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Addiction to protein kinase CK2: A common denominator of diverse cancer cells?

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ABSTRACT

At variance with most oncogenic protein kinases whose malignancy is generally due to genetic alterations conferring constitutive activity, CK2 is a highly pleiotropic Ser/Thr protein kinase naturally endowed with constitutive activity and lacking gain-of-function mutants. Nonetheless CK2 is abnormally elevated in a wide variety of tumors and there is strong evidence that it operates as a cancer driver by creating a cellular environment favorable to neoplasia: notably, CK2 plays a global role as an anti-apoptotic and pro-survival agent, it enhances the multi-drug resistance (MDR) phenotype, it assists the chaperone machinery which protects the "onco-kinome" and it promotes neo-angiogenesis. Based on this scenario we propose that the implication of CK2 in neoplasia is an example of "non oncogene addiction", i.e. over reliance of the perturbed cellular signaling network on high CK2 level for its own maintenance. Consistent with this, an ample spectrum of diverse types of cancer cells have been already shown to rely on high CK2 level for their survival, as judged from their response to specific CK2 inhibitors and silencing of endogenous CK2 catalytic subunits. Remarkably, among these are cells whose cancer phenotype arises from the genetic alteration of onco-kinases (e.g. Abl and Alk) different from CK2 and insensitive to the CK2 inhibitors used in those experiments. Based on these premises, CK2 could represent a "multi-purpose" target for the treatment of different kinds of tumors.

1. Introduction

A rising concept in molecular medicine is that most human diseases are related to communication disorders, due to alterations in signaling pathways. This gave rise to the neologism *Signal Transduction Therapy* (STT) to denote strategies aimed at counteracting the pathological consequences of such alterations. Whenever applicable, protein kinases are the first choice targets in STT because they are enzymes, thus their catalytic activity can be readily and effectively turned off by active site-directed inhibitors which are respectful of the overall conformation of the kinase. This latter, therefore, in its inhibited form, is acting as a dominant negative with respect to the active molecules thus contributing to the amplification of the inhibitory effect, and possibly accounting for the observation that sometimes the in vivo efficacy of the kinase inhibitors is greater than it would be expected based on the degree of inhibition of the target kinase [1].

Of course, in order to make sense as a drugable target, a kinase needs not only to be susceptible to (a) potent, selective and cell permeable inhibitor(s): firstly and more importantly its activity must be relatable to a cell dysfunction. This is quite often the case of protein kinases whose unscheduled and/or abnormally elevated activity is among the major causes of global diseases, with special reference to cancer.

As a general rule in fact protein kinases are normally silent enzymes whose activity is turned on only in response to specific stimuli. However, a number of genetic alterations can occur which bypass the physiological mode of activation of a given kinase, giving rise to a constitutively active enzyme no more subjected to its physiological mechanism of control. The molecular alterations that interfere with protein kinase activities and are causative of cancer might be several, including gain/loss of function and gene deletion (as in the cases of Map kinase kinase 3 [2] or some specific PKC isoforms [3]); collectively taken, the involved kinases are usually referred to as "oncokinome". Among them, several examples are known of protein kinase whose pathogenic mutations promote uncontrolled and/or untimely activation. These represent the majority of the "drugable kinome", i.e. that proportion of the kinome whose members have been related to human diseases. The size of the drugable kinome, already including now-a-days more than 150 members [4], is continuously increasing, consistent with the concept that protein kinases alone make up >22% of the drugable genome [5], although they are encoded by less than 2% of the human genome [6].

Abbreviations: ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; MDR, multi-drug resistance; MM, multiple myeloma; NF-kB, nuclear factor-kB; PDK1, 3′-phosphoinositide-dependent kinase-1; PI3K, phosphatidylinositol-3 kinase; PIP2, phosphatidylinositide 4,5-diphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate; PML, promyelocytic leukemia gene; PTEN, phosphatase and tensin homolog deleted on chromosome 10; PTK, protein tyrosine kinase; STT, signal transduction therapy

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Among genetic alterations conferring oncogenic properties to protein kinases, the consequences of translocations giving rise to fusion proteins with the tendency to aggregate are particularly well documented [7]. This mimics, under basal conditions, dimerization followed by trans-autophosphorylation and activation, normally occurring only upon binding of the agonist to the extra-cellular moiety of the receptor protein tyrosine kinase. This mechanism underlies the generation of several known oncogenic kinases, individually responsible for specific malignancies, exemplified by Chronic Myeloid Leukemia (CML) and Acute Lymphoblastic Leukemia (ALL), caused by the generation of two different constitutively active forms of the prototype of oncogenic protein tyrosine kinases (PTKs), Abl. This case is particularly popular also because the development of an Abl inhibitor, Gleevec (Imatinib), represented the first and most spectacular example of STT [8]. By similar gene translocation mechanism, the chimeric constitutively active forms of other PTKs are generated for which a cause/effect relationship with specific tumors could be established. Sometimes, the genetic alterations responsible for malignancy are instead point mutations or even gene amplification, this latter being responsible for increasing the level of the protein kinase and therefore of its basal activity without any obvious alteration in its regulatory properties.

Quite often, the relatedness of a specific tumor to the abnormal activity of a given kinase is not as straightforward as in the case of Abl or Alk, and it may hardly conform to the simplistic paradigm: "one mutated kinase, one type of tumor". Rather, bearing in mind that cancer is a multifactor disease and that malignant growth requires the concomitant occurrence of a substantial number of alterations in cell physiology [9], it is conceivable that an individual kinase might contribute to the onset of different kinds of tumors.

