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SUMOylation: A link to future therapeutics

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Abstract

SUMOylation, much of a similar process like ubiquitination catches attention across various research groups as a potential therapeutic target to fight various infectious and cancerous diseases. This idea take its strength from recent reports which unearth the molecular mechanisms of SUMOylation and its involvement in important diseases distributed across various kingdoms. At the beginning SUMOylation was considered a process affected only by viral diseases but subsequent reports enlighten its role in diseases caused by bacteria as well. This enhances the SUMOylation canvas and demanded more in-depth study of the process. The present review is an attempt to study the regulatory mechanism of genes when the natural SUMOylation pathway is disturbed, the cross-talk among SUMOylation and other post translational modifications, the role of miRNAs in controlling the function of transcripts, loading of RNA species into exosomes and the possible SUMOylation related therapeutic targets.

Introduction

The innate immune responses across kingdoms are tightly regulated to fight attacking pathogens. Post translational modification of proteins like acetylation, methylation, ubiquitination and SUMOylation have predominant role in activation/deactivation of immune responses by regulating various cellular processes including transcription, DNA repair, proliferation and apoptosis as these have the potential to relocate the protein to different organelles and modify its biological function. The deep understanding of those post translational mechanisms could provide insights in controlling several disease conditions and develop therapeutics based on those post translational modification markers.

The small ubiquitin like modifiers (SUMO) proteins discovered in 1997 (Mahajan et al., 1997) has since been recognized as family of important modification proteins unlike ubiquitination which is involved in degradation of proteins, instead it modulates the function of target proteins. The covalent conjugation of SUMO molecules to

protein residue lysine on a typical consensus sequence ψ K χ D/E (where ψ is large hydrophobic residue, K is the target lysine, D/E is acidic residue and χ represent any amino acid) (Rodriguez et al., 2001; Sampson et al., 2001). The process of SUMOylation is carried out by a cascade of three enzymes (E1, E2 and E3). E1 is a SUMO activating enzyme SAE1, while E2 is conjugating enzyme e.g. Ubc9 and E3 is SUMO ligase. The SUMOylation reaction is reversed by SENPs termed as deSUMOylation having distinct regulatory roles. Till date four SUMO molecules have been reported in mammals viz., SUMO1, SUMO2, SUMO3 and SUMO4. The sequence similarity of SUMO2 and SUMO3 are almost 97% hence are often reported collectively as SUMO2/3. Various kinds of stimuli like oxidative stress often increase the rate of SUMOylation. A recent report shows the exposure to cigarette smoke alters the microRNA expression by SUMOylation of DICER (Gross et al., 2014). Viruses and chemical toxins also causes an increase in SUMOylation, a well known example is of proteins like p53. The role of SUMOylation in various disease pathways and its consequence is depicted in Figure 1.

Most of the biological fluids if not all have special vesicles called exosomes which serves as a mode of communication between cells, become an active area of research for immune related responses. These have the specific repertoires of mRNA, miRNA and other non coding RNA. All these RNA species can be transferred functionally to recipient cells. A recent report indicated the mechanism by which miRNA is localized into exosomes by recognizing its specific motif and loaded through a protein heterogeneous nuclear ribonucleoprotein A2B1 (hnRNP A2B1) (Richard et al., 2013). Interestingly hnRNP A2B1 binding to miRNA is controlled by SUMOylation. This finding suggests that loading of miRNA in exosomes can be altered by identification of specific motifs or changes in expression levels of hnRNP A2B1 hence making exosomes important in drugs discovery. The discovery of PML/SUMO pathway that hinder viral replication by SUMO conjugation and might be increasing the number of SUMO targets, indicates a possible role in senescence or stem cell self renewal. (Sahin et al., 2014). Ubiquitination maintains the balance in cyclin-dependent kinase (CDK) activity by degradation of cyclins to maintain proper cell cycle progression. The glioblastoma, a deadly brain cancer have been linked to SUMOylation of CDK6 by SUMO1 which stabilizes the protein that in turn leads the cell cycle towards cancer progression (Bellail et al., 2014). The patients of another important cancerous disease the granulosa cell tumors reported to have mutation in FOXL2 at C134W. This mutation is recently linked to sequential post translational modifications where it undergo hyperphosphorylation at serine 33 by GSK3 β which causes

