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In silico analysis of COSMIC retrieved P body gene mutations in breast cancer

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ABSTRACT

P bodies (Processing bodies) are mRNP granules and are involved in mRNA decay, gene silencing by miRNA or siRNA, deadenylation and decapping. These are dynamic and shuttle their components with stress granules, ribosomes and stalled mRNAs within them can assemble to polysomes. Research suggests that several components of stress granules and P bodies contribute to carcinogenesis. In corroboration, COSMIC (catalogue of somatic mutations in cancer) database documents somatic mutations of P body genes. In our study, we have retrieved the somatic mutations from COSMIC for critical P body genes such as *DCP1B*, *EIF4E*, *XRN1*, *MOV10*, *CNOT6*, *HTT* and *GEMIN5* and examined for their deleteriousness using various online tools such as PolyPhen, MutationTaster and STRUM. A total of 5, 2, 17, 11, 8, 22 and 15 breast cancer mutations were retrieved for *DCP1B*, *EIF4E*, *XRN1*, *MOV10*, *CNOT6*, *HTT* and *GEMIN5* respectively. Of these, our analysis has identified 18 mutations (*DCP1B*-1, *EIF4E*-1, *MOV10*-1, *GEMIN5*-2, *CNOT6*-2, *HTT*-9 and *XRN1*-2) to be deleterious. Also, our 3D molecular dynamic studies suggest that HTT and EIF4E mutations induce perturbations in the mutant proteins. P body dynamics are marked by interactions between P body proteins and other cellular components and our results give insights to examine the P body dynamics on such mutation landscapes.

Processing bodies (PBs) are 100–300 nm mRNP granules that control the gene expression by mRNA regulation. They were first described as XRN1 (5′-3′ exoribonuclease) granules in murine fibroblast cells (Anderson et al., 2015). P bodies were primarily associated with degradation of deadenylated mRNAs through *XRN1* pathway. However, recent research studies have revealed other functions of P bodies. In addition to RNA decaying, P bodies act as transient reservoirs for mRNAs before their transport to polysomes (Brengues et al., 2005). It has been reported that the protein components of P bodies are involved in various mRNA metabolisms such as ARE (AU-rich elements) mediated mRNA degradation, nonsense-mediated decay, gene silencing by miRNA or siRNA, negative regulation of miRNA pathway, binding to telomere or telomerase, transcription, splicing, mRNA trafficking, mRNA stabilization, translation inhibition or activation, deadenylation, decapping, 5′-to-3′ exonuclease activity, helicase activity, endonuclease activity, ubiquitin ligase activity, cap-binding activity and response to viruses (Zheng et al., 2011). There are several other cellular granules such as PML (promyelocytic leukaemia) bodies, Cajal bodies, paraspeckles and stress granules (SGs). Stress leads to phase separation which results in the formation of stress granules and stress-induced processing bodies and the stresses include heat shock, oxidation stress, UV radiation, osmotic stress and nutrient starvation (Guzikowski et al., 2019). PBs and SGs possess no membranes and they interact with each other exchanging their components (Guzikowski et al., 2019).

P bodies are not merely sites of mRNA storage or degradation but they can modulate cellular signaling pathways, metabolic machinery and thus can have implications on pathogenesis of cancer (Anderson et al., 2015). More than 60 proteins are identified as components of P bodies (Zheng et al., 2011). Several of these proteins have been identified to have roles in cancer. For example, cytoplasmic polyadenylation element-binding protein 1(*CPEB1*) is characterized as a tumor suppressor and it is downregulated in breast and colorectal cancer cell lines, and promoter methylated in diffuse gastric cancer (Fernández-Miranda and Méndez, 2012). *XRN1* (*5′-3′ exoribonuclease*) is characterized to be a tumor suppressor in osteogenic sarcoma (Venkatesh and Suresh, 2013). GEMIN5 (*gem* [nuclear organelle] associated protein 5) overexpression reduces the cell motility in a breast cancer cell line (Lee et al., 2008). RNASET2 (ribonuclease T2) suppresses ovarian tumor suppression by recruiting M1 subtype of macrophages in the tumor microenvironment (Acquatia et al., 2013). Stress granule-associated protein G3BP2 (G3BP stress granule assembly factor 2) regulates breast tumor initiation (Gupta et al., 2017). Several deleterious SNPs (Single nucleotide polymorphisms) have been documented in the

Abbreviation: P bodies, Processing bodies; COSMIC, catalogue of somatic mutations in cancer..

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