

Role of the TMPRSS2-ERG gene fusion and autophagy in DNA damage and repair of prostate cancer

Alexandru Almasan
Cleveland Clinic Foundation, USA

This lecture will address two topics on DNA damage and repair in prostate cancer (PCa). The fusion between TMPRSS2, an androgen-regulated oncogene, and an ETS transcription factor estrogen-regulated gene, ERG accounts for > 60% of PCa. Exposure to genotoxic agents, such as ionizing radiation (IR) produces DNA damage and its toxicity is augmented when the DNA repair is impaired. Poly-ADP-ribose-Polymerase (PARP) inhibitors are most effective in cells deficient in DNA repair. Interestingly, cells that harbor TMPRSS2-ERG show γ H2AX and 53BP1 IR-induced foci constitutively, indicative of persistent DNA damage that was absent if the gene fusion was depleted. This response correlated with the ability of TMPRSS2-ERG protein to bind to DNA-PKcs on the chromatin and, as a result, inhibited its kinase activity. DNA-PKcs deficiency caused by TMPRSS2-ERG destabilized critical NHEJ DNA repair components. The kinase activity was restored and the DNA damage response diminished, when TMPRSS2-ERG was depleted by siRNA. Therefore, the presence of TMPRSS2-ERG, by inhibiting NHEJ, enhanced radio sensitization of PCa cells by PARP inhibition. Senescence was also an important response following IR in cells expressing TMPRSS2-ERG due to inhibition of DNA-PKcs. Following IR, cells expressing TMPRSS2-ERG had also elevated Rad51 foci, indicating sustained DNA damage-induced homologous recombination (HR). Thus, by inhibiting NHEJ, TMPRSS2-ERG provides a synthetic lethal interaction with HR after the DNA replication block induced by PARP inhibition. Similar to TMPRSS2-ERG, autophagy inhibition also blocked NHEJ repair. These findings provide unique mechanistic insights into NHEJ misregulation in human tumor cells, in which defects in NHEJ core components are rare.

Biography

Alexandru Almasan is a Professor of Molecular Medicine and Co-Leader of the Cell Death Regulation Program at the at Case Western Reserve University Comprehensive Cancer center. During the last 20 years, his laboratory has focused on the basic mechanisms of cancer therapy, with an interest in the molecular basis of the DNA damage signals in mammalian cells following ionizing radiation leading to cell death and proliferation control. He has published more than 70 papers and is serving as an editorial board member of 8 scientific journals. His expertise was sought by the BMCT (full term) and CAMP NIH study sections.

ALMASAA@ccf.org