EDITORIAL

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Protein Kinase CK2 and Angiogenesis

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Abstract

CK2 is an ubiquitously expressed protein kinase, which is composed of two catalytic α- and α'- and two non-catalytic β-subunits. CK2 protein levels and kinase activity is elevated in rapidly proliferating cells including cancer cells. There is increasing evidence that CK2 also plays an essential role in angiogenesis, either by interaction or phosphorylation of growth factors or by phosphorylation or binding to proteins in signalling cascades, which are implicated in angiogenesis. Over the last ten years a great number of inhibitors for CK2 were detected, two of them are now in clinical phase II trials for the treatment of cancer patients. Some of these inhibitors were also found to be active in the inhibition of angiogenesis. Thus, CK2 inhibitors probably together with inhibitors of other signalling molecules involved in angiogenesis might be powerful tools for the treatment of cancer and cancer connected angiogenesis (**Adv Clin Exp Med 2014, 23, 2, 153–158**).

Key words: protein kinase CK2, cancer, angiogenesis, retina, neovascularization.

In 1954, Burnett and Kennedy discovered protein kinase CK2, which was for a long time known as casein kinase II [1]. CK2 is a conserved, ubiquitously expressed serine/threonine protein kinase. CK2 exists as a holoenzyme consisting of two catalytic α- or α'-subunits and two non-catalytic β-subunits and as free CK2α, CK2α' or CK2β' subunits or associated with other cellular proteins. Although CK2α and CK2α' are encoded by two independent genes localized on two different chromosomes, the amino acid sequence shows a 90% sequence identity within the N-terminal 330 amino acids. The C-terminal domain, however, are completely different, with CK2α having a 20 amino acid sequence not present in CK2α' [2]. Experiments in yeast and mice have shown that CK2α and CK2β are essential for viability. CK2α' knockout mice are viable but male mice are sterile [3–8]. This observation suggests a functional specialization between CK2α and CK2α' where CK2α can at least partially compensate for the loss of CK2α'. Among other protein kinases CK2 has the unique ability to use ATP as well as GTP as phosphate donors. CK2 prefers phosphorylate serine or threonine residues within clusters of acidic residues. By examining a great number of substrates a minimal consensus sequence for CK2 has been defined as S/T-x-x-D/E [9]. CK2 seems to be regulated by its subcellular localization [10] and by binding to other cellular proteins or non-protein factors [11]. Since both, CK2α and CK2β are phosphorylated, it seems also reasonable that both are regulated by phosphorylation and dephosphorylation. Moreover, enzyme composition such as the CK2 holoenzyme or free CK2α and also oligomerisation to trimers or tetramers and higher oligomeric forms might be implicated in the regulation of CK2 kinases activity [12, 13].

CK2 is involved in several signalling pathways including cell proliferation, differentiation and apoptosis. Elevated levels of CK2 and an elevated protein kinase activity have been observed in various cancers including breast [14], prostate [15], kidney [16], colorectal [17], head and neck [18] and lung [19]. Rapid cell proliferation is in general associated with an overexpression of CK2, which favours the suggestion of CK2 as an anti-apoptotic factor. Down-regulation of CK2 in cancer cells either by antisense RNA, siRNA, overexpression of kinase-dead CK2 mutants or pharmacological inhibitors resulted in the induction of apoptosis [20–22].

Interestingly, the role of CK2 in normal, non-cancer cells is barely investigated. There is some indication that CK2 plays a role in spermatogenesis [8, 7, 23] as well as during certain stages of embryogenesis [24, 25]. Furthermore, it was shown by several groups that CK2 seems to be an important

