

Targeting histone H3K36me3-deficient cancers: lessons from yeast

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SETD2 is a tumour suppressor, which is frequently mutated in a range of different cancer types. SETD2-dependent tri-methylation of histone H3K36 performs a number of cellular functions and has been recently shown to play a key role in maintaining genome stability through facilitating checkpoint activation and DNA double-strand break (DSB) repair. Here we define a role for Set2-dependent H3K36me in promoting efficient DNA replication in fission yeast. Loss of Set2 results in inefficient dNTP synthesis and DNA replication. Moreover, loss of Set2 was synthetic lethal following Wee1 inactivation, resulting in replication arrest and subsequent mitotic catastrophe. Wee1 inactivation resulted in increased usage of inefficient DNA replication origin firing and DNA damage accumulation, which in a *set2Δ* background resulted in critically reduced dNTP levels, replication fork collapse, Mus81-dependent DNA damage and cell death. Accordingly, deletion of gene encoding the RNR inhibitor Spd1 suppressed this synthetic lethality. Together, these findings identify a key role for Set2 in facilitating DNA replication and viability in response to CDK1-induced replication stress. These findings are being exploited to target SETD2-deficient cancer cells.