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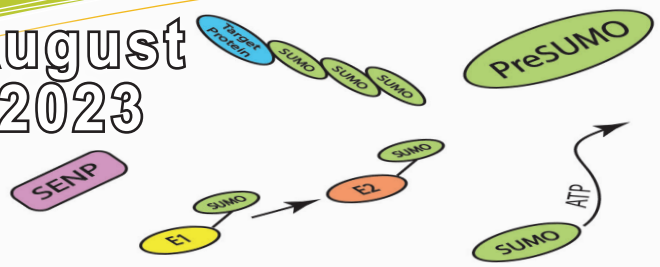

Leveraging SUMOylation To Regulate Immune Response

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Leveraging SUMOylation To Regulate Immune Response

Introduction

The small ubiquitin-like modifier 1 (SUMO1) was first identified in 1997[1] and since then, several isoforms (SUMO2, SUMO3, SUMO4, SUMO5), the SUMO enzymatic machinery (E1, E2, E3), and de-SUMOylases (SENPs) have been identified and characterized[(reviewed in 2)] (see Figure 1). Furthermore, it has been shown that this critical post-translational modification can selectively modify thousands of target proteins in a regulated fashion to control the protein's localization, stability, and function; thereby, modulating critically important cellular processes like DNA repair, stress response, cellular trafficking, and many others[(reviewed in 2)]. Thus, it is not surprising that dysregulation of SUMOylation has been linked to many diseases including cancer. There are many examples where dysregulation of SUMOylation acts on the cancer cell directly to augment its proliferation, migration, and metastasis[(reviewed in 3)]. Of equal importance, there is compelling evidence that SUMOylation facilitates cancer progression by modifying the tumor microenvironment and disrupting normal immune surveillance. In this newsletter, the effects of SUMOylation on the immune cells in both cancer and host immune responses are discussed.

SUMOylation – Immune Cell Maturation

The body's immune response to pathogens occurs by two mechanisms known as innate and adaptive immunity. Innate immunity involves the rapid, non-specific response to pathogens that is mounted by a diverse array of immune cells including macrophages, neutrophils, natural killer cells, and dendritic cells. Conversely, adaptive immunity, which is the "secondary" response is a highly-specific and targeted response to pathogens carried out by lymphoid lineage B and T cells. There is significant crosstalk between innate and adaptive immune cells which creates an effective strategy to both remove pathogens and generate subsequent memory responses. Several studies have been performed where SUMOylation machinery has been selectively knocked out in immune cells[(reviewed in 4,5)]. In most cases, the effective loss of SUMOylation significantly altered immune cell development. For example, the SUMO protease SENP1 has been shown to be highly expressed in the early stages of T cell and B cell development. Knockout of SENP1 in mice resulted in significantly smaller thymus and reduced T-cell precursors[6]. Similarly, T cell-specific knockout of the E2 enzyme Ubc9 produced reduced CD4 and CD8 positive T-cells[7].

Dysregulation of SUMOylation Leads to Evasion of Immunosurveillance in Cancer

Most tumor cells can be recognized by innate and adaptive immune cells and in many cases tumor progression depends on the suppression of immune cell activation in the tumor microenvironment. Regulation of immunosurveillance can occur through SUMO-dependent mechanisms in the immune cells; for example, overexpression of SUMO 2 in a transgenic mouse model led to enhancement of IL17-CD8+ T cells that effectively targeted cancer cells and led to decreased tumor growth[8]. In another example, Ubc9-specific depletion in macrophages in mice led to reduced prostate cancer progression through reducing the tumor-associated macrophage phenotype via a STAT4-dependent mechanism. Interestingly, suppression of cancer progression in this model also depended on immune cell crosstalk whereby ubc9 knockout in macrophages also produced enhanced CD8 + T cells[9]. Additionally, SUMO-dependent signaling in the cancer cell has been identified as a critical mechanism for immunosurveillance. In a study

