ABSTRACT

The hormone estrogen, when bound to its receptor (ER) triggers a cascade of signalling events that result in the proliferation of normal mammary glands. This hormone can also regulate gene expression at the transcriptional level by activating ER-dependent genes and post-transcriptionally by modulating the expression of microRNAs (miRNAs) that alter mRNA stability and translation. The pre-mRNA splicing factor 4 kinase PRP4K (PRPF4B), is an essential kinase that is a component of the U5 snRNP and functions in spliceosome assembly. In this study I demonstrated that PRP4K is expressed in the normal mammary duct epithelial cells of the mouse, and that estrogen induces PRP4K gene and protein expression in ER+ human MCF7 breast cancer cells. Furthermore, I found that PRP4K levels are regulated by estrogen via the estrogen receptor alpha, encoded by the ESR1 gene. Thus by modulating levels of PRP4K, estrogen may affect pre-mRNA splicing in tissues expressing ESR1. As a first step towards the characterization of this novel mode of pre-mRNA splicing regulation, I sought to determine the mechanisms behind the hormonal regulation of PRP4K. Although my promoter studies indicated that estrogen does not regulate PRP4K directly at the transcriptional level, I identified several putative binding sites for miRNAs in the 3′-UTR of PRP4K. Several of these miRNAs, including miR-21, are estrogen regulated and/or deregulated in breast cancer. Using ER+ MCF7 breast cancer cells and a dual luciferase reporter system, I have demonstrated that the 3′-UTR of PRP4K can indeed regulate luciferase gene expression and that miR-21 over expression modulates this regulation. Furthermore, the Dellaire laboratory previously demonstrated that PRP4K is a novel biological marker for taxane response in ovarian cancer patients and reduced levels of PRP4K correlate with intrinsic and acquired taxane resistance in both breast and ovarian cancer. Here, I have demonstrated that treatment with tamoxifen, an inhibitor of estrogen signalling, can decrease PRP4K levels in MCF7 breast cancer cells reducing their sensitivity to the taxane paclitaxel. Thus, I have demonstrated that PRP4K is novel estrogen regulated kinase, whose expression can be inhibited by tamoxifen in ER+ breast cancer cells impacting their response to taxanes. These data raise the possibility that by treating ER+ breast cancer patients with anti-estrogen therapies such as tamoxifen, we may inadvertently alter the response of their cancers to taxane therapy.