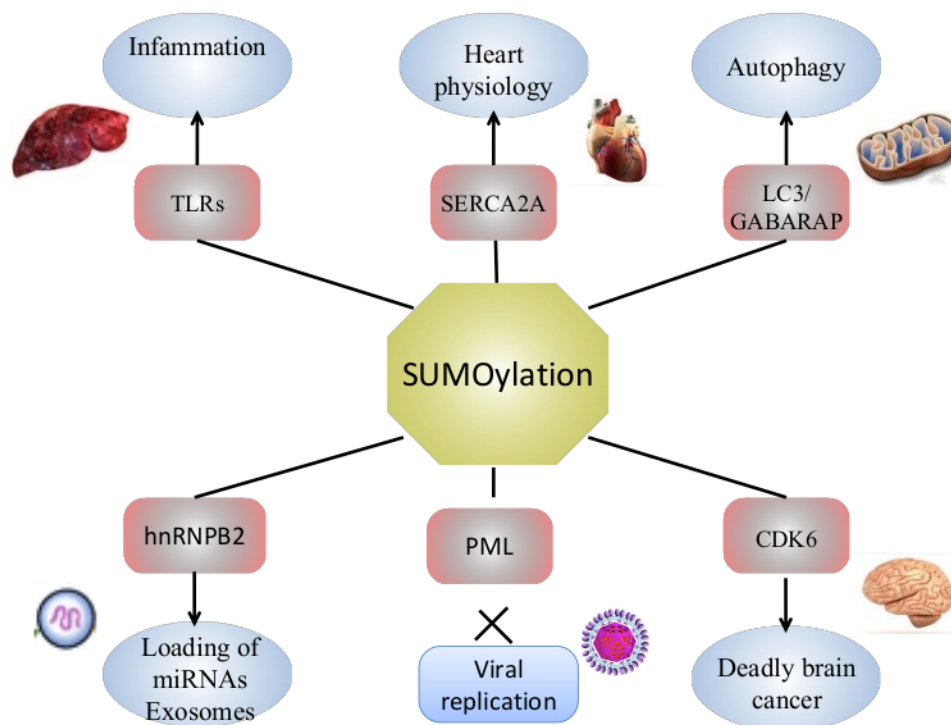


Figure 1. SUMOylation have important roles in different disease consequences.

MDM2 related ubiquitination results in proteasomal degradation (Kim et al., 2014). The FOXL2 in normal patients however is phosphorylated hence allows its SUMOylation leading to stabilized protein.

These recent developments on regulatory role of post translational modifications especially SUMOylation and their cross-talks further open a window to develop epigenetic drugs that may have an answer to many of the untreated infectious and cancerous diseases. In present attempt, we also have summarized the recent advances regarding SUMOylation that might be useful in drug development.

SUMOylation and Inflammatory Pathway

The families of receptors including Toll Like Receptors, NLR and RIG receptors initiates NF- κ B against attacking pathogens by recognizing the pathogen associated molecular patterns (PAMPS) and danger associated molecular patterns (DAMPs). In mammals an operative immune response is achieved by the functional activation of key inflammatory responses like the production of cytokines characterized by proliferation, differentiation and recruitment of blood cells to site of injury which plays a critical role in immune responses. The TLRs are broadly differentiated into two groups based on its location. Several