In this respect, the most intriguing example is provided by the prototype of "constitutively active" protein kinases, CK2. This acronym, derived from the misnomer "casein kinase 2", denotes a ubiquitous, Ser/Thr specific, acidophilic kinase, whose catalytic subunits (α and/or α') are in their active conformation in the absence of any previous phosphorylation and either combined or not with a dimer of its non-catalytic β-subunit (reviewed in [10,11]). Owing to such an uncommon lack of strict control, presumably reflecting its terrific pleiotropy [12] CK2 does not conform to the general paradigm outlined above, merely because only active forms of it apparently exist: although a molecular model of polymerized CK2 has been proposed as a putatively inactive and regulatable enzyme [13], no evidence for the in vivo existence of this or other inactive forms has been provided so far. In addition, mutations causing a gain-of-function of CK2 have never been reported, while its physiological concentration in yeast is one of the highest found of a protein kinase [14], suggesting that also in human cells CK2 might be one of the more represented kinases.

Collectively taken these properties would argue against the possibility that unscheduled CK2 activity might be causative of neoplasia. In sharp contrast with this expectation, however, we have to admit that arguments supporting the implication of CK2 in cancer are numerous, sound and convincing.

2. CK2 as a cancer driver

Although it is hardly conceivable that untimely activation of CK2 due to genetic alterations might be causative of malignancy per se, many arguments support the notion that, whenever CK2 reaches a critical threshold, it may become a cancer driver, to mean that it creates an environment particularly susceptible to the development of tumor phenotype. Some of these arguments are merely coincidental, nevertheless they strongly suggest that cells where CK2 activity is stochastically higher than average will afford a number of selective advantages to the tumor.

Remarkably, CK2 level has been found to be invariably higher in malignant cells [15–17] than it is in normal cells of the same type, every time a reliable comparison of this kind could be done. In hindsight it is felt now-a-days that such elevated CK2 is neither the cause nor the consequence of neoplastic transformation while it may well reflect the tendency of the tumor, regardless of the genetic accidents causing it, to preferentially "colonize" those cells where CK2 is higher. This seems also to reflect in a correlation between the grading of the malignancy and the level of CK2: the higher is this latter, the worse the prognosis is [16]. Fig. 1 schematically illustrates some of the effects promoted by abnormally high CK2 level which is found in the majority of cancer cells. Part of this information was obtained by treating cells with fairly selective CK2 inhibitors (reviewed in [18,19]). In some cases, however, the implication of CK2 was confirmed by either challenging the efficacy of the inhibitor with CK2 mutants refractory to inhibition, or was assessed by alternative approaches. Looking at Fig. 1, it appears that high CK2 activity is favoring neoplastic growth in several respects: it enhances the transforming potential of oncogenes [20,21]; it stabilizes most of the onco-kinome through phosphorylation of the co-chaperon CDC37 which is critical to preserve many onco-kinases in their active conformation [22]; it counteracts the efficacy of anti-tumor drugs, notably of imatinib [23] and melphalan [24]; it contributes to the multi-drug resistance phenotype [25]; it supports neo-vascularization [26] and, most importantly, it generates an ample spectrum of pro-survival signals whose selective advantage is particularly evident for those tumors whose phenotype is largely dependent on defective apoptosis. Many of these functions, notably persistency of growth signals, evasion of apoptosis, sustained angiogenesis, are among those essential alterations in cell physiology which collectively dictate malignant growth [9].

At variance with other protein kinases whose role in apoptosis may substantially vary depending on the type of cells and their metabolic conditions, CK2 always behaves as an anti-apoptotic agent impinging on different cellular functions, signaling pathways and biochemical reactions – summarized in Table 1 – which, at a cursory glance, may look unrelated among each other, while they ultimately cooperate to promote cell survival. These include some very general functions required for normal cell growth and proliferation, such as promotion of rRNA and tRNA biogenesis, but also more specific interventions on signaling pathways crucially implicated in determining call fate (notably the PI3K/Akt, NF-κB and Wnt pathways) and on biochemical events, such as DNA repair and caspase inactivation which are deeply affecting programmed cell death.

As schematically illustrated in Fig. 2, CK2 is a multisite regulator of both the NF-κB and the Wnt signaling pathways, its effect being in both cases an enhancement of the transcriptional activity which is essential to regular development, but, if untimely reactivated, can also lead to oncogenesis (reviewed in [32]). More in details, NF-κB is normally sequestered in the cytosol by the binding to its inhibitor IκB, whose proteolytic degradation is therefore required before NF-κB is released, translocates to the nucleus, and functions as transcription factor for anti-apoptotic and pro-proliferative genes. CK2 acts at different levels

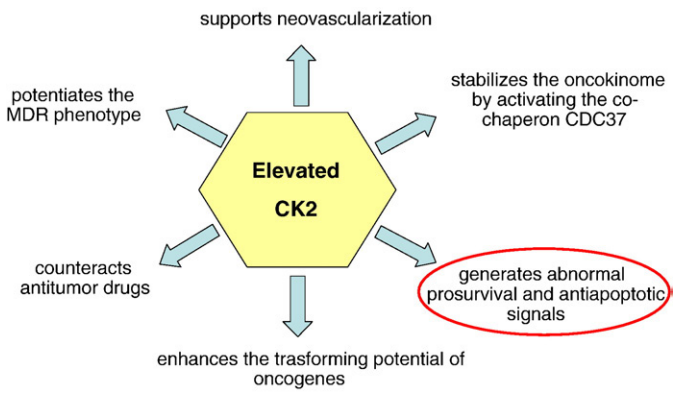

Fig. 1. Effects promoted by abnormally high CK2 levels.