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RNA post-transcriptional modifications in Prostate Cancer

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Epigenetic modifications are well known to induce changes in gene expression regulation that are not heritable. In the past decade, great effort has been made in characterizing and understanding epigenetic changes that occur during disease states like cancer. However, the epigenetic landscape has grown increasingly complicated, encompassing DNA methylation, the histone code and nucleosome positioning. DNA cytosine-5 methylation is one of the most studied epigenetic mark and its function is quite well established. RNA can be also post-transcriptionally modified. More than 100 modifications have been found and they can occur in transfer RNA, ribosomal RNA, messenger RNA or other non-coding RNAs. Post-transcriptional modifications in RNA are known for more than four decades but their function remains unknown.

Recent findings have shown that methylation of tRNA at cytosine-5 (m5C) can modulate protein translation and also regulate stress responses in cancer stem cells. Lack of m5C in tRNA leads to tumour growth. In this work, we will focus our attention in transfer RNA (tRNA) modifications and particularly in 7-methylguanosine (m7G). In yeast, this modification is carried out by Trm8p/Trm82p protein complex, yeast orthologues of human METTL1 and WDR4. m7G modification of tRNA occurs widely in eukaryotes and bacteria, it is nearly always found at position 46, and is one of the few modifications that confers a positive charge to the base. This methylation is predicted to confer more stability to the RNA against degradation, and loss of tRNA m7G in yeast reduces cell growth. Thus we hypothesize that m7G in tRNA may confer cell growth advantages to cancer cells.

Computational analyses of human cancer genomic datasets (TCGA, cBioportal) revealed that both METTL1 and WDR4 are upregulated in primary prostate cancer and its increased expression correlated with metastasis. The upregulation of METTL1 and WDR4 by qPCR and western blot analysis of primary prostate tumours from a cohort of 14 patients corroborated our findings. Interestingly, our results point at a potential regulation of METTL1 and WDR4 in prostate cancer downstream PI3 kinase pathway activation. In prostate cancer cell lines, we further observed that METTL1 and WDR4 expression was elevated in cells with high self-renewal capacity (a feature of cancer-initiating cells). In line with this notion, preliminary evidence suggests that METLL1 silencing decreases both anchorage-dependent and -independent growth

PI3 kinase pathway is activated in a large fraction of prostate tumours, driving cell growth, proliferation and protein translation. Thus, we conclude that regulation of m^7G tRNA methylase expression in prostate cancer by this pathway could contribute to its oncogenic activity. In the future, we want to ascertain the contribution of m^7G to self-renewal and cancer-initiating cell capacity in cancer, and to elucidate the mechanism by which PI3 kinase signalling could regulate these methylases.