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Calcium-Binding Proteins and RAGE

From Structural Basics to Clinical Applications

Edited by

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Preface

A major direction in medical research leading to clinical applications targets the regulation of intracellular calcium and the various human diseases associated with an altered homeostasis of this global second messenger. These diseases include, for example, cardiomyopathy, inflammation, brain disorders, diabetes, and cancer.

After entering the cell, Ca^{2+} binds reversibly to specific Ca^{2+}-binding and sensor proteins that fulfill multiple cellular functions. The human genome contains over 200 genes coding for this large protein family, characterized by a common helix–loop–helix structural motif, the EF-hand.

In the 1960s troponin was discovered by Ebashi [1] as the first intracellular Ca^{2+}-sensor protein, regulating muscle contraction. Today highly sensitive cardiac-specific troponin assays are routinely used in most hospitals to diagnose patients with acute coronary syndrome (ACS).

Calmodulin interacts with more than 300 variable target sequences, regulating many biological functions. New strategies are described in this book to quantify calmodulin–target interactions. These techniques can be applied to analyze the interaction between any calcium-binding protein with its binding partner.

In 1971 muscle parvalbumin was the first Ca^{2+}-binding protein to have its amino acid sequence and 3D structure resolved. On this basis, Kretsinger developed the concept of the EF-hand structural motif [2]. Today parvalbumin is known as a marker of a subpopulation of GABAergic neurons in the brain and as a major food allergen sharing the allergenic potential of many other Ca^{2+}-binding proteins. Parvalbumin and S100A1, when introduced by gene therapy, are able to restore heart function in animal models.

These and other examples, included in this book, underline the diagnostic and clinical importance of this family of proteins in human diseases and as drug targets. For example, longistatin—a plasminogen activator from vector ticks (blood-sucking ectoparasites affecting humans and animals)—is a candidate for the development of anti-tick vaccines.

S100 proteins (first described by Moore;[3]) constitute the largest family within this EF-hand superfamily [4]. Most S100 genes are clustered on a region of human chromosome 1q21 (for nomenclature see: [5] and update [6]) that is prone to chromosomal rearrangements. Several S100 proteins are secreted, and they exert the role of cytokines through the activation of various cell surface receptors, e.g., the Receptor for Advanced Glycation Endproducts (RAGE), an immunoglobulin-like multi-ligand receptor for AGEs, amyloid beta peptides, HMGB1, TTR, and several S100 proteins. This receptor and its ligands are associated with Alzheimer's disease, inflammation and cancer. The interaction of RAGE with its ligands is described, using the Surface Plasmon Resonance (SPR) technology. Site-specific blocking of RAGE by specific inhibitors, antibodies, or selected peptides that target RAGE or its ligands is also described, using phage display technology. This approach is presently discussed as a therapeutic strategy to attenuate cell toxicity.

This volume is a collection of chapters written by leading experts in the field, containing state-of-the-art, lab-based methods and easy-to-follow protocols for daily use. These methods and techniques are generally applicable—after modifications—and are not restricted to Ca^{2+}-binding proteins and their targets.

Methods and protocols include:

Calcium-measurements, structural analysis, target binding, and localization: Intracellular Ca^{2+}-measurement in single cells using ratiometric calcium dyes; protein expression systems; equilibrium and flow dialysis and isothermal calorimetry to determine metal binding; isotope labeling of proteins for NMR analysis; crystallization and X-ray analysis using a synchroton source; fluorescence anisotropy; Surface Plasmon Resonance (SPR); Phage display selection; super-resolution light microscopy, and human cell line authentication.

Screening methods: HPLC-ES-MS analysis of body fluids; GST-pulldown to screen for novel Ca^{2+}-binding proteins; grafting approach with luminescence resonance energy transfer to search for viral Ca-binding motifs; primer extension microarray for the analysis of genes associated with disease ; in vivo screening of S100B inhibitors in melanoma.

Clinical Chemistry: Diagnostic and prognostic use of cardiac troponin; S100B as a biomarker for traumatic brain injury, certain neurodegenerative disorders, and malignant melanoma.

Therapy: In vivo S100A1 gene delivery to correct heart failure; Nesfatin and diagnosis and treatment of obesity.

I am very grateful to all contributors for making this volume interesting for basic and medical researchers, cell biologists, clinicians, clinical chemists, and the diagnostic industry. I am also thankful to my wife Erika Heizmann for her patience and understanding during the process of editing this book.

Zürich, Switzerland *Claus W. Heizmann*

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