TLRs including (TLR1, TLR2, TLR4, TLR6 and TLR10) are located on membrane while (TLR3, TLR7, TLR8 and TLR9) are located in endosomes (Zohaib et al., 2015). Innate immunity is bestowed by highly conserved toll signalling pathway which is regulated by several factors, one among them is β -arrestin Kurtz (Krz) which is reported as inhibitor of toll signalling in embryo of *Drosophila* (Tipping et al., 2010). It is recently proven experimentally that a conserved sequence of Krz interacts with SUMO protease Ulp1 and affects SUMOylation. The loss of Krz or Ulp1 causes same kind of inflammatory phenotypes. Furthermore a mutation in Krz and Ulp1 causes similar dose dependent synergistic effects providing grounds for the two proteins involvement in same pathway. The altered levels of Krz can affect the deconjugation ability of Ulp1 so is involved in controlling systemic inflammation and toll signalling at SUMOylation level (Anjum et al., 2013). As the interaction between β -arrestin and SENP1 is conserved it can be suspected that the control mechanism might be similar in other organisms. This will be of interest to see whether mammalian β -arrestins have role in Toll/NF κ B signalling regulation (Anjum et al., 2013).

NF κ B activation is controlled by various post translational mechanisms including phosphorylation, acetylation and ubiquitination. A transcription factor p65 also known as

RelA, is involved in NFkB heterodimer formation, nuclear translocation and activation. A recent report of the negative regulation of PIAS3 mediated SUMOylation of RelA subunit of NFkB is surfaced unearthing the biochemical mechanism of transcriptional suppression (Liu et al., 2012). Subsequently SUMO2/3 contribution in Ikbα (the inhibitor of NFkB) [5] reported (Aillet et al., 2012). Another interesting finding a SUMO specific protease SENP6 as attenuator of TLR inflammatory pathway is reported in which the scientists have shown that deficiency of SENP6 trigger proinflammatory genes induced by NFkB. The SUMO2/3 is conjugated on Lys 267 of NEMO (a SUMO modified protein substrate) thus stops deubiquitinase CYLD to bind with NEMO which is reversed by SENP6 by de-SUMOylating the NEMO explaining the essential role of SENP family in TLR signalling and inflammation (Liu et al., 2013).

TLRs initiate inflammatory responses by sensing pathogen associated molecular patterns (PAMPs) and through production of tissue damage (Medzhitov and Hong 2009). The transcriptional activation of many TLR-responsive genes initially requires a de-repression step in which the nuclear receptor co receptor (NCoR) is removed from the promoters of target genes to relieve basal repression (Ogawa et al., 2004). The liver X receptors (LXRs) ligand dependent SUMOylation has found to be responsible for suppression of TLR4 induced transcription through blocking the NCoR clearance step (Venteclef et al., 2010). Recently a mechanism underlying the blocking of NCoR clearance is found in which coronin 2A (CORO2A) of NCoR complex of previously unknown function, mediates the NCoR turnover induced by TLR by interacting with oligomeric nuclear actin. SUMOylated LXRs blocks NCoR turnover by binding to SUMO2/3 binding motif in CORO2A and prevent actin recruitment (Huang et al., 2011). The finding of Huan et al., (2011) discover a CORO2A actin dependent mechanism for the de-repression of inflammatory response genes that are differentially regulated by phosphorylation and by nuclear receptor signalling pathways that control immunity and homeostasis. The discovery of TLRs remains an interest to immunologists and the interaction of SUMOylation makes it more complicated yet another feasible avenue for epigenetic drug targets.

The past several years have accumulated promising evidence for SUMOylation to be integral part of innate immune system by regulating type I IFNs to a number of viral infections. The receptors that recognizes viral nucleic acids such as TLRs and RLRs triggers the signalling pathways to produce IFNs and stimulate gene expression controlling these pathways (Everett et al., 2013). The SUMOylation of two prominent cytosolic RLRs, retinoic acid inducible gene I (RIG-I) and MDA5 enhances their ability to activate the IFNβ promoter (Fu et al., 2011; Mi et al., 2010). The cross talk of ubiquitination and SUMOylation is very important in producing functional immune responses and must be tightly controlled. There are several reports which shows the close connection of ubiquitination and SUMOylation to produce type I IFN response which interacts with mitochondrial anti viral proteins (MAVS). The ubiquitination of Lys63 initiates type I IFN response and SUMOylation of RIG-I promotes its ubiquitination (Mi et al.,