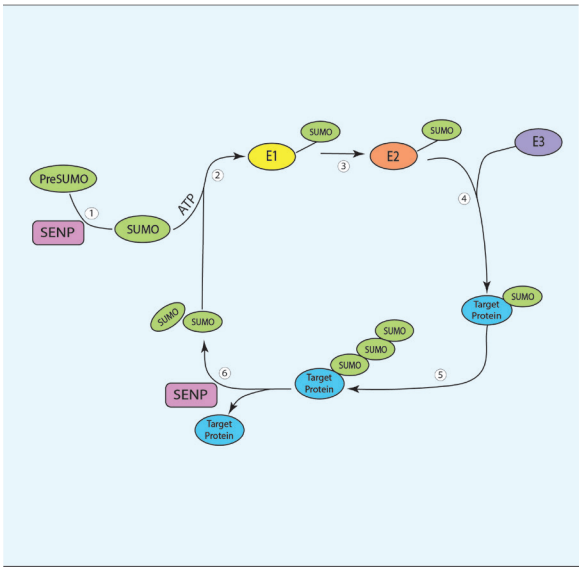

Figure 1. Schematic of the SUMOylation and deSUMOylation processes

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by Zitti et al., researchers found that inhibiting SUMOylation of the DNAM1 activating receptor led to its translocation to the cell surface and increased recognition of the multiple myeloma cancer cell by natural killer cells, which was one of the first examples of an innate immune activating ligand that was regulated by SUMOylation[10]. In patients with hepatocellular carcinoma, IL-33 appears to localize to the nucleus at a higher rate. A recent study attributed this localization to SUMOylation of IL-33 by the E3 ligase Ran BP2[11]. This enhanced localization promoted cancer progression through IRF1 regulation of PD-L1 which prevented cytotoxic T-cell activity. In a complementary study, activated SUMOylation was shown to suppress MHC class I, thus allowing cancer cells to evade CD8+ T cell-mediated immunosurveillance[12].

Dysregulation of SUMOylation Modulates Host Immune Response

While an adequate immune response is required to combat pathogenesis, an inadequate response results in disease susceptibility. Immune cell activation is regulated by transcription factors, signaling cascades, and post-translational modifications including SUMOylation, which has been identified as a particularly important mechanism(reviewed in 5). A recent study utilized transgenic mice where the critical nuclear factor of activated T cells (NFATc1) specific isoform could not be SUMOylated, and these mice had high IL-2 levels, enhanced Treg cell proliferation, and suppressed IL-17 release[13]. This led to enhanced protection against experimental autoimmune encephalomyelitis and graft-versus-host disease providing additional evidence of a role for SUMOylation in immune cell activation. A supporting study utilized a mouse model where Ubc9 was knocked out in Treg cells, and the results supported the idea that SUMOylation is important for Treg cell proliferation, activation, and homeostasis[14]. Because of its integral role in immune cell activation, it is not completely surprising that pathogens have hijacked the SUMO machinery to evade immune surveillance. One of the earliest examples came from L. monocytogenes which produces a pore-forming toxin listeriolysin that catalyzes the degradation of Ubc9[15]. Since then, many other pathogens have been shown to target Ubc9 stability as a mechanism to disrupt SUMOylation and immune cell function(reviewed in 5). Additionally, some pathogens have adapted mechanisms to utilize the SUMO machinery to modify their target proteins to enhance their infection strategy. SARS-CoV nucleocapsid protein was shown to interact with Ub9 and become SUMOylated, which promoted nucleocapsid assembly and SARS-CoV infectivity[16]. Another recent study showed that SUMO1 modification of the matrix protein of the influenza A virus led to enhanced stability and ultimately viral replication[17]. Regulation of SUMOylation machinery is a critical mechanism for the host immune response and pathogenesis of invading organisms.

Summary and Future Directions

This collection of findings highlights the important role that SUMOylation plays in immune cell development. It is interesting that the SUMOylation process has been highly targeted as a means to disrupt proper immune function, so much so, that both cancer and pathogens have targeted this PTM mechanism to evade immune surveillance. Because of SUMO's role in cancer, researchers have begun developing drugs to target the SUMO pathway(reviewed in 2). Interestingly while, it was initially thought that disrupting SUMO function with these E1 inhibiting drugs would primarily disrupt cell cycle progression in cancer cells, it was shown that the second-generation SUMO E1 inhibitor, TAK981, also induced anti-tumor immunity[18].

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SUMO 2/3 Affinity Beads	**Beads**	2 x 400 ul	ASM24-beads
Ubiquitin Affinity Beads	**Beads**	40 reactions	UBA01-beads
Control for IgG Beads	**Beads**	10 reactions	CIG01-beads
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