Sterical hindrance promotes selectivity of the autophagy cargo receptor NDP52 for the danger receptor Galectin-8 in antibacterial autophagy

With the strong support from National Natural Science Foundation of China, the research team of Professor Shi Yunyu from the University of Science and Technology of China, collaborated with Professor Felix Randow's groups from the MRC Laboratory of UK, published their research findings in an article "Sterical Hindrance Promotes Selectivity of the Autophagy Cargo Receptor NDP52 for the Danger Receptor Galectin-8 in Antibacterial Autophagy" in *Science Signal* (**2013**, 6(261): ra9).

Selective autophagy is an important effector mechanism of cell autonomous immunity, in particular against invasive bacterial species. When *Salmonella* infection, anti-bacterial autophagy is activated by rupture of bacteria-containing vacuoles. Luminal galactoside glycans are exposed to the cytosol and bind to specific 'eat-me' signals such as Galectin-8 which selectively recruits the cargo receptor, the nuclear dot protein 52kDa (NDP52) to stimulate autophagy, a process of intracellular degradation of the damaged vesicular structures and associated bacteria. Nevertheless, how specificity between NDP52 and Galectin-8 is achieved remains unknown.

Prof. Shi's group solved the crystal structure of the binding domain of NDP52 in complex with the carbohydrate recognition domain of galectin-8. The carbohydrate binding domains of galectin-8 form compact bent β-sandwich structures presenting its concave surface to glycans, whereas the convex surface binds NDP52. NDP52 formed a hooklike structure that bound to a hydrophobic pocket on galectin-8. In this pocket, Ala^{323} is a key specificity determinant and poorly conserved in other galectins. And it turns out that replacing it experimentally with any other residue occurring in this very same position on other galectins completely abrogates binding. Therefore, this study showed the selectivity of NDP52 for galectin-8 is due to sterical hindrance occurring in other galectins, thereby explaining the selectivity of NDP52 for galectin-8 and how galectin-8 activates autophagy in *Salmonella*-infected cells.

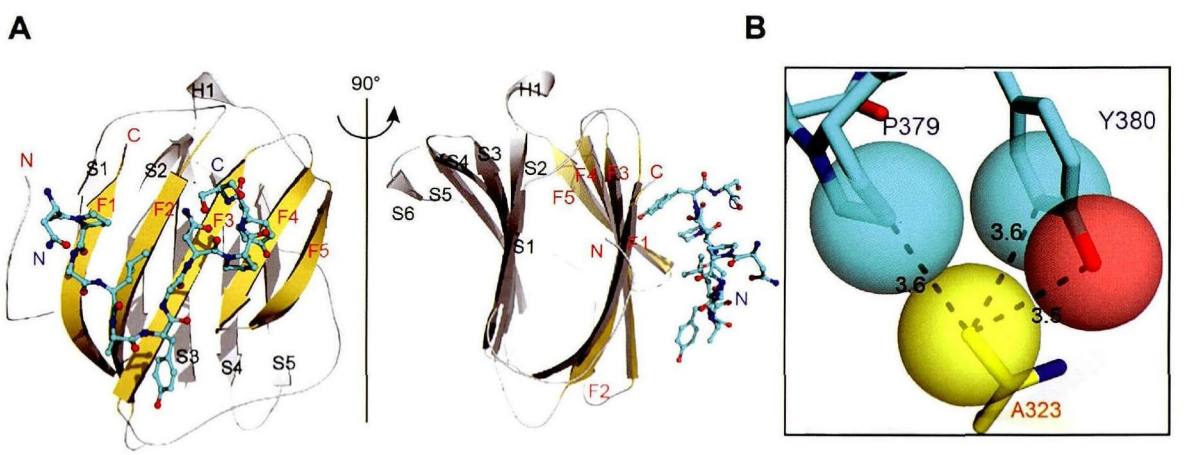

Figure **A** Cartoon representation of the carbohydrate recognition domain of Galecitn-8 (yellow and gray) in complex with the binding domain of NDP52 (cyan). F1 to F5 and S1 to S6 indicate numbering of β-strands. **B** Close-up view of Gal8 Ala^{323} (yellow) in contact with the γ-carbon of the NDP52 Pro^{379} and the ε-carbon and hydroxyl oxygen of the NDP52 Tyr^{380} side chain (blue and red). Van der Waals volumes of key atoms rendered as transparent spheres.