Novera

Commentary

A metabolic vascular axis redefines therapeutic targeting in rosacea erythema

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Rosacea is a highly prevalent chronic inflammatory skin disorder that affects millions of individuals worldwide [1], with persistent facial erythema representing its most defining and therapeutically challenging feature. Despite its substantial clinical burden, which includes psychosocial distress and reduced quality of life, long-term control of erythema remains difficult to achieve. Current therapies, such as topical α-adrenergic agonists [2] including brimonidine, primarily induce transient vasoconstriction but are limited by short duration, rebound erythema, and local adverse effects. These shortcomings reflect a deeper gap in the field, namely an incomplete understanding of the molecular mechanisms that drive pathological vasodilation. A recent study [3] published in Cell provides a conceptual advance by identifying a previously unrecognized metabolic vascular signaling axis centered on α-ketoglutarate, its receptor OXGR1, and downstream Gq MYL9 signaling. By integrating clinical metabolomics, mechanistic biology, structural analysis, and drug development, this work establishes a coherent framework linking metabolic adaptation to vascular tone regulation. Similar to recent advances in other biomedical fields that connect microenvironmental signals with disease mechanisms, this study reframes rosacea erythema as a metabolically regulated and therapeutically tractable process rather than a purely vascular abnormality.

A protective metabolic signal: α-KG in rosacea erythema

A key insight from this work is the identification of α-ketoglutarate as a protective metabolite in rosacea. Clinical metabolomic profiling revealed that circulating α-KG levels are elevated in patients and positively correlate with erythema severity. Although such a correlation might initially suggest a pathogenic role, functional experiments clearly demonstrate the opposite. In the LL37-induced rosacea-like mouse model, both oral and topical administration of α-KG significantly reduced erythema, attenuated vascular dilation, and suppressed inflammatory responses. These results indicate that the elevation of α-KG reflects a compensatory response that attempts to restore vascular homeostasis. This finding challenges the conventional interpretation of metabolite accumulation and emphasizes the importance of distinguishing between causative and adaptive metabolic changes. This conceptual shift positions rosacea as a disease in which endogenous metabolic signals act to counterbalance vascular dysregulation. It also highlights the broader principle that metabolites can function as active regulators of tissue physiology rather than passive biomarkers.

OXGR1 links metabolic sensing to vascular contraction

Building on this observation, the study identifies OXGR1 as the receptor that mediates the effects of α-KG. OXGR1 is selectively expressed in vascular smooth muscle cells within the skin, suggesting a direct role in controlling vascular tone. Mechanistically, α-KG binding activates Gq signaling, leading to phospholipase C activation, intracellular calcium elevation, and activation of myosin light chain kinase. This cascade results in phosphorylation of MYL9 and contraction of vascular smooth muscle cells, ultimately suppressing abnormal vasodilation. The necessity of this pathway is demonstrated through genetic approaches, as vascular smooth muscle cell specific deletion of Oxgr1 or Gq abolishes the protective effects of α-KG. The identification of itaconate as an additional endogenous ligand further supports the idea that OXGR1 functions as a metabolic sensor integrating multiple signals to regulate vascular responses. Together, these findings establish a direct molecular link between metabolism and vascular contraction in rosacea, expanding the current framework of disease pathogenesis beyond inflammation and neurovascular dysregulation.

Structural basis of ligand recognition and receptor activation

A major strength of this study lies in its structural characterization of OXGR1. Using cryo electron microscopy, the authors resolved multiple structures of the OXGR1 Gq complex in different ligand-bound states, including α-KG, itaconate, and the synthetic agonist A-1. These structures reveal a distinctive dual acidic binding pocket composed of a small acidic pocket and a central acidic pocket, which together enable specific recognition of dicarboxylic acid ligands. This configuration provides a clear explanation for ligand selectivity and for the higher potency of α-KG compared with itaconate. Notably, OXGR1 exhibits a non classical activation mechanism. Unlike many class A GPCRs, it does not rely on the canonical W6.48 toggle switch. Instead, conformational changes are transmitted through an alternative network of aromatic residues including F113, Y82, Y118, and F257. This finding expands the current understanding of GPCR activation and underscores the structural diversity of metabolite sensing receptors. These insights demonstrate how structural biology can reveal unexpected signaling principles and provide a foundation for rational drug design.

