatic cancer in nude mice. Taken together, these results provide evidence for CM-5-induced ROS-mediated destabilization of Hsp90 chaperone activity resulting in Hsp90-Cdc37 disruption leading to apoptosis, suggesting its potential as a specific target in pancreatic cancer.

### Biography

Dr. Chitra Mandal, did her M.Sc. in Chemistry and Ph.D. in Bio Organic Chemistry from Indian Institute of Science, Bangalore, the most prestigious Institute in India. After that she moved to University of Pennsylvania, USA for her Post Doctoral work on Molecular Immunology on antibody diversity. Then she joined at CSIR-Indian Institute of Chemical Biology, Kolkata, India during 1982 and currently working as a 'Scientist H'. Now she is leading the CSIR-Innovation Complex, Kolkata for translation research. Dr Mandal's Glycobiology group is deeply involved in understanding the mystery of glycosylation mainly sialylation of biomolecules to understand the disease biology. Her specific interest is on O-acetylated sialic acids specifically induced in patients with leukemia and visceral leishmaniasis and their potential applications in medical research. Her recent interest is on identification of anti-cancer lead herbal molecules and potential target leads to knowledge based therapeutics. She has published >130 papers, 14 patents and transferred three technologies to Industries. Twenty students were awarded Ph.D degree under her direct supervision. She is an elected fellow of all three prestigious Indian academies, Indian National Science Academy (F.N.A.), the Indian Academy of Sciences (F.A.Sc) and The National Academy of Sciences (F.N.A.Sc) and West Bengal Academy of Science and Technology for her contribution in the field of Glycobiology in health and Diseases. She is a recipient of many honors and awards. She is a recipient of Sir J.C. Bose national fellowship by DST, Dr. Yellapragada SubbaRow Memorial Lecture" by The Indian National Science Academy, "National Women Bioscientist award (senior) by Department of Science and Technology, "Senior Scientist Oration Award" by the Indian Immunology Society, 'BioTech Product and Process Development and Commercialization Award' by Department of Biotechnology, 'Kshanika Oration Award' by Indian Council of Medical Research, 'The P B Rama Rao Memorial Award' by the Society of Biological Chemist and 'Smt Chandaben Mohanbhai Patel Industrial Research award' by Vividhlaxi Audyogik Samshodhan Vikas Kendra (VASVIK) for her overall contribution in the biomedical field and transferring three technologies to the Industries. She is a life member of many Academic Professional Societies in India.

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