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Characterization of a novel antagonist for the human platelet thromboxane A2 receptor

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Despite the well-documented involvement of thromboxane A2 receptor (TPR) signaling in thrombotic diseases, there are currently no antagonists available for clinical use. To this end, previous work has defined the C-terminus of the second extracellular loop (C-EL2) of TPR as the ligand binding site. Since EL2 contains the ligand binding pocket, we hypothesized that an antibody (designated C-EL2Ab) that targets this domain exhibits biological activity. Our results demonstrated the C-EL2Ab blocked human (in vitro) and mouse (in vitro and ex vivo) platelet aggregation triggered by the TPR agonist U46619, dose-dependently; whereas control experiments revealed that it did not produce any detectable effects on aggregation by ADP. Separate control experiments indicated that normal rabbit IgG and an antibody which targets a TPR domain separate from those involved in ligand recognition, failed to inhibit aggregation in response to TPR activation. Consistent with the notion that C-EL2Ab serves as a selective antagonist for TPRs, it was found to displace a radio-labeled TPR antagonist (i.e., [^{3}H]SQ29,548) from its platelet TPR binding sites. Finally, it was found that intravenous tail injections of C-EL2Ab significantly prolonged the time for occlusion in a carotid artery thrombosis model, whereas it did not produce any detectable effects on tail bleeding time. Collectively, these results clearly demonstrate that C-EL2Ab exerts TPR-specific anti-platelet/antithrombotic activity, making it the first function-blocking antibody against these receptors. Moreover, the identification of a functionally active TPR sequence will significantly aid molecular modeling study predictions for organic derivatives which possess in vivo activity.

Biography

Fadi T. Khasawneh completed his Ph.D from the University of Illinois at Chicago in 2007, and a Bachelor in Pharmacy from Jordan University of Sciences and technology in 1999. Dr. Khasawneh joined the College of Pharmacy at Western University in 2008. His research interests are in the area of thrombosis development, and the signaling pathways involved in human platelet activation. He has published more than 15 papers in reputed journals, has two pending patents, serves as an editorial board member for several journals, and is a Peer Reviewer for the American Heart Association.

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