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Phosphorylation of Transglutaminase 2 (TG2) at serine-216 plays a role in TG2 mediated activation of nuclear factor-kappa B and in the downregulation of PTEN

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Transglutaminase 2 (TG2) and its phosphorylation have been consistently found to be upregulated in a number of cancer cell types. At the molecular level, TG2 has been associated with the activation NF-κB, Akt and in the downregulation of PTEN. However, the underlying mechanism involved is not known. We have reported that PKA induced phosphorylation of TG2 at serine-216 (Ser216) regulates TG2 function and facilitates protein-protein interaction. However, the role of TG2 phosphorylation in the modulation of NF-κB, Akt and PTEN is not explored. We investigated the effect of TG2 phosphorylation on NF-κB, Akt and PTEN using embryonic fibroblasts derived from TG2 null mice ($MEF^{tg2-/-}$) overexpressing native TG2 or mutant-TG2 (m-TG2) lacking Ser216 phosphorylation site. PKA activation in TG2 overexpressing $MEF^{tg2-/-}$ cells resulted in an increased activation of NF-κB and Akt phosphorylation in comparison to empty vector transfected control cells. These effects were not observed in $MEF^{tg2-/-}$ cells overexpressing m-TG2. Similarly, a significant downregulation of PTEN at both, the mRNA and protein levels were found in cells overexpressing TG2 in comparison to empty vector control and m-TG2 transfected cells. Furthermore, Akt activation correlated with the simultaneous activation of NF-κB and a decrease in PTEN suggesting that the facilitatory effect of TG2 on Akt activation occurs in a PTEN-dependent manner. Similar results were found with MCF-7 and T-47D breast cancer cells overexpressing TG2 and m-TG2 further supporting the role of TG2 phosphorylation in NF-κB activation and in the downregulation of PTEN. Collectively, these data suggest that phosphorylation of TG2 at Ser216 plays a role in TG2 mediated activation of NF-κB, Akt and in the downregulation of PTEN. Blocking TG2 phosphorylation may provide a novel strategy to attenuate NF-κB activation and downregulation of PTEN in TG2 overexpressing cancers.

Biography

Mishra has completed his Ph.D. from University of Delhi, India and postdoctoral studies from University of Louisville School of Medicine, USA and University of Manitoba, Canada. He is currently Associate Professor of Medicine at the University of Manitoba and has published more than 40 papers in peer-reviewed journals.

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