Alterations in Nucleolar Structure and Gene Expression Programs in Prostatic Neoplasia are Driven by the MYC Oncogene

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Increased nucleolar size and number are hallmark features of many cancers. In prostate cancer, nucleolar enlargement is one of the earliest morphological changes associated with development of pre-malignant prostate intraepithelial neoplasia (PIN) lesions and invasive adenocarcinomas. However, the molecular mechanisms that induce nucleolar enlargement in PIN and prostate cancer remain largely unknown. We show that activation of the MYC oncogene, which is over expressed in most human PIN and adenocarcinomas, leads to formation of enlarged nucleoli and increased nucleolar number in prostate luminal epithelial cells in vivo. In prostate cancer cells in vitro, MYC expression is needed for maintenance of nucleolar number, and a nucleolar program of gene expression. To begin to decipher the functional relevance of this transcriptional program in prostate cancer, we examined FBL (encoding fibrillarin), a MYC-target gene, and report that fibrillarin is required for proliferation, clonogenic survival, and proper rRNA accumulation/processing in human prostate cancer cells. Further, fibrillarin is over expressed in PIN lesions induced by MYC overexpression in the mouse prostate, and in human clinical prostate adenocarcinoma and PIN lesions, where its expression correlates with MYC levels. These studies demonstrate that the activation of the MYC oncogene drives nucleolar hypertrophy and a nucleolar program of gene expression in prostate epithelial cells, thus providing a molecular mechanism responsible for nucleolar enlargement in prostatic neoplasia.