2010). There is no doubt that some viruses could have evolved mechanisms to use those pathways for their benefits. One of the example is a deadly Ebola virus that has caused intense fears across the globe for having potential to cause a deadly pandemic. Furthermore, it impairs dendritic cells (DCs) and the important protein VP35 which inhibits IFN production by multiple mechanisms including inhibition of RIG-I pathway or IKKε and TBK1, that activates the transcription factor IRF3 and IRF7 hence subsequently activates transcription of IRF7. The blocking of interferon production could be an important therapeutic target in case of Ebola and SUMOylation inhibitors of IRF7 could be of interest to pharmacists treating Ebola.

A diagram depicting how SUMOylation could be used as therapeutics target in inflammatory disease condition is shown in Figure 2.

SUMOylation and miRNAs: A combined therapeutic target

miRNAs remain a target of interest to pharmaceutical companies as key players in modulating gene expression by interacting with mRNAs post-translationally. The involvement of miRNAs in important diseases of heart and brain, the signalling pathways controlling chemokines and cytokines production, its interaction with expression of important genes and ubiquitous presence makes it important targets of therapeutics. There are more than 1000 miRNAs reported and classified in mammals till date (Schiano et al., 2015). Several disease conditions are been implicated to different miRNAs. The role of miRNAs in various signalling pathways including TLRs signalling and RLRs signalling and its participation in NLRs immune response mediation has thoroughly reviewed by Zhou et al., (2014). Recently many miRNAs are reported to have important roles in cardiovascular diseases. miR-33 an intronic miRNA is first reported with transcription regulator of sterol regulator binding gene SRBP2 involved in cholesterol metabolism (Rayner et al., 2010). Moreover, several other miRNAs including miR-92a (Loyer et al., 2014), miR-146a/b (Takahashi et al., 2010), miR-195 (Latanico et al., 2009), have been reported to have important regulatory roles in cardiovascular diseases. There are several miRNAs reported to have association with myocardial infarction (MI) like miR-126 associated with diabetes (Zampetaki et al., 2010), hyperlipidemia (Sun et al., 2010) and age (Fukushima et al., 2011) the high levels of presence makes the patients with 2.7 fold higher risks of MI. On the other hand lower levels of miR-223 associated with diabetes (Zampetaki et al., 2010) is reported with high risks of MI. These studies makes miRNAs important candidates for diagnostic and prognostic biomarkers.

The repertoires of mRNA, miRNA and other non coding RNAs in body are exosomes. It is interesting to note that these exosomes [22] be transferred to recipient cells with functional RNAs. Both in-vivo and in-vitro studies supports the functional relevance of exosomes (Rocoro et al., 2013; Zhang et al., 2010). The [29]somes can potentially be used as biomarkers (D'Souza et al., 2012; Peinado et al., 2012), vaccines (Thery et al., 2002) and gene therapy (Lai et al., 2012). The mechanisms involved in loading of different

