Structural Studies of Mouse Galectin-4 N-Terminal Domain

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Galectins are an evolutionarily conserved family of 15 different lectins found in various combinations in virtually every type of animal cell. Galectins are defined as a family of β-galactoside binding proteins which are characterized by the presence of a carbohydrate recognition domain (CRD). Although galectins have not signal sequence for their transferring through the membrane, they can be externalized across the membrane by non-classical secretory pathways. Recent studies demonstrated that galectins participate in many biological processes, such as cell adhesion, cell cycle control, apoptosis, signal transduction, immune response and malignity.

Based on a basic domain structure (~130 aa), the galectin family can be divided into a prototype monovalent monomer or dimer subfamily (galectin-1, -2, -5, -7, -10, -11, -13 and -14), chimera type members (galectin-3 and -15) and tandem-repeat subfamily (galectin-4, -6, -8, -9, and -12) [1].

Galectin-4 is a prototype molecule of monomer divalent galectin members which shares a high structural similarity to mouse galectin-6 [2]. The presence of two non-identical core domains separated by a link region suggested the possible role of tandem-repeat galectin members in crosslinking function [3]. Rather than crosslinking one molecule is believed that these members can crosslinking two distinct type of ligand. Therefore, a binding specificity for each domain was recently studied in rat and human galectin-4 [4]. These studies confirm that both domains differ in saccharide recognition, selectivity and affinity to particular types of oligosaccharides[5], supporting the hypothesis for a clustering or crosskicking function of galectin-4. This was also supported by Braccia et al [6] demonstrating that galectin-4 can function as a core raft stabilizer in the microvillar membrane vesicles of intestinal brush border. Ideo et al [7] demonstrated recently that galectin-4 binds to O-linked sulfoglycans [8] and to sulfated glycosphingolipids and carcinoembirionic antigen in patches on the cell surface of human colon adenocarcinoma cells.

Galectin-4 is a cytosolic protein expressed only in alimentary tract. Strong expression can be induced, however, in cancers from other tissues including breast and liver. Because of its distinct induction in breast and other cancers, it may be valuable diagnostic marker and target for the development of inhibitory carbohydrate based drugs [9].

We have already solved structure of N-terminal domain in complex with lactose (Fig.1) at resolution 2.1 Å.
Figure 1

a) Overall view of the complex CRD1-lactose.
b) Detail view of interacting lactose in the binding site.
c) Solvent accessible surface of galectin is coloured by electrostatic potential.

Crystals of free N-terminal domain of mouse galectin-4 at resolution 3 Å we measured during our visit in Hamburg (7.-9.11. 2006).