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RARRES3 regulates signal transduction through post-translational protein modifications

Tzu-Hui Hsu[1] and Tsu-Chung Chang[2,*]

[1]Genomics Research Center; Academia Sinica; Taipei, Taiwan, ROC; [2]Department of Biochemistry; National Defense Medical Center; Taipei; Taiwan, ROC

We recently reported that retinoic acid receptor responder 3 (RARRES3)-mediated protein deacylation resulted in significant inhibition of the transformed properties of breast cancer cells. This finding suggests a key role of RARRES3 in the regulation of growth signaling and metastasis in cancer cells and as a potential therapeutic target for cancer therapy.

Retinoic acid receptor responder 3 (RARRES3) is a class II tumor suppressor that belongs to the HREV-107 protein family. Proteins of this family share 4 conserved domains: a proline-rich motif located at the N-terminus followed by a conserved H-box, the NC motif (NCXHFV), and a C-terminal transmembrane domain.[1] These proteins are growth regulators and have recently been classified into the NC protein family together with the lecithin:retinol acyltransferase (LRAT)-like family and NlpC/P60 superfamily.[2] Previous results indicated that overexpression of RARRES3 suppresses cell growth, induces apoptosis, and promotes terminal differentiation of keratinocytes. As a downstream target of the tumor protein p53 (TP53), the type I tumor suppressor RARRES3 was recently shown to modify the acylation status of Wnt/β-catenin signaling factors through its phospholipase activity (**Fig. 1**).[3,4] These studies linked the enzymatic activity of RARRES3 to its functional role in modulation of the epithelial-mesenchymal transition (EMT) process, cancer cell stemness, and Wnt/β-catenin signaling activity. It is interesting to note that RARRES3 has also been shown to block tumor metastasis by promoting cellular differentiation signals through its intrinsic phospholipase $A_{1/2}$ catalytic activity.[5]

Fatty acyl moieties such as myristate and stearate serve to anchor soluble proteins onto the cytoplasmic surfaces of the plasma membrane, whereas palmitate augments the protein–membrane association of substrates that are already associated with or inserted into the membrane. The thioester-linked palmitate attachment forcefully drives protein substrates into specific membrane domains to facilitate protein interaction or signaling transduction.[6] Attachment of an acyl moiety on one or more cysteines by protein acyltransferases results in the translocation of protein substrates from the endoplasmic reticulum or Golgi apparatus to the plasma membrane. In contrast, removal of fatty acyl moieties causes the protein to become trapped in intracellular compartments, which may further enhance protein recycling or degradation. Thus, protein acylation can serve as a switch, regulating not only the protein–membrane binding affinity, but also the biological activities of the protein by interfering with functional complex formation. Recent studies have shown that protein acylation effectively influences the physiological function of canonical Wnt/β-catenin signaling in cells of different origins. Fatty acid moieties serve as secondary regulators to modulate protein conformation and stability of Wnt/β-catenin signaling molecules.[7] Similarly, the dynamic acylation cycle also regulates the shuttling of small GTPase H-Ras and its signaling activity.[8] The unique reversibility of protein acyl modification allows peripheral membrane proteins to rapidly pass back and forth between distinct intracellular

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*Correspondence to: Tsu-Chung Chang; Email: tcchang@ndmctsgh.edu.tw

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membrane compartments to modulate subcellular signaling transductions.

By regulating the acylation status of signaling proteins, RARRES3 effectively inhibits H-Ras and Wnt/β-catenin signaling activities in a manner dependent on post-translational modification.[4] It should be noted that RARRES3 also suppresses many other signaling molecules including phosphatidylinositol 3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK), which are involved in the control of the stemness and EMT properties of cancerous cells.[1,9,10] Thus, these studies indicate a novel role of the class II tumor suppressor RARRES3 in the inhibition of cell growth signaling and corresponding downstream responses in cancer cells by modulating the post-translational modification of signaling molecules. Considering the emerging importance of Wnt/β-catenin signaling in cell differentiation and tumorigenesis, the role of the p53-RARRES3 axis in Wnt/β-catenin signaling may represent a potential target for cancer therapy.

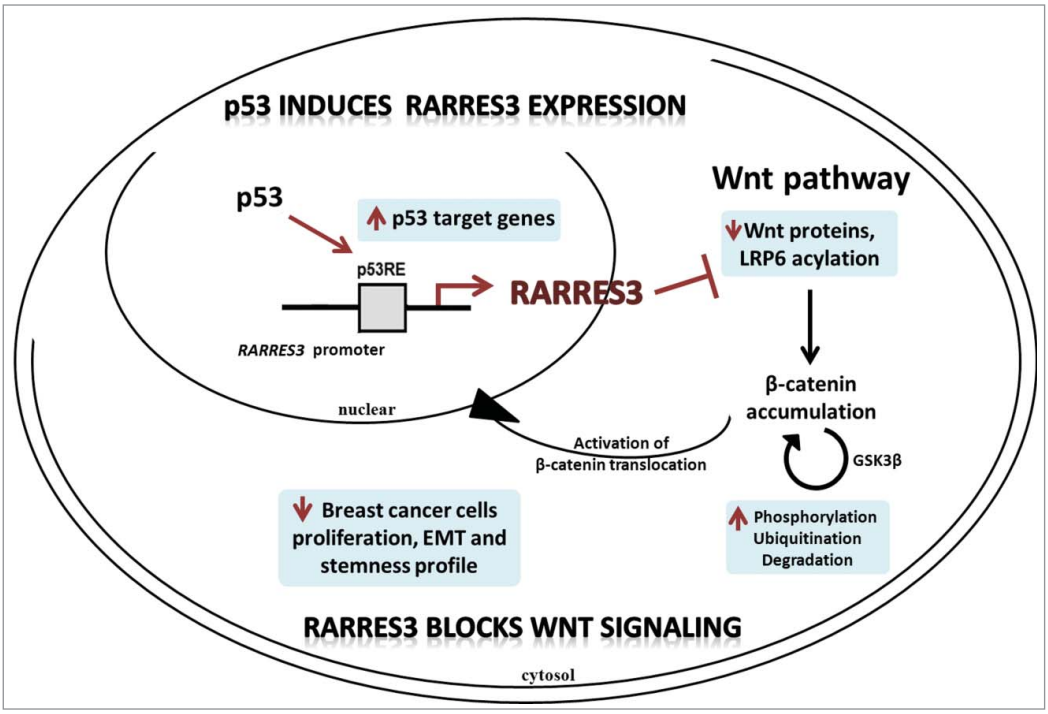

Figure 1. Role of the p53–RARRES3 axis in the control of Wnt/β-catenin signaling. p53, a type I tumor suppressor, induces the expression of RARRES3, which exerts its tumor suppressive activity through the modulation of Wnt/β-catenin signaling. The increased expression of RARRES3 causes protein deacylation of Wnt/β-catenin signaling molecules, leading to retention of LRP6 in the Golgi apparatus and suppression of Wnt/β-catenin signaling activity. Inhibition of Wnt/β-catenin signaling results in GSK3β-mediated phosphorylation of β-catenin. The subsequent ubiquitination and degradation of β-catenin disrupts β-catenin translocation, leading to suppression of the transformed properties of human cancer cells, including cell proliferation, EMT, and stemness profiles of breast cancer cells. Abbreviations: EMT: epithelial-mesenchymal transition; GSK3β: glycogen synthase kinase 3β; LRP6: lipoprotein receptor-related protein 6; p53RE: p53 response element; RARRES3: retinoic acid receptor responder 3.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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