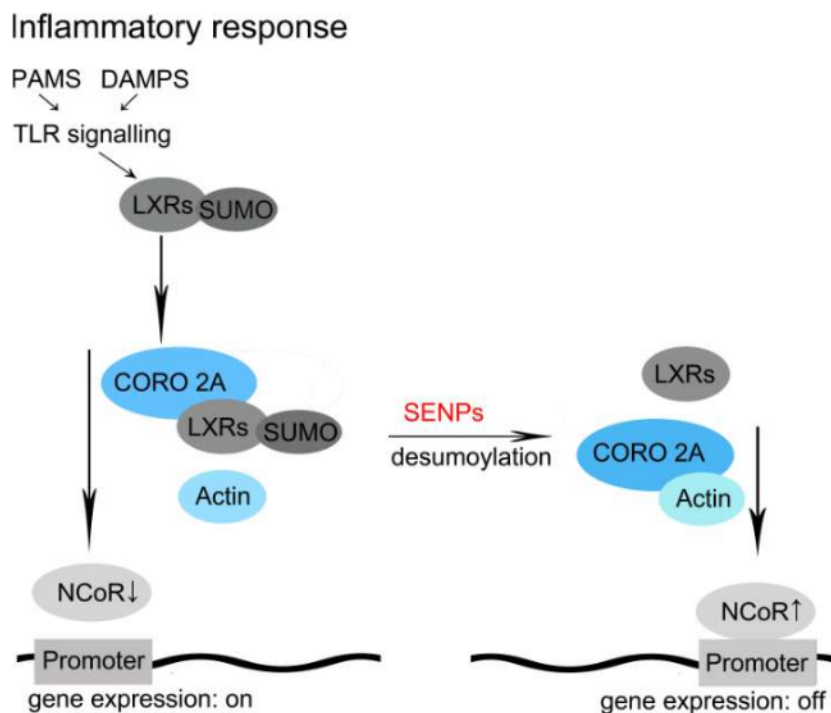


Figure 2. SUMO mediated inflammatory response that can be mediated as a therapeutic target.

miRNAs in exosomes is of high interest as these could later determine its specificity for use as therapeutics. A recent report identifies hnRNPA2B1, an RNA binding protein, as playing an important role in sorting of miRNAs in exosomes. More interestingly, hnRNPA2B1 is SUMOylated, hence indicating it as an important control in sorting of miRNAs and opening an avenue for further research on SUMOylation and miRNAs as combined therapeutic targets. Further research is required in the cross talk of SUMOylation and miRNAs.

Recently it has been shown that SERCA2a gene expression is beneficial for heart failure patients and is SUMOylated by SUMO1 (Kho, Lee et al., 2011; Oh, Lee et al., 2014), the knockdown of which is implicated to have a crucial role in heart failure. It is further shown that miR-146a is targeting the 3' UTR of SUMO1, causing its lower expression. This makes miR-146a and SERCA2a gene SUMOylation a combined target of therapies for heart failure patients (Oh, Lee et al., 2014).

The enhanced production and conjugation of SUMO1/2/3 to target proteins after interferon induction through a miRNA-based mechanism involving Lin28 and let-7 axis helps impede virus replication (Sahin, Ferhi et al., 2014). It has been demonstrated that SUMOylation improves the antiviral ability of interferon against HSV1 and HIV (Sahin, Ferhi et al., 2014). This finding hence shows the integrated interferon-responsive PML/SUMO pathway that reduces viral

replication through SUMO conjugation and increased SUMO targets. They further investigated the role of SUMO induction on the replication of B-Murine Leukemia virus, suppressing the IFN-induced viral replication to four fold that was severely hampered by SUMO1 inactivation. It can be inferred that higher SUMOylation contributes extensively to various viral infections. It can be a promising therapy based on the interaction of IFN-triggered SUMO-based proteins that can promote the clearance of undesirable proteins through proteolytic clearance.

¹² Apurinic/ apyrimidinic endonuclease 1 (APE1) is a multifunctional enzyme of base excision repair (BER) pathway capable of DNA repair and is involved in the redox activation of various transcription factors (Bhakat et al., 2009). The N-terminal carries out redox reactions and C-terminal carries out the repair functions (Barzilay et al., 1995; Xanthoudakis et al., 1994). Various post-translational mechanisms are reported to regulate the functions of APE1, including SUMOylation (Tell et al., 2009) and miRNAs affecting the expression of APE1 may cause disease conditions, making it a possible target of therapeutics. These novel interactions of SUMOylation pathway and miRNAs in complex and major diseases stress further research to translate experimental results into functional therapeutic targets.

