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Interplay between the MYC oncoprotein, cyclin-dependent kinases and E3 ubiquitin ligases

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ABSTRACT

Mammalian cells grow, divide, and die in a precise and orderly fashion. For cells to grow and maintain their integrity they need to communicate at both intracellular and extracellular level. This communicative circuit is maintained by means of many different factors functioning at different level to for example receive, transmit and respond to the delivered message. Among these factors are transcription factors whose function is to regulate expression of genes downstream of transmitted signals. Myc is a transcription factor that is estimated to regulate 10%-15% of the genes in the genome and that plays an essential role in various cellular processes required for cell growth, cell division and survival. Often communication between the factors involved in signaling involves addition of small molecule moieties such as phosphate, acetyl, ubiquitin or methyl groups that is exerted through the function of enzymes like kinases, histone acetyltransferases, E3 ubiquitin ligases or histone methyltransferases.

E3 ubiquitin ligases tag their substrates by mono or polyubiquitin chain molecules that will dictate the fate of the targeted protein. Ubiquitylated proteins are usually degraded by a cellular degradation machinery called the proteasome. However, depending how ubiquitin chain is formed it can serve other roles than for protein degradation, for instance in transcription.

The work presented in this thesis provides insights into underlying the role of a kinase, Cdk2 as well as two E3 ubiquitin ligases, SCF^{FBXO28} and VHL in the regulating the function of Myc transcription factor/proto-oncoprotein.

Deregulated function of Myc plays an important role in the development of many different cancer types. Despite extensive studies on the function of Myc the mechanism underlying its deregulation is still elusive. Another oncoprotein whose deregulation is involved in development of different cancers is Ras. Myc and Ras are known to cooperate in cellular transformation but the mechanism underlying their cooperation is unclear. In paper I we provided a mechanism by which these two oncogene work together in tumor development. We show that Cdk2 kinase phosphorylates Myc at Ser-62 and that this phosphorylation is important for Myc-mediated regulation of genes involved in cellular senescence. We show that Myc in this way suppresses Ras-induced senescence, which is one of the barriers for tumor development. This unique role of Cdk2 provides a potential therapeutical advantage to combat Myc and /or Ras-driven tumors.

In paper II we identify a new E3 ubiquitin ligase, SCF^{FBXO28} that was found to target Myc for ubiquitylation and to play a critical role in regulation of Myc function in tumor progression. Our data further suggest that SCF^{FBXO28} plays an important role in transmitting Cdk activity to Myc function during the cell cycle, emphasizing the Cdk-FBXO28-Myc axis as a potential molecular drug target in Myc-driven cancers.

In paper III we show that Myc interacts with the tumor suppressor protein von Hippel Lindau (VHL) which is part of an E3 ubiquitin ligase complex. VHL was found to promote ubiquitylation of Myc in a non-proteolytic fashion. We showed that VHL associates together with Myc at a subset of Myc target genes throughout the genome and activate or repress the expression of bound genes with functions in cancer development, gene expression, metabolism and other function. We also found that VHL and Myc bind to the MYC locus and regulate the *MYC* gene expression. Our data reveal novel functions and new modes of regulation of two of the most important oncoproteins and tumor suppressor proteins in human cancer, c-Myc and VHL, respectively. We anticipate that this work will have preclinical and potential clinical implications for cancer biology and treatment.

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