protein kinase for a variety of different cellular processes in developing organs and organogenesis [5, 6, 26, 27]. In the differentiation of pre-adipocytes into adipocytes, CK2 was found to be accompanied by a decrease in the protein level and in the kinase activity [28, 29]. Inhibition of CK2 kinase activity at the beginning of the differentiation process prevented differentiation, whereas, inhibition of CK2 activity at later time points had no effect on the differentiation process, which indicates that CK2 only plays an early role in differentiation of pre-adipocytes into adipocytes [28]. There is another example where CK2 contributes to differentiation processes of cells. CK2 phosphorylates the DNA binding protein Ikaros [30, 31], a master regulator of hematopoiesis especially in the differentiation of thymocytes. Hyperphosphorylation of Ikaros by CK2 leads to its ubiquitin-mediated degradation and thus inhibits the Ikaros-dependent T cell differentiation. In addition, there is some indication that CK2 phosphorylation might regulate Ikaros stability and turnover [30]. Moreover, there is a large body of experimental evidence that CK2 plays a crucial role in self renewal, commitment and blood cell lineage specification by influencing signalling cascades such as the Wnt/β-catenin, the Hedgehog and PI3K/PTEN pathways [32–36].

A direct link of CK2 to the energy metabolism of cells is provided by the observation that CK2 activity and the CK2 protein expression level are elevated under hypoxic conditions. Moreover, CK2 regulates the hypoxia inducible transcription factor-1α (HIF-1α) activity [37]. It plays a regulatory role in the metabolism of carbohydrates and fatty acids (for review see [38]). Recently, CK2 was shown to be implicated in the regulation of insulin production in β-cells of the pancreas [39–41]. In addition, glucose regulates the subcellular localization and the activity of CK2 supporting the idea about an active role of CK2 in cell metabolism [41].

Angiogenesis plays a critical role in human physiology that ranges from reproduction and foetal growth to wound healing and tissue repair. It is a multistep process which has to be tightly regulated in a spatial and temporal manner between various factors, extracellular matrix components and endothelial cells. According to the multitasking of CK2 mentioned in the introduction to this review, it is not surprising that CK2 also plays an essential role in angiogenesis.

CK2 and Angiogenesis

Angiogenesis is the growth of new capillaries from existing blood vessels. Angiogenesis can be a hallmark of wound healing, the menstrual cycle, cancer growth and various ischemic and inflammatory diseases. Furthermore, tumour growth is associated with new blood vessel formation. Since CK2 is elevated in tumours and plays a role in antiapoptotic signalling, it was an open question whether CK2 might also play a role in the vessel formation in tumours or other rapidly proliferating tissues. Endometriosis is a frequent gynaecological disease, which depends crucially on angiogenesis, supplying endometriotic lesions with oxygen and nutrients. It was recently shown that inhibition of the CK2 kinase activity suppresses vascularization of developing endometriotic lesions [42]. Blood vessel formation in endometriotic lesions is a complex process which is driven by angiogenic growth factors such as the vascular endothelial growth factor (VEGF), the fibroblast growth factor (FGF) and the platelet derived growth factor (PDGF). Interestingly, it was shown that phosphorylation of the Proline-Rich-Homeo domain protein PRH by CK2 inhibits the DNA binding activity of PRH. This inhibiting effect of PRH on genes encoding components of the VEGF signalling pathway is abrogated by CK2 phosphorylation [43] indicating that VEGF may be one target of CK2 in regulating angiogenesis. It was also recently shown that oxidized phospholipids induced the expression of VEGF in foetal human retinal pigment epithelial (RPE) cells [44]. Inhibition of CK2 in these primary RPE cells resulted in a significant inhibition of the upregulation of VEGF by oxidized phospholipids [45] further supporting the idea that CK2 is acting via VEGF in the process of angiogenesis.

Another growth factor, which is implicated in angiogenesis, namely FGF is known for quite some time as a binding partner of the regulatory CK2β subunit. Moreover, this binding of FGF to CK2β stimulates CK2 kinase activity at least towards nucleolin as a substrate [46]. Later on, it was shown that FGFs are substrates for CK2 [47]. It was also shown that PDGF, the other growth factor implicated in angiogenesis, is phosphorylated by CK2. The CK2 phosphorylated form of PDGF has an elevated anti-angiogenic activity [48, 49]. Recently, it turned out that PDG induced the CK2α' subunit expression [50].

Very similar results were reported for the pigment-epithelium-derived factor (PEDF). PEDF phosphorylated by CK2 exhibited a strong anti-angiogenic activity [49]. Most of these experiments were performed with glutamic acid mutants, which mimic CK2 phosphorylation indicating that a negative charge at the CK2 phosphorylation sites is sufficient for the anti-angiogenic activity.