These studies explore the role of SUMOylation and miRNAs involvement in various diseases and provides a probable target of therapeutics hence stresses researchers to more vigorously study these interactions to utilize it for efficient and appropriate therapies based on SUMOylation proteins, its targets and miRNAs interactions.

SUMOylation and anticancer drugs

Cancer is commonly defined as uncontrolled mitosis. The deregulation of several proteins like RB (Ledl et al., 2005), SENP1 (Veltman et al., 2005), PIAS3 (Wang and Banerjee 2004), PIASy (Ueda et al., 2003), SUMO1 (Villalva et al., 2002), SUMO2 (Lee 2004) etc. by SUMOylation and its involvement in cancers of different kinds provides an opportunity to exploit SUMOylation as anticancer drug target. Several strategies to date have been implied to use SUMOylation in anti cancer therapies. Recent researches in the field promises it as one of the consistent future therapeutic target.

Cancer is often treated with anthracyclines and taxanes, but it often loses its therapeutic efficacy which is linked to DNA damage. The forkhead transcription factor (FOXO1) is shown to have a critical role in resolving DNA damage response and genotoxic agents resistance. This is achieved by controlling transcription of a family of genes involved in DNA double strand damage sensing and recombining homologous repair genes. The role of FOXO1 has also been elucidated in action of taxanes (Monteiro et al., 2012; Zhang et al., 2012; Park et al., 2012). The efficacy of these genotoxic and cytotoxic drugs depends on their ability to resolve the DNA damage response and the control of cell cycle from G2 to M phase (Chien et al., 2008; Alvarez-Fernandez et al., 2010). Recently Myatt et al., (2014) reported that SUMOylation is involved in weakening of FOXO1 activity resulting in delayed mitotic activity in response to cytotoxic drugs (Myatt et al., 2014).

Heat shock protein (HSP90) is important for numerous cell signalling proteins both in normal and cancerous cells. The recent clinical data provides an evidence of HSP90 as an important therapeutic strategy to cancer treatment if inhibited (Neckers and Workman 2012). Targeting housekeeping gene like HSP90 for cancer treatment remains under strong scepticism as it is ubiquitously present and maintains protein homeostasis (Neckers and Workman 2012). The ability of cancer cells to exploit HSP90 for two purposes including maintenance of activated onco-proteins and buffer the stress induced by malignant lifestyle (Neckers and Workman 2012). The action mechanism of these drugs was not known before Mollapour et al., (2014), who uncovered the role of asymmetric SUMOylation of N domain of both yeast K178 and human K191 facilitates the recruitment of ATPase activating co-chaperone Aha1 and binding of HSP90 to inhibitors (Mollapour et al., 2014). This indicates that an increased HSP90 SUMOylation sensitizes yeast and mammalian cells to HSP90 providing a mechanism of cancer cells sensitivity to these drugs (Mollapour, et al., 2014).

Autophagy, an important process of homeostasis maintenance, by which organisms remove harmful aggregates by a cytosolic cargo system to lysosomes (Dikic et al., 2010), the dysfunction of which causes certain neurological disorders and cancers (Levine and Kroemer, 2008; Rubinsztein, 2006). The findings of specific Ub binding receptors responsible for selective autophagy and the SUMOylation of autophagy-specific Ub like modifiers LC3/GABARAP provides a link between ubiquitin-proteasome system (UPS) and autophagy, hence provides selective autophagy as another means to remove harmful proteins that might cause cancers including multiple myeloma (Hoang et al., 2009).

p53 SUMOylation is carried out by SUMO1 at Lys386 in a cross-talk between acetylation in regulating p53 DNA binding and controlling its transcriptional activity. SUMOylation is involved in both induction and repression of p53 activity (Wu and Chiang, 2009). The activity of p53 is under tight control in normal cells to maintain homeostasis while this regulatory control is disrupted in most cancerous conditions. It can be suspected that sudden activation or loss of p53 may result in death of cells. The involvement of SUMOylation in regulation of p53 might be important in future p53 based anticancer therapies.