Structure guided development of a selective OXGR1 agonist

Building on the structural findings, the authors performed virtual screening and rational optimization to identify A-1, a highly selective and potent OXGR1 agonist. A-1 exhibits approximately sixty fold higher potency than α-KG and shows strong selectivity for OXGR1 without activating related receptors such as GPR91 or P2X4. In preclinical models, topical application of A-1 effectively reduces erythema to a degree comparable with brimonidine. Importantly, A-1 does not induce rebound vasodilation or contact dermatitis, suggesting an improved safety and tolerability profile. These properties likely reflect its mechanism of action, which enhances an endogenous regulatory pathway rather than imposing an artificial vasoconstrictive signal. A-1 therefore represents a promising therapeutic candidate and illustrates the power of structure guided drug development in identifying targeted treatments for complex diseases.

Conceptual advances and broader implications

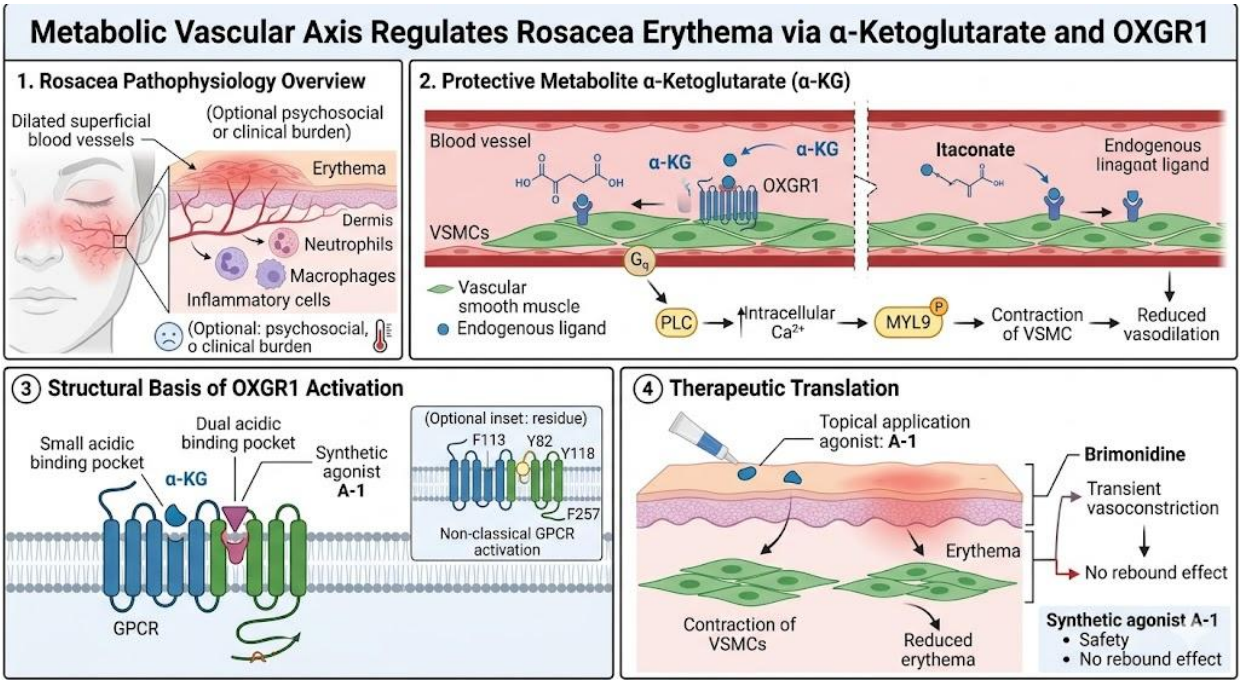

Figure 1. Rosacea erythema is regulated by a metabolic vascular axis involving α-ketoglutarate (α-KG) and its receptor OXGR1. Dilated dermal blood vessels and inflammatory cell infiltration characterize the disease (1). α-KG, elevated in patients as a compensatory signal, binds OXGR1 on vascular smooth muscle cells, activating Gq signaling, phospholipase C, intracellular calcium influx, and MYL9 phosphorylation, which induces vessel contraction and reduces erythema; itaconate serves as an additional endogenous ligand (2). Structural analysis reveals that OXGR1 contains dual acidic binding pockets that selectively recognize α-KG and the synthetic agonist A-1, and that receptor activation proceeds via non-classical conformational changes involving key aromatic residues (3). Topical A-1 enhances this endogenous pathway, suppressing erythema without rebound vasodilation or local adverse effects, providing a mechanism-based therapeutic strategy superior to transient vasoconstriction by brimonidine (4). This figure illustrates the integration of metabolic signaling, vascular contraction, and therapeutic intervention in rosacea.

This study provides several important conceptual advances. First, it establishes a metabolic GPCR vascular contraction axis as a central mechanism regulating skin vascular homeostasis. This framework may extend to other conditions characterized by abnormal vasodilation. Second, it identifies OXGR1 as a new therapeutic target for rosacea erythema. Targeting this receptor offers a more specific and potentially more durable approach compared with existing therapies. Third, the study exemplifies a complete translational pipeline that spans clinical observation, mechanistic investigation, structural analysis, and therapeutic development. This integrative strategy mirrors successful approaches in other areas of biomedical research and highlights the value of interdisciplinary collaboration. Finally, the work supports the emerging concept that endogenous metabolites can be harnessed as therapeutic signals, opening new avenues for precision medicine.