The transforming growth factor β (TGF-β) superfamily of proteins is implicated in the regulation

of cell proliferation, differentiation, embryonic development, wound healing and angiogenesis [51]. In most tissues, TGF-β proteins signal through a family of related TGF-β receptors. In endothelial cells, TGF-β proteins also signal through activitin like kinase 1 (Alk-1). Alk-1 null mice exhibit embryonal lethality due to vascular defects [52]. It was shown that CK2β specifically interacts with Alk-1 and by this interaction enhances Alk-1 signalling. This finally results in an inhibition of endothelial cell migration [53]. These functions of CK2β are consistent with its binding to and regulation of other serine/threonine kinases including Mos [54], A-raf [55] and Chk-1 [56].

Retinal neovascularization and angiogenesis play essential roles in a disorder called proliferative diabetic retinopathy (PDR) which occurs in response to insufficient tissue oxygenation. A variety of growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), insulin like growth factor-1 (IGF-1) and the platelet-derived growth factor (PDGF) are implicated in the retinal neovascularization of proliferative diabetic retinopathy. All these growth factors were already identified as interaction partners or substrates for CK2.

In addition to its interaction with various growth factors which are implicated in angiogenesis, CK2 can phosphorylate many key signalling molecules that are mediating the action of angiogenic growth factors. By phosphorylating [57–59] or interacting with Akt [60, 61], CK2 can modulate the activity of several angiogenic mediators simultaneously. Furthermore, CK2 is acting upstream of ERK1/2 and p38 MAPK and might thus also modulate the MAP kinase pathway, which is initiated by VEGF and IGF-1 [62, 63]. Interestingly, it was also shown than CK2 can modulate HIF-1α either directly [64, 37] or by the phosphorylation of the HIF-1α interacting VHL protein [65].

In order to develop strategies for the treatment of diseases, inhibitors of CK2 were tested. Two CK2 inhibitors, namely emodin and tetrabromobenzotriazole (TBB), were found to significantly reduce retinal neovascularization [66]. Later on, it was tested whether the effect of CK2 inhibitors would be enhanced if they were contributed with other anti-angiogenic drugs with a different mode of action. A significant increase in inhibition of angiogenesis was observed with a combination of the somatostatin analogue octreotide in combination with TBB [67]. In a subsequent study, it was shown that bone marrow derived human stem cells injected into the vitreous of neonatal mice can incorporate into the retinal neovasculature. Administration of a CK2 inhibitor significantly reduced this incorporation [68]. Thus, beside its impact on the growth factors, CK2 may interfere with human stem cell recruitment during angiogenesis.

Recently, CK2 was found to be co-localized with F-actin containing stress fibres in the microvascular endothelial cell [69]. In a follow-up study, it was shown that inhibition of CK2 leads to a reduction of CK2 at the stress fibres. These results suggest a role of CK2 in the control of cell contractility and motility which may account for the suppressing effect of inhibition of CK2 on retinal neovascularization [70]. Using a completely different type of CK2 inhibitor, namely the cyclic peptide CIGB-300, it was recently shown that CK2 inhibition leads to an inhibition of the migration capability of human umbrical vein endothelial cells (HUVEC) and a reduced formation of capillary-like tube structure [71]. These newly developed very specific CK2 inhibitors open new windows for the treatment of cancer cells. Not only does CK2 inhibition results in the induction of apoptosis in various cancer cells, but, as presented here, it additionally becomes evident that CK2 inhibition also leads to a retarded or blocked angiogenesis. Moreover, combination therapies with CK2 inhibitors and other drugs such as octreotide was shown to be significantly more efficacious in inhibiting retinal neovascularisation than either drug alone [67]. Another study has also shown a synergistic blocking effect on ocular neovascularisation by inhibitors of VEGF and PEDF-B signalling [72]. Based on new and potent CK2 inhibitors, optimal drug combinations may soon emerge for the efficient treatment of cancer cells. They have to be tested for safety and clinical trials.

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