

**P038** Cross-talks between ubiquitylation and acetylation in the regulation of p53

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The tumor suppressor p53 plays major roles in response to DNA damage. Its activation involves numerous post-translational modifications, and can lead to cell-cycle arrest, apoptosis or senescence, depending on the damage and the cell context. Among p53 post-translational “modifiers” are multiple ubiquitylation E3s, including Hdm2 that is a central regulator of its stability. We found that the protein PCAF possesses in addition to its well-established acetyltransferase activity an ubiquitylation activity that directly mediates Hdm2 ubiquitylation and degradation, and thus also indirectly controls p53 stability. Interestingly, PCAF activates the pro-apoptotic functions of p53, via acetylation of lysine 320 of p53. Strikingly, we found in our investigations that this lysine is also the target for ubiquitylation by E4F1, a new Ub-ligase. This latter modification favors the cell-cycle arrest functions of p53, at the expenses of its pro-apoptotic functions, by both direct competition with PCAF-dependent acetylation and promotion of the recruitment of p53 at promoters of specific target genes. Altogether, these results shed new light on how the complex functions of p53 can be finely tuned by intricate and coordinated modifications of lysine residues.