3.11: Molecular Aspects of Calcium Ion-Regulated Intracellular Processes (Part 1)

So far we have mainly discussed the routes and means by which the concentration of Ca^{2+} ions in the cytoplasm can be transiently increased and brought back to resting levels. But changing the cytoplasmic Ca^{2+} concentration is not enough. In order to influence the cellular machinery, the Ca^{2+} ions must interact with different proteins, *intracellular Ca^{2+} receptors* if you like. These intracellular Ca^{2+}-receptor proteins must have certain properties in order to function.

i. Their Ca^{2+}-affinity must be such that their Ca^{2+}-binding sites are essentially unoccupied at resting levels of free Ca^{2+} (~10^{-7} M) and occupied at levels reached upon stimulus (generally assumed to be 10^{-5} to 10^{-6} M). This means that the binding constants K_B^{Ca2+} should be ~10^6 M^{-1}.
ii. We should also remember that Ca^{2+} must exert its function in the presence of a number of other ions; in mammalian cells the intracellular concentration of "free" Mg^{2+} ions is around 1 mM, and that of K^+ ions around 100 to 150 mM. The receptors must therefore have an adequate selectivity for Ca^{2+}.
iii. In response to Ca^{2+} binding, a Ca^{2+} receptor must undergo some kind of conformation change that either alters its interaction with other molecules or changes its activity if it is an enzyme.
iv. Finally, there are *kinetic* considerations. In many cells a rapid response is essential, and therefore the receptors must be able to interact swiftly—within milliseconds—with incoming Ca^{2+} ions, and the ions must also be able to depart almost as rapidly.

A few proteins have been discovered that qualify as intracellular Ca^{2+} receptors. The best known of these is *calmodulin* (CaM), which appears to be present in all eukaryotic cells. Most of the cellular responses elicited by Ca^{2+} appear to result from interactions between the Ca^{2+}-calmodulin complex and various other target enzymes and proteins.[75] Another important Ca^{2+}-receptor protein is *troponin C* (TnC), which occurs in muscle cells and is instrumental in mediating muscle contraction.[76] These two types of proteins are highly homologous, as we shall see, and may be considered members of a superfamily of closely related intracellular Ca^{2+}-binding proteins. This superfamily has been given the name "the calmodulin superfamily," and close to 200 distinct family members are presently known.[77] Not all members of the superfamily may qualify as Ca^{2+} receptors; some like *parvalbumins* and *calbindins* (see Section IV.A) appear to have a role in intracellular transport and/or Ca^{2+}-buffering. For others, such as the *S-100* proteins[78] found predominantly in brain tissue, and *calcimedins*,[79] isolated from smooth muscle, the biological function is still unclear.

One Ca^{2+} receptor with enzymatic activity is *protein kinase C*. Its activity is markedly increased in the presence of Ca^{2+}, and it has a high calcium-binding constant (see Table 3.2) in the presence of diacylglycerol or **phorbol esters**.[80]

During recent years, groups interested in the role of Ca^{2+} in secretion and in the control of membrane cytoskeleton have identified some intracellular Ca^{2+}/phospholipid-binding proteins that appear to be distinct from the calmodulin superfamily; these include *lipocortin*, *endonexin*, *calelectrin*, *p36*, and *calpactin*.[81-83] These membrane-binding proteins are collectively called *annexins*,[84] and contain repeated domains distinct from EF-hands. The Ca^{2+} sites are very similar to that observed in phospholipase A_2, as shown by the recently determined x-ray structure of annexin V.[172] A condensed overview of the interaction of Ca^{2+} with intracellular proteins is shown in Figure 3.16. We will now go on to discuss the molecular properties of some of the proteins mentioned above, starting with calmodulin.

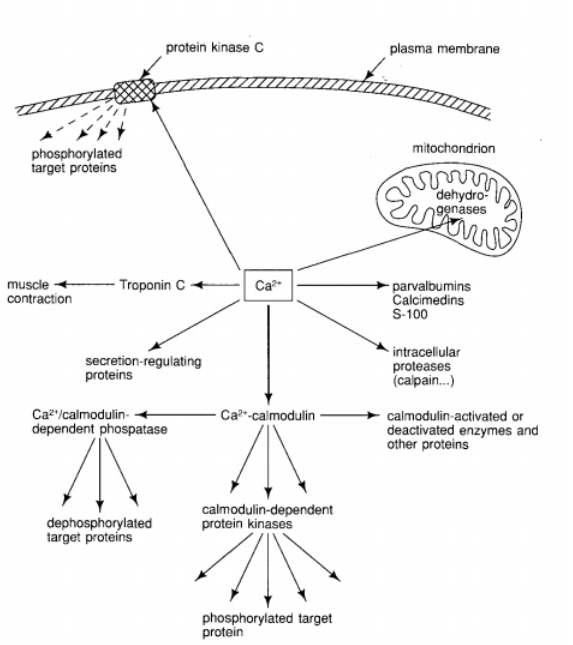

Figure 3.16 - Condensed overview of the interaction of Ca^{2+} with intracellular proteins.