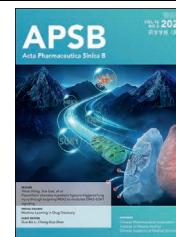




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COMMENTARY

Targeting MEK2 by paeoniflorin: Mechanism underlying its protection against hypobaric hypoxia-induced lung injury



KEY WORDS

Paeoniflorin;
Chemical proteomics;
MEK2-ERK2-SGK1
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—induced lung injury

With the increasing frequency of high-altitude travel, mountaineering, military deployment, and occupational exposure to extreme environments, hypobaric hypoxia-induced acute lung injury and high-altitude pulmonary edema (HAPE) have emerged as significant medical challenges¹. These disorders are characterized by abrupt onset, rapid progression, and marked interindividual susceptibility². In severe cases, respiratory failure may develop within a short period of time. Current clinical management relies largely on oxygen supplementation and supportive therapy, while mechanism-based pharmacological interventions remain limited. In this context, integrating natural medicine into a framework of precision molecular pharmacology, through the identification of direct molecular targets and coherent signaling pathways, has emerged as an important direction for advancing both high-altitude medicine and research on stress-related lung injury.

In the context of high-altitude medicine, therefore, modernization of traditional Chinese medicine therapeutics should not be confined to reiterating that a given compound “reduces lung injury.” Rather, it requires answering a more precise question: from which direct molecular target does the drug initiate its action, and how is this initial event transmitted through sequential

signaling processes to produce measurable biological outcomes? For many years, mechanistic studies of natural products have focused largely on downstream phenotypic readouts—such as reduced cytokine levels, decreased ROS accumulation, or altered phosphorylation of selected pathways—without providing direct evidence for the molecular starting point³. Under such circumstances, different studies conducted at varying doses, exposure times, or model systems often identify distinct “key pathways,” making it difficult to establish stable and transferable molecular conclusions. To genuinely support translational advancement, mechanistic investigation should satisfy at least three criteria: demonstration of direct drug–target engagement, verification of target necessity through genetic or pharmacological perturbation, and consistency of the mechanistic cascade across cellular and *in vivo* levels^{4–5}.

In recent years, rapid advances in chemical proteomics have facilitated a transition from isolated examples of target identification to more reproducible and broadly applicable strategies⁶. Methods such as limited proteolysis–mass spectrometry (LiP-MS) enable detection of ligand-induced conformational changes under near-physiological conditions, thereby allowing potential targets to be screened without reliance on chemical labeling⁷. Activity-based protein profiling (ABPP), particularly alkyne-tagged probe-based strategies developed upon click chemistry and LC–MS proteomics, has further expanded the capability to identify protein targets of small-molecule compounds through covalent or activity-dependent labeling approaches⁸. Complementary techniques including CETSA and thermal proteome profiling (TPP) permit evaluation of target engagement within intact cells, effectively bridging target discovery and functional validation⁹. Additional approaches, including drug affinity responsive target stability (DARTS)¹⁰ and the peptide-centric local stability assay (PELSA)¹¹, have also continued to evolve. Ongoing methodological refinements aimed at improving sensitivity and analytical resolution are enabling the identification of an

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expanding spectrum of protein targets for natural medicine. Notably, several representative studies have successfully applied these approaches to define direct protein targets of classical natural medicines, thereby moving the field from “black-box” phenotypic observation toward mechanism visualization^{12–14}.

Paeoniflorin (Pae), a principal bioactive constituent derived from *Paonia* species, has long been reported to exert anti-inflammatory and antioxidant effects, showing protective activity in models of lung injury. However, previous mechanistic explanations largely focused on downstream pathway modulation, without definitive evidence of direct molecular engagement. Without a defined target, mechanistic interpretations often remain associative rather than causal. Indeed, natural medicines frequently interact with complex signaling networks, and identifying the dominant regulatory node is essential for mechanistic clarity⁷.

