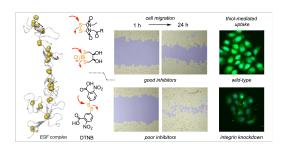
Inhibition of Cell Motility by Cell-Penetrating Dynamic Covalent Cascade Exchangers - Integrins Participate in Thiol-Mediated Uptake

F. Coelho¹, S. Saidjalolov¹, D. Moreau², O. Thorn-Seshold³, S. Matile¹

¹Department of Organic Chemistry, University of Geneva, 1211 Geneva, Switzerland, ²Department of Biochemistry, University of Geneva, 1211 Geneva, Switzerland, ³Department of Pharmacy, Ludwig-Maximilians University of Munich, 81377 Munich, Germany

Thiol-mediated uptake (TMU) is the process of internalization facilitated by the continuous exchange (CAX) between activated disulfides and exofacial thiols on transmembrane proteins. This process can be inhibited by using hydrophilic surface-thiol-reactive agents preventing any other molecule to participate in any CAX. TMU cascades are a complex mechanism which is not yet well understood due to its dynamic nature and fleeting intermediates. Recently, we demonstrated that TMU is not a single target process but rather involves a network of transmembrane proteins meshed in a dynamic fashion.1 The most relevant example is the direct dependence of asparagusic acid to transferrin receptor for TMU.² These results drove our attention to thiol/disulfide rich transmembrane proteins that might be potentially involved in TMU. Integrins, a family of glycoprotein receptors responsible for mediating the process of cell migration and evasion, viral uptake, and wound healing, were speculated to be part of TMU. The activation of the integrin is caused by the change of conformation after redox exchange between Protein Disulfide Isomerase (PDI) and the thiol/disulfide-rich leg of the b-subunit of integrin. Inspired by this, we tested our TMU inhibitor library in a cell migration assay. Results show that migration was indeed inhibited in three different cell lines and across three different coatings. The antimigratory activities exceeds that of Ellman's reagents and correlates globally with their abilities to penetrate cells.3 Most importantly, knockdown experiments support the conclusion that the integrins are involved in TMU as in the antimigratory properties. Now, we found that the integrin superfamily is an exchange partner to participate in TMU - biggest finding since the transferrin receptor (the only known until now). These results thus (a) introduce dynamic covalent cascade exchange chemistry to the control of cell motility, (b) expand the CAX drug discovery space from anti-viral toward antithrombotic and anti-tumor potential, and (c) they confirm integrins as exchange partners in the dynamic TMU networks that deliver matter into cells. Opens doors to further advances in the field of drug delivery.



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- [3] Filipe Coelho, Saidbakhrom Saidjalolov, Dimitri Moreau, Oliver Thorn-Seshold, Stefan Matile, *JACS Au*, **2023**, 3, 1010–1016.