

Non-Confidential Description - PSU No. 3262

“Inhibition of PAD4 with α -amidine or siRNAs to Inhibit Cancer Cell Growth Through the p53 Pathway”

Field/Keywords:

Biochemistry, Molecular and Cancer Biology

Links:

[Inventor website](#)

Inventors:

Yanming Wang , Pingxin Li, Ming Li, Hongjie Yao,
Paul Thompson (University of South Carolina),
Yuan Luo (University of South Carolina).

Background

The p53 tumor suppressor is a DNA-binding transcriptional factor that recruits both coactivators and corepressors to regulate the expression of its target genes, which in turn regulates cell growth, proliferation, and apoptosis. Dynamic histone modifications play important roles in gene regulation. For example, the histone acetyltransferase (HAT) p300/CBP and the protein Arg methyltransferases (e.g., PRMT1 and CARM1) were found to regulate the expression of p53-target genes. However, less is known about how the steady state balance of histone modifications is achieved to allow the appropriate level of p53-target gene expression. I have previously reported that peptidylarginine deiminase 4 (PAD4) can demethylinate/citrullinate histones to regulate gene expression in the breast cancer MCF-7 cells. Recently, my group has found that PAD4 interacted with p53 and regulates the expression of p53 target genes (Li et al., 2008; Yao et al., 2008). The knockdown PAD4 by siRNAs elevated the expression of p21/WAF1/CIP1, an inhibitor of the cell cycle progression, leading to decreased cell growth while increased apoptosis. Further, after the treatment of cells with a recently reported PAD4 inhibitor, CI-amidine, the p53 protein was stabilized and the expression of p21/WAF1/CIP1 was increased. PAD4 and histone citrullination were detected at the p53 target gene p21, suggesting that PAD4 plays a direct role in the expression of p53 target genes. Our results suggest histone Arg modifications as one mechanism underlying p53-mediated gene expression.

Invention Description

Our work found that PAD4 interacts with p53. PAD4 was recruited to the p53-target gene promoters, and that the inhibition of PAD4 activates the expression of the p53 target gene p21. As the expression of the p53 target genes, such as p21/WAF1/CIP1 etc., is key to the choice between survival and apoptosis in cancer cells, the function of PAD4 is likely important in regulating the cell growth and proliferation. Based on our results, we propose that PAD4 represses the expression of p53 target genes thereby facilitating the growth and proliferation of cancer cells. For the goal of cancer treatment, PAD4 is an ideal target. With PAD4 depletion by siRNAs or or inhibition by the compound CI-amidine, we can turn on the expression of p53 target genes thereby preventing the growth of cancers.

Advantages

- Novel
- Cancer treatment potential
- Potential anti-cancer drug tested

Contact: Matthew D. Smith
Sr. Technology Licensing Officer
The Pennsylvania State University

Phone: (814) 863-1122
Fax: (814) 865-3591
E-mail: mds126@psu.edu



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Sr. Technology Licensing Officer
The Pennsylvania State University

Phone: (814) 863-1122
Fax: (814) 865-3591
E-mail: mds126@psu.edu