

SUMO in cancer

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Modifications of the proteins play key roles in controlling protein activity and hence cell function. This is mainly due to their ability to rapidly and reversibly change the behavior of the modified protein. These modifications regulate the localization of their substrates in the cell, their interactions with partner molecules such as proteins or DNA, their biological/enzymatic activity as well as their stability. Modification by ubiquitin is unusual in that the modifier itself is a small protein. A number of ubiquitin-like modifications have been described and, among these, modification by SUMO (Small Ubiquitin-like Modifier) is one of the most extensively studied.

Unlike ubiquitination, modification by SUMO (sumoylation) does not generally tag proteins for proteasomal degradation but rather alters their function and/or localization. While the list of known substrates does not cease to grow, more than a hundred are now known, only for a limited number the biochemical consequence of modification has been studied in detail. Most of the major SUMO substrates are located in the cell nucleus, they include transcription factors or co-factors, chromatin-associated proteins including histones and chromatin modifying enzymes, as well as proteins involved in DNA repair, recombination or chromosome structure. A simple, unifying function of sumoylation has remained elusive. If, in some cases, sumoylation was shown to regulate the substrate's protein function as in the case of most transcription factors, its enzymatic activity, its localization and/or its stability, the functions of this modification remains in large part obscure for the majority of these. Some recent work linked SUMO-interaction with ubiquitin conjugation. In certain situations, the modification of specific proteins by SUMO triggers their ubiquitination which in turn leads to their degradation. Thus in some cases, sumoylation can be seen as a degradation signal. The variety and severity of the phenotypes observed in various organisms upon inactivation of one or another component of the SUMO modification pathway confirms that sumoylation, which is conserved from plants to humans, is intimately tied to the basic activities and challenges faced by eukaryotic cells. In this context, we have shown that inactivation of a specific enzyme of the SUMO pathway (the E2 enzyme Ubc9) in mice leads to early embryonic lethality associated with major defects in the cell nucleus.

Sumoylation is a highly dynamic process and the steady-state level of SUMO-conjugated proteins is maintained by a fine equilibrium between conjugating (E1, E2, E3) and de-conjugating (SENPs) activities. It is therefore likely that perturbation of this equilibrium will manifest itself in disease processes. Notably, the SUMO pathway is expected to play important roles in oncogenic transformation in that a number of oncoproteins or tumor suppressors have been shown to be SUMO-modified and thus regulated in their activity. Also numerous proteins involved in the maintenance of proper chromosome structure and function as well as chromatin-associated proteins figure among the known SUMO substrates. Moreover, we could show recently that the SUMO E3 ligase PIASy is a major regulator of cellular senescence, one of the major anti-tumor mechanisms, and that it plays an important role in the control of telomere length. Telomeres are stretches of DNA which protect the ends of the chromosomes. Each time a cell divide, the telomeres become shorter. Cells normally can divide only about 50 to 70 times, after that the cells become senescent or die. In cancer cells, an enzyme called telomerase becomes activated and prevents the telomeres from getting shorter. The cancer cell can thus replicate indefinitely. Another major SUMO target is PML, a protein involved in acute promyelocytic leukemia (APL) as a fusion with the retinoic acid receptor α (RAR α). It has been shown that sumoylation of the PML-RAR α oncoprotein is required for the acquisition of the leukemogenic phenotype.

The main objective of the work developed in the lab is to better understand the mechanisms and functions of the SUMO pathway in both normal and pathologic cell/organism contexts. To this end, distinct but complementary approaches are taken: a 'structural' approach seeks to identify novel actors in this pathway, whereas more 'mechanistic' approaches center on the role of sumoylation *in vivo* mainly focusing on oncogenic processes. By performing this work, we expect to advance our knowledge on the basics of sumoylation biology and to reveal SUMO-related mechanisms involved in the development of human cancer which should provide new targets for therapeutic intervention. As for anti-tumor strategies developed based in the context of the ubiquitin system, therapeutic applications seeking to modulate the sumoylation of certain substrates in cancer become feasible objectives. The use of peptide inhibitors, analogous to those used in the proteasome inhibition, of RNAi or of anti-sense oligonucleotides capable of interfering with sumoylation is under development. In parallel, studies aimed at modulating the activity of SUMO E3 ligases or desumoylases are currently underway. The fact that these enzymes are numerous and impart specificity to the modification reaction makes them potentially ideal therapeutic targets.