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How miRs and mRNA deadenylases could post-transcriptionally regulate expression of tumor-promoting protein PLD

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ABSTRACT

Phospholipase D (PLD) plays a key role in both cell membrane lipid reorganization and architecture, as well as a cell signaling protein *via* the product of its enzymatic reaction, phosphatidic acid (PA). PLD is involved in promoting breast cancer cell growth, proliferation, and metastasis and both gene and protein expression are upregulated in breast carcinoma human samples. In spite of all this, the ultimate reason as to why PLD expression is high in cancer cells *vs.* their normal counterparts remains largely unknown. Until we understand this and the associated signaling pathways, it will be difficult to establish PLD as a *bona fide* target to explore new potential cancer therapeutic approaches. Recently, our lab has identified several molecular mechanisms by which PLD expression is high in breast cancer cells and they all involve post-transcriptional control of its mRNA. First, PA, a mitogen, functions as a protein and mRNA stabilizer that counteracts natural decay and degradation. Second, there is a repertoire of microRNAs (miRs) that keep PLD mRNA translation at low levels in normal cells, but their effects change with starvation and during endothelial-to-mesenchymal transition (EMT) in cancer cells. Third, there is a novel way of post-transcriptional regulation of PLD involving 3′-exonucleases, specifically the deadenylase, Poly(A)-specific Ribonuclease (PARN), which tags mRNA for mRNA for degradation. This would enable PLD accumulation and ultimately breast cancer cell growth. We review in depth the emerging field of post-transcriptional regulation of PLD, which is only recently beginning to be understood. Since, surprisingly, so little is known about post-transcriptional regulation of PLD and related phospholipases (PLC or PLA), this new knowledge could help our understanding of how post-transcriptional deregulation of a lipid enzyme expression impacts tumor growth.

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1. Introduction: post-transcriptional regulation of messenger RNA

There are many regulatory points of control in the pathway from DNA to protein that affect when and how a gene is expressed. Transcriptional control is the predominant form of regulation for most genes (Alberts, 2002). However, after RNA polymerase has bound to the gene's promoter and RNA synthesis has started, post-transcriptional regulation can still control the amount of gene that is ultimately expressed and for many genes, post-transcriptional control is essential. Post-transcriptional control of gene expression is important for cellular functions across biological contexts. It comprises a complex regulatory network that contributes to cell-type and organism specific gene expression patterns. Additionally, there is a large involvement of post-transcriptional dysfunction present in numerous genetic disorders and cancer.

When a eukaryotic gene is transcribed in the nucleus, the primary transcript (newly made RNA molecule) is called a pre-mRNA. This pre-mRNA has to go through some modifications to become a mature mRNA molecule that can leave the nucleus and be translated. Those modifications include capping, splicing, addition of poly(A) tail, RNA editing, nuclear degradation (exosome), sequence-specific nuclear export mRNA, all of which occur in the cell nucleus. More post-transcriptional control mechanisms occur in the cytoplasm, such as stability and lifetime in the cytosol and small regulatory RNAs, specifically microRNA (miRs), that can be considered translation regulators. 3′-mRNA deadenylases can operate both in the nucleus and in the cytoplasm (Fig. 1).

Microarray analysis has indicated that close to 50% of the changes in inducible gene expression occur at the level of mRNA stability (Weng et al., 2005) highlighting the exquisite level of post-transcriptional regulation. All of these post-transcriptional regulations that occur in both the nucleus and the cytoplasm determine the level of gene expression and how much of the transcripts are ultimately translated into proteins (Garneau et al., 2007). For the purpose of this review we will concentrate on the mRNA stability and miR post-transcriptional events. As we will see later in detail, mRNA regulatory elements that play a critical role in identifying specific transcripts for post-transcriptional regulation typically reside within the 3′ untranslated region (3′UTR) of the mRNA.

2. PLD as an example to apply new post-transcriptional control mechanisms

Extensive studies exist on the enzymatic regulation of phospholipid phospholipases A, C and D. However, little is known about their transcriptional and especially post-transcriptional regulation. This is surprising considering the central role these phospholipases play in lipid metabolism and cell signaling. The discrete number of articles found in the scientific literature, some of which are cited below, offer a glimpse of how valuable post-transcriptional control could be for lipid enzyme signaling. For example, regarding PLA2, insulin-like growth factor-I (IGF-I) destabilizes mRNA of the type II sPLA2. Conversely, IL-1beta stimulates the transcription rate and gives rise to a very stable mRNA (Jacques et al., 1997). PLA, regulation of lipolytic activities by PLA2 depends on the transcriptional regulators LetA/S and RpoS, inducing the expression of virulence traits, and on post-transcriptional activators like the zinc metalloprotease ProA (Banerji et al., 2008). Inhibition of endogenous miR-338 with anti-miR-338 increased the mRNA and protein expression of PLA2G4B in decidual cells with a proposed role in human pregnancy and parturition (Montenegro et al., 2009).

Downstream phospholipid catabolism by PLA2 produces arachidonic acid that can be used in prostaglandin synthesis by PGEs. A group of selected miRs regulate mRNA expression M-type phospholipase A2 receptor (PLA2R1) in normal human mammary epithelial cells and cancer cell lines (Menschikowski et al., 2015). There are several RNA sequence elements within the 3′UTRs of the genes involved in the PGE(2) pathway, that are predicted to be binding sites for miRNAs and RNA-binding proteins, both of which appear to be central regulators of PGE(2) synthesis and function (Moore et al., 2011). Regarding another phospholipase, PLC, a particular group of miRs (miR-200b, miR-200c, and miR-429) target PLC (PLCG1) during