Galectins are a group of soluble β-galactoside-binding lectins that play many important regulatory roles in inflammation, immunologic response and cancer. A total of 15 galectins have been identified. Galectin-3 is the most widely studied member of the galectin protein family [1, 2].

Galectin-3 is a mid-size protein (29 to 35 kDa) consisting of an N-terminal domain with tandem repeats of short amino acid segments (a total of approximately 120 amino acids) linked to a single C-terminal carbohydrate-recognition domain (CRD) of about 130 amino acids. It can interact with carbohydrates, which involves the C-terminal domain, and with unglycosylated molecules, such as cell surface and extracellular receptors, which involves the N-terminal domain [3].

As other galectins, galectin-3 does not contain a signal sequence, therefore it is localized primarily in the cytoplasm, and occasionally, in the nucleus and mitochondria. Galectin-3 is found in epithelial cells, fibroblasts, dendritic cells and inflammatory cells. In addition, galectin-3 can be secreted and function in extracellular space. It can form pentamers upon binding to multivalent carbohydrates, therefore it is capable of crosslinking glycans on the cell surface, and in this manner initiating transmembrane signaling events and affecting various cellular functions [4].

Galectin-3 is known for its role in tumorigenesis and progression through regulating cell proliferation, apoptosis, cell adhesion, invasion, angiogenesis and metastasis. Expression of galectin-3 is modulated in many different cancers. Measurement of serum galectin-3 can be helpful in diagnosis and prognosis for specific cancer types, such as thyroid and prostate [5].

One of the more interesting and well characterized effects is the role of galectin-3 in the promotion of fibrosis. Fibrogenesis or scarring is a consequence of certain types of injury and inflammation, which are central pathophysiological mechanisms in the development and progression to heart failure. Expression of galectin-3 is low in a healthy human heart; however, as heart failure progresses galectin-3 becomes significantly up-regulated. It is released by activated cardiac macrophages stimulating additional macrophages, pericytes, myofibroblasts, and fibroblasts, which in response signal cellular proliferation and secretion of procollagen I. Procollagen I irreversibly crosslinks to form collagen and results in cardiac fibrosis [6 – 10].

Involvement of galectin-3 in fibrosis has also been demonstrated in liver [11] and kidney [12].
Inhibition of galectin-3 appears to prevent progression of fibrosis. Recent publications describe the tetrapeptide, N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) that causes inhibition of cardiac fibroblast proliferation and collagen synthesis. Ac-SDKP is a naturally occurring anti-inflammatory and antifibrotic peptide that is hydrolyzed almost exclusively by angiotensin-converting enzyme (ACE), and plasma concentration of Ac-SDKP is increased substantially by ACE inhibitors. Rats overexpressing cardiac ACE have decreased Ac-SDKP concentration and increased fibrosis in heart tissue [13]. Other studies include galectin-3 knock-out mice, use of small interfering RNA that can silence galectin-3 gene activity and use of carbohydrate molecules, which can deactivate galectin-3.

Because of the unambiguous association of galectin-3 with the disease development, progression and poor outcome, measurement of galectin-3 in patients diagnosed with chronic heart failure may have diagnostic and therapeutic implications.

Recently, the FDA has approved for market an assay manufactured by BG Medicine, Inc. (Waltham, MA) for galectin-3 to supplement standard risk assessment in patients with chronic heart failure [14]. BGM Galectin-3 is currently available at Pacific Biomarkers. The test is based on the common ELISA utilizing two monoclonal antibodies against galectin-3. One rat monoclonal anti-mouse galectin-3 antibody is coated onto the surface of wells as a capture antibody to bind galectin-3 molecules in samples, while the other mouse monoclonal anti-human galectin-3 antibody is provided in solution and functions as the tracer antibody for detecting galectin-3 molecules bound to the capture antibody [15].

Clinical effectiveness and prognostic value of BGM Galectin-3 levels have been demonstrated in sub-studies of several heart-failure trials, including the Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH), and The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION). Galectin-3 levels were found to be significantly associated with cardiovascular mortality and heart failure-related hospitalization. Levels greater than 17.8 ng/mL are indicative of galectin-3 mediated heart failure and are associated with increased risk of adverse outcomes. Plasma galectin-3 levels less than 25.9 ng/mL, independent of symptoms, clinical findings, and other laboratory measures, predict a patient who is likely to have rapid progression of heart failure, resulting in hospitalization and death. In addition, doubling of galectin-3 levels over the course of 6 months, irrespective of baseline value, identifies a high-risk patient in whom additional care management efforts and advanced therapies could be warranted. It is important to note that galectin-3 testing is indicated for use in patients previously diagnosed with chronic heart failure and cannot be used to diagnose heart failure. Results of testing or measurement of galectin-3 should be interpreted in conjunction with clinical evaluation as an aid in assessing the prognosis of patients diagnosed with chronic heart failure [16 – 18].

Galectin-3 results should be interpreted with caution. Levels may be increased in patients with certain forms of cancer, in other conditions associated with organ fibrosis, and in patients with a history of therapeutic use of murine monoclonal antibodies (IgG) or fragments, or who have known autoimmune disorders. Additionally, specimens with high levels of gamma globulins (>2.5 g/dL) may cause false elevation in results.

Galectin-3 appears to be a culprit biomarker that mediates the development of heart failure. Availability of the galectin-3 assay might enable the study and development of disease-modifying therapies to inhibit remodeling and stop the progress of heart failure.
REFERENCES