Ubc9, the only well established E2 enzyme responsible for SUMOylation related cellular pathways impacts cellular growth and cancer development. Recent studies have indicated its up regulation in various cancer types including lung and breast cancer (Wu et al., 2009). Ubc9 shows 5.7 fold higher expression in cancer breast tissue than in normal and mi-RNA30 family especially miR-30e negatively regulate its expression. Moreover the expression of miR-30e is lower in tumours (Wu et al., 2009). These results reveal the new cross-talk among Ubc9 and miRNA regulation of Ubc9 in cancerous cells providing a possible target for therapeutics to precisely regulate Ubc9 expression as anticancer therapeutics.

Over half of all the tumor types shows over expression of Myc onco-proteins mostly through, translocations or chromosomal amplifications and mutations in pathway regulation of the expression of Myc genes (Boxer et al., 2001; Oster et al., 2002). This over expression of Myc genes is thought to be responsible for cancer through disruptions in ubiquitin-proteasome system (Hoellein et al., 2014). It is argued and consequently proven by Hoellein et al., (2014) that SUMOylation plays critical roles in Myc dependent tumorigenesis showing over expression of genes involved in SUMOylation pathway both in humans and mouse lymphoma causing increased SUMOylation in these tumors while inhibiting SUMOylation through genetic means causes inhibition of Myc driven proliferation, stimulating G2/M phase cell cycle arrest, apoptosis and polyploidy (Hoellein et al., 2014). Furthermore, a rapid regression is observed in Myc lymphoma by inhibiting SUMOylation in-vivo both genetically and pharmacologically (Hoellein et al., 2014) hence providing yet another SUMOylation related therapeutic target that can be used in Myc driven lymphomas.

Akt, a proto-oncogene is a key player in cell proliferation and tumour formation. It has been recently discovered that Akt is SUMOylated at K276 (Rong et al., 2013), of which previous reports shows only ubiquitination, phosphorylation and acetylation for its [35] activation. The E17K a cancer derived mutant in Akt1 was more efficiently SUMOylated as compared to wild type Akt, while the loss of SUMOylation extensively hampers E17K mediated Akt1 proliferation and tumorigenesis ability (Rong et al., 2013) hence providing another SUMOylation related therapeutic target for cancer treatment. The involvement of SUMOylation with important proteins that causes various cancers makes it an interest to pharmaceutical companies to explore further its therapeutic applicability for next generation anti cancer therapeutics.

Conclusion

The immune responses of organisms are highly versatile and capable of modulating itself to better adopt the defence mechanisms against pathogens. Several mechanisms play important roles in providing such defences. The dysfunction in these mechanisms can cause severe malfunctioning of the immune system. The detail investigations into these mechanisms can reveal ways to mend those dysfunctions. Present review summarized the recent advances in SUMOylation understanding and its application as a therapeutic target. We also tried to establish the close link of SUMOylation and miRNAs which can be targeted in several diseases for developing epigenetic drugs. The recent advances in genomics possess a great potential to use those recent researches in post translational mechanisms including SUMOylation and miRNA for future therapeutics and next generation chemotherapies.

Acknowledgments

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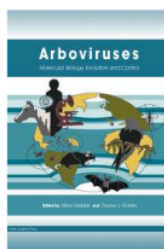
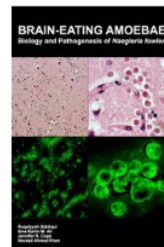
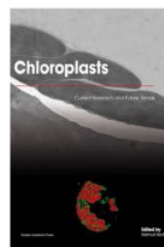
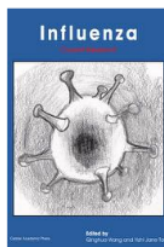
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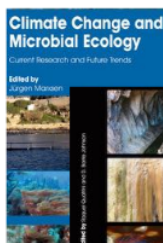
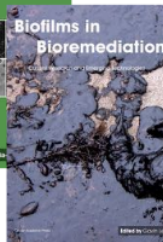
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