

Two modifications, one protein: The multiple roles the histone acetyltransferase, pCAF, plays in post translational modifications.

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Immune responses can be broken down into two major categories: innate responses, which are non-specific and adaptive responses, which adapt to best deal with individual pathogens. The specificity of adaptive immunity stems from the ability of adaptive immune cells to recognize molecular differences between pathogens. One protein involved in this process is called Major Histocompatibility complex class II (MHC II). MHC II is expressed on immune cells termed antigen presenting cells (APCs) where MHC II molecules present pathogen derived peptides to immune cells termed thymocytes, or T cells. T cells use their own cell surface receptors to recognize the pathogen derived peptides presented by MHC II in order to initiate adaptive immune responses to the invading pathogen. To regulate adaptive immunity, MHC II gene expression is tightly controlled at the level of gene expression by a master regulator, the Class II Transactivator (CIITA). CIITA is in turn regulated by a series of post-translational modifications (PTMs) which control CIITA activity. CIITA is modified by multiple PTMs including ubiquitination, phosphorylation, and acetylation. Previous data from our lab indicates the importance of ubiquitination to CIITA's transactivity, and therefore to the regulation of MHC II expression. Monoubiquitination of CIITA increases CIITA transactivity resulting in increased cell surface expression of MHC II. CIITA is further modified by acetylation on Lysine (K) 141 and 144. This acetylation is mediated by the Histone Acetyl Transferase (HAT), p300/CBP Associated Factor or pCAF. Recent data from our lab suggests pCAF can also act as an ubiquitin E3 ligase, thus indicating a bi-functional role for pCAF in regulating CIITA activity and MHC II expression. Our preliminary data suggests CIITA ubiquitination levels and transactivity increase in the presence of over expressed pCAF. To better understand the differentiation of pCAF's HAT and ligase roles in CIITA regulation; we used acetylation mutants of CIITA to show pCAF's interaction with CIITA is not dependent on pCAF's HAT activity. Future work will focus on determining the type of ubiquitin linkages pCAF facilitates to CIITA and elucidate the roles pCAF plays in regulating the web of post-translational crosstalk that regulates CIITA and in turn drives adaptive immune responses.