The study featured in this issue provides a compelling example of methodological rigor¹⁵. Using Lip-MS under near-physiological conditions, the authors identified MEK2 as a direct binding target of paeoniflorin and subsequently validated this interaction through molecular dynamics simulation, CETSA, DARTS, surface plasmon resonance, and genetic intervention strategies. MEK2 is a core kinase within the canonical MAPK signaling cascade, traditionally associated with proliferative regulation. However, emerging evidence suggests that MAPK networks also function in stress adaptation and metabolic reprogramming in a context-dependent manner¹⁶. In this issue of *Acta Pharmaceutica Sinica B*, Wu et al.¹⁵ demonstrates that paeoniflorin enhances MEK2–ERK2 interaction and promotes ERK2 phosphorylation, leading to upregulation of SGK1. SGK1 is widely recognized as a critical mediator of cellular stress responses, contributing to ion homeostasis, mitochondrial stability, and cell survival¹⁷. Through this MEK2–ERK2–SGK1 axis, paeoniflorin preserves mitochondrial integrity and suppresses oxidative stress and ferroptosis, thereby alleviating hypobaric hypoxia-induced lung injury.

In hypoxia-associated lung injury, mitochondrial function has increasingly been recognized as a central determinant of cellular fate¹⁸. Hypoxia does not merely reflect insufficient energy supply; rather, it initiates a cascade of interconnected disturbances, including redox imbalance, disruption of intracellular calcium homeostasis, and progressive accumulation of lipid peroxidation. Together, these alterations amplify inflammatory responses and drive cellular injury toward an irreversible state. Recent studies have highlighted ferroptosis—a form of regulated cell death driven by lipid peroxidation—as a critical contributor to hypoxia-related organ damage, closely linked to inflammatory amplification as well as dysregulation of iron and lipid metabolism¹⁹. At the mitochondrial level, aberrant opening of the mitochondrial permeability transition pore (mPTP) is widely regarded as a pivotal transition point at which reversible stress responses evolve into sustained cellular injury. mPTP opening promotes reactive oxygen species accumulation, calcium overload, and loss of membrane potential, thereby establishing a self-reinforcing cycle that compromises cellular recovery and homeostasis²⁰. Consequently, integrating upstream signaling regulation with mitochondrial functional changes and ferroptotic processes provides a more coherent framework for understanding how drug actions are ultimately translated into protective outcomes. Such integration represents an essential step toward achieving mechanistic precision in natural medicine pharmacology.

Despite establishing an impressive target–signal–phenotype cascade, several questions merit further investigation. First, the

precise molecular bridge connecting MEK2/ERK2 activation to SGK1 induction remains to be elucidated. Whether specific transcription factors, post-translational modifications, or scaffold proteins mediate this connection is not yet fully defined. Given the complex feedback architecture of MAPK networks, further mapping of downstream signaling dynamics will enhance mechanistic resolution¹⁶. Furthermore, interactions between natural medicines and proteins are often influenced by experimental context. Variations in dosage, duration of exposure, or biological models may alter the principal interacting proteins detected and the downstream signaling patterns observed. This implies that a “core target” defined under specific experimental conditions may not fully represent the entire spectrum of molecular interactions that the compound engages within a complex pathological environment²¹. Finally, advancing from single-compound target elucidation toward multi-component synergistic network analysis represents a crucial next step in the modernization of traditional medicine research²².

Overall, this study exemplifies a strategic evolution in natural medicine pharmacology: beginning with unbiased target fishing and culminating in mechanistic closure through multi-level validation. By identifying MEK2 as a direct molecular target of paeoniflorin and establishing the MEK2–ERK2–SGK1 axis in hypobaric hypoxia-induced lung injury, the work reshapes our molecular understanding of stress adaptation in pulmonary tissue. In the context of increasing global exposure to extreme environments, such integrative approaches may bridge traditional medicine development with precision therapy.

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