Adhesion GPCRs CD97 and GPR56: From structural regulation to cellular function

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Adhesion GPCRs CD97 and GPR56: From structure regulation to cellular function

Cheng-Chih Hsiao

Cells correspond with their environment through receptors that translate extracellular signals into intracellular messages. Members of the large superfamily of G protein-coupled receptors (GPCRs) control various physiological functions and have been implicated in numerous diseases. Adhesion GPCRs are noncanonical GPCRs with a bipartite structure that results from an autocatalytic cleavage event. The design of adhesion GPCRs and their ability to interact with matricellular molecules have raised questions regarding their mechanism of activation and molecular functions. This thesis focuses on the mechanism and implications of autoproteolysis as well as on the functions of adhesion GPCRs CD97 and GPR56. We show that N-glycosylation affects autoproteolysis in CD97 and demonstrate that autoproteolytic cleavage is necessary for CD97 to perform cellular functions in cell aggregation, adhesion, migration, tumorigenesis, and apoptosis. A second part of the thesis indicates molecular mechanisms by which GPR56 mutations cause a cortical malformation, known as bilateral frontoparietal polymicrogyria, and describes a novel role of GPR56 in immunity. We obtained evidence that GPR56 in human natural killer cells is induced by the transcription factor Hobit, inhibits immediate effector functions by associating with the tetrspanin CD81, and declines upon cellular activation. GPCRs are known for the excellent duggability; about 50% of all modern therapeutic drugs target GPCRs and, obviously, adhesion GPCRs, like CD97 and GPR56, hold promises for the development of novel intervention strategies.
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Cheng-Chih Hsiao
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Adhesion GPCRs CD97 and GPR56:
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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. D.C. van den Boom
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
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door

Cheng-Chih Hsiao
geboren te Chia-Yi, Taiwan
Promotiecommissie

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