Molecular Insights into Janus Kinase Inhibitor Interactions with Model Intestinal Epithelial Membranes: From Langmuir Monolayers to Asymmetric Bilayers

Michalina Zaborowska-Mazurkiewicz

University of Warsaw, Faculty of Chemistry, Pasteura 1, 02-093 Warsaw, Poland

mzaborowska@chem.uw.edu.pl

Most drugs administered to humans influence the organization and surface properties of biological membranes, thereby modulating cellular functions. The epithelial membrane of the small intestine constitutes the first barrier in drug absorption and is a key target for anti-inflammatory therapies based on Janus kinase inhibitors (JAKs). Despite their widespread clinical use, the molecular mechanisms underlying JAK–membrane interactions remain insufficiently understood.

In this study, multicomponent lipid systems mimicking the intestinal epithelial membrane were employed, progressing from Langmuir monolayers to asymmetric bilayer architectures. The models comprised physiologically relevant lipid mixtures (PC/SM/PE/PS/PI), including asymmetric bilayers with an inner leaflet (DPPC:DPPE:DMPS) and an outer leaflet (POPC:POPE:SM) reflecting inflammation-related membrane conditions. Selected JAK inhibitors were incorporated into these systems and analyzed using complementary surface-sensitive, spectroscopic (PM-IRRAS), electrochemical (capacitance measurements), and atomic force microscopy (AFM) techniques, enabling systematic evaluation of drug-induced effects in both membrane leaflets.

The results demonstrate that JAK inhibitors interact specifically with lipid components, with their effects strongly dependent on chemical structure and lipophilicity. More lipophilic compounds induce membrane fluidization, modulate phase separation, and promote defect healing within lipid layers. These findings reveal structure–interaction relationships governing drug localization and affinity for lipid headgroups. A detailed understanding of these processes provides valuable insight into the molecular basis of JAK-based anti-inflammatory therapies and supports their optimization to enhance efficacy while minimizing adverse effects.

Keywords:

Janus kinase inhibitors (JAK inhibitors); drug–membrane interactions; intestinal epithelial membrane; asymmetric lipid bilayers; Langmuir monolayers;

Acknowledgements:

This work was financially supported by the Polish National Science Center (MINIATURA Project No. 2024/08/X/ST4/00411). The study was partly carried out at the Biological and Chemical Research Center, the University of Warsaw. Supported by the Foundation for Polish Science (FNP)