Protein kinase CK2

More than 40 years ago Kennedy and Burnett isolated a phosphotransferase from liver extracts which does not fit into the scheme of all other kinases yet found. It was a heterotetrameric enzyme consisting of two catalytic α- or α´- and two regulatory β– subunits which preferred serine or threonine residues within acidic consensus sequences as targets and which could use GTP besides ATP as phosphate donor. Because of the preferred *in vitro* substrate the enzyme was called casein kinase II. Meanwhile, the name of the enzyme was changed to **protein kinase CK2** in order to meet all the diverse aspects of the kinase which is much more than phosphorylating casein. Among the more than 300 substrates discovered yet are a lot of proteins which are implied in transcription/translation, DNA replication/repair, proliferation and cell cycle control. The activity of some of these proteins is changed upon phosphorylation by protein kinase CK2. A peculiar feature of CK2 is that it not only acts as phosphotransferase but can also influence the biological activity of some proteins like topoisomerase I by pure interaction. Moreover, from recent work there is strong evidence that CK2 not only occurs as a tetrameric holoenzyme in the cell but also as individual subunits. Free α- as well as free β- subunits have been found in the cell responsible for selective functions.

Protein kinase CK2 is a highly conserved enzyme. It has been found from yeast to man and in all cells and tissues with a different expression level. Although its true function is not yet known life without CK2 is impossible. Yeast cannot survive when the catalytic α-subunit is deleted. Knocking out the regulatory β- subunit leads to a misshapen cell which has lost its polarity. Up to now only CK2 α´- knockout mice could be generated which show a normal phenotype except spermatogenesis. They suffer from oligospermia and the surviving sperms are deformed (globozoospermia). Also the α- and the β- subunit were deleted but no viable organisms or stable cell lines could be generated from the knock-out mice. On the other hand, overexpression of the catalytic subunit in cooperation with another oncogene leads to transformation of the cells. Overexpression of the β- subunit also leads to an altered phenotype.

These observations together with the fact that CK2 activity is enhanced in proliferating cells underline the importance of CK2 for the growth of a cell and an organism, respectively. Because of the significance of the enzyme there shall be no doubt that its activity has to be strictly regulated. But the regulation of the enzyme activity remains a mystery up today. None of the known second messenger molecules is able to regulate the activity of the kinase. It has been even proposed that the enzyme is constitutively active, but nobody has yet found the antagonist which may be regulated instead. Several attempts have been made to correlate the signalling induced by a growth factor to changes in expression and activity of the enzyme. In spite of a lot of different experimental approaches there is still uncertainty to attach the CK2 action to a single signal transduction pathway. In recent papers there is more and more evidence that CK2 interferes with the MAP kinase pathway, the NFκ B network or the wnt - signalling cascade. But, that is surely not the whole truth.

A potential means to regulate the activity of the enzyme is not only a timely co-ordination but also being at the right place at the right time. And indeed, CK2 changes the subcellular localisation upon addition of growth hormones from cytoplasm to nucleus, especially nuclear matrix but also nucleosomes and nucleolus, where it phosphorylates growth promoting substrates. But these locations are not the only ones where CK2 has been detected. CK2 is found in nearly each compartment of the cell starting with the plasma membrane where it acts as an ectoenzyme, mitochondria, endoplasmic reticulum, Golgi complex, cytoskeleton and centrosomes, which act as microtubuli organising centre MTOC. The localisation of CK2 at those cellular components which are indispensable to shape a cell and to help her to integrate into a tissue are mostly interesting, also for the aspect of transformation of a normal to a cancerous cell.

The occurrence of CK2 in nearly every compartment of the cell is possibly achieved by anchoring to diverse proteins. The appearance in a certain compartment of the cell might be regulated by events or factors not yet known. Brought to the right place CK2 fulfils most of its diverse functions by phosphorylation of specific substrates, thus leading to a changed biological activity of them. How protein- protein- interactions in these various compartments might also contribute to the regulation of CK2 activity remains to be elucidated.