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EDITORIAL

PTM-centered therapy in malignant tumors: A new story of colchicine

KEY WORDS

Colchicine;
SAE1;
Post-translational modifications (PTM)-centered therapy;
Malignant tumors

Post-translational modifications (PTMs) involve the addition or removal of specific chemical groups to proteins in a covalent manner, which regulates their activity, localization, folding, and interactions with other biological macromolecules. PTMs contribute to the diversity of proteins, enabling them to carry out complex life processes[1]. It has been well-recognized that abnormal PTMs are closely related to the occurrence, development, and therapeutic resistance of malignant tumors[1]. Taking multiple myeloma (MM), the second most common hematologic malignancy, as an example, the delicate balance of protein homeostasis and post-translational regulation is crucial to its disease progression[2]. These insights have led to the success of bortezomib, the first-line treatment for MM patients[3]. To date, more than 650 types of PTMs have been described. For most of these modifications, there lacks an effective approach to targeting PTMs for therapeutic prospects, which constitutes a cutting-edge scientific area in the field of drug development.

Natural products and synthetic derivatives, which contribute to nearly 50% or more of the FDA-approved antitumor drugs[4], has been a rich reservoir for anti-tumor drug development. Recently, the explosive growth of the knowledge in cancer therapy and innovative technologies resolving the complexity of the multi-faceted pharmacological effects of natural products have provided new opportunities to rediscover natural products and revitalize anticancer drug discovery. For example, lobeline, an alkaloid from the herbal medicine lobelia known for various pharmacological properties in treating anxiety and depression and alcohol abuse, has been recently reported for the activity in promoting polarization of tumor-associated macrophages (TAMs) toward M1-like TAMs, while inhibiting their polarization toward M2-like TAMs. These insights lead to the discovery that combination therapy using lobeline and immuecheckpoint blockade exhibits stronger anti-tumor effects[5].

Colchicine is a one of the oldest remedies still in use today. It has been used for the treatment of myeloid leukemia and malignant lymphoma, yet the molecular mechanism remains unclear[6,7]. The study by Yang's group[8] provides novel mechanistic insights underlying the potential of the colchicne in treating MM. In this work, SUMO1-activating enzyme subunit 1 (SAE1) was identified as a potential target for colchicine. The study applied natural compound probes derived from Traditional Chinese Medicine (TCM) combined with multi-omics techniques to discover the potential target SAE1 in MM. The authors discovered that colchicine can disrupt the SUMOylation of p27 and affect its liquid−liquid phase separation (LLPS). Mechanistically, the authors elucidated the functional importance of PTMs in the LLPS of intrinsic disordered (IDR) proteins and confirmed that colchicine can target SAE1 to disrupt the SUMOylation of p27 that exhibited a key role in promoting MM development.

SAE1, which forms an ATP-dependent thioester bond between the mature SUMO protein and SAE2/UBA2 and leads to subsequent conjugation, activation, and ligation in the SUMO protein modification processes, plays a crucial role in SUMOylation. SAE1 has been identified as a potential biomarker for disease progression and prognosis in glioma, hepatocellular carcinoma, and triple-negative breast cancer[9,10]. The research by Yang's group provided the first evidence that colchicine can inhibit MM malignancy by directly targeting the E74 site of SAE1. This finding may open a new avenue for targeting the SAE1-mediated SUMOylation.

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It is interesting that the expression of p27, a classic tumor suppressor for cell proliferation, was increased due to the overexpression of SAE1, ultimately leading to the progression of MM. The authors thoroughly investigated the pro-oncogenic mechanism of p27 and found that SAE1 can facilitate the nuclear export of p27 *via* SUMOylation-mediated LLPS during tumor cell malignancy. They found that p27 could interact with CRM1, a nuclear export receptor, and mutations at the SUMOylation sites of p27 reduced its ability to bind to CRM1. These findings proposed a model of how tumor cells escaped from the growth-inhibiting effects of the tumor suppressor p27, which provides evidence for the double-edged sword role played by p27 in tumors. These findings also suggest that suppressing droplet formation or LLPS may be an effective strategy to intervene the nucleocytoplasmic localization of p27.

Collectively, this work by Yang's group not only provides new evidence—the application of colchicine in treating MM, but also lays the foundation for building a system for screening malignant tumor targets and developing precision medicine strategies, as well as achieving the reconstruction of the therapeutic value of commercial drugs.

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