Limitations and future directions

Several limitations should be considered. The study relies primarily on an LL37 induced mouse model, which captures acute inflammatory responses but does not fully reflect the chronic and heterogeneous nature of human rosacea. Future studies should validate these findings in additional models and in clinical settings. Although A-1 shows promising efficacy and safety in preclinical experiments, its pharmacokinetics, long term safety, and clinical effectiveness remain to be determined. Clinical trials will be essential to assess its translational potential. The regulation of α-KG metabolism in rosacea is not fully understood. Elucidating the upstream pathways that control its production, and utilization may reveal additional therapeutic targets. In addition, the potential role of OXGR1 in neurovascular interactions remains unexplored. Given the importance of neural regulation in rosacea, this represents an important direction for future research. Finally, it will be important to determine whether this metabolic vascular axis operates in other inflammatory or vascular skin diseases, which could broaden its clinical relevance.

Conclusions and outlook

In conclusion, this study represents a major advance in the understanding and treatment of rosacea erythema. By identifying a metabolic pathway that regulates vascular contraction and by translating this knowledge into a targeted therapeutic strategy, the authors provide a compelling example of mechanism driven innovation. More broadly, the work highlights the importance of integrating metabolism, receptor biology, and structural insights to uncover new therapeutic opportunities. Targeting the α-KG OXGR1 axis has the potential to transform the clinical management of rosacea and may serve as a model for the development of precision therapies in dermatology. As research continues to uncover the interplay between metabolic signals and tissue physiology, similar strategies are likely to emerge across a wide range of diseases, paving the way for more effective and durable treatments.

Funding

This work was supported by the Natural Science Foundation of Hunan Province (2022JJ30852).

Author Contributions

Z.R. and J.W. conceived the initial concept for this manuscript. Z.R. and J.W. wrote the first draft of the manuscript, which was revised by all authors. All authors contributed to and approved the manuscript.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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