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REVIEW

Protein kinase CK2 in breast cancer: the CK2β regulatory subunit takes center stage in epithelial plasticity

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Abstract Structurally, protein kinase CK2 consists of two catalytic subunits (α and α′) and two regulatory subunits (β), which play a critical role in targeting specific CK2 substrates. Compelling evidence shows the complexity of the CK2 cellular signaling network and supports the view that this enzyme is a key component of regulatory protein kinase networks that are involved in several aspects of cancer. CK2 both activates and suppresses the expression of a number of essential oncogenes and tumor suppressors, and its expression and activity are upregulated in blood tumors and virtually all solid tumors. The prognostic significance of CK2α expression in association with various clinicopathological parameters highlighted this kinase as an adverse prognostic marker in breast cancer. In addition, several recent studies reported its implication in the regulation of the epithelial-to-mesenchymal transition (EMT), an early step in cancer invasion and metastasis. In this review, we briefly overview the contribution of CK2 to several aspects of cancer and discuss how in mammary epithelial cells, the expression of its CK2β regulatory subunit plays a critical role in maintaining an epithelial phenotype through CK2-mediated control of key EMT-related transcription factors. Importantly, decreased CK2β expression in breast tumors is correlated with inefficient phosphorylation and nuclear translocation of Snail1 and Foxc2, ultimately leading to EMT induction. This review highlights the pivotal role played by CK2β in the mammary epithelial phenotype and discusses how a modest alteration in its expression may be sufficient to induce dramatic effects facilitating the early steps in tumor cell dissemination through the coordinated regulation of two key transcription factors.

Keywords Protein kinase CK2 catalytic subunit (CK2α) · Protein kinase CK2 regulatory subunit (CK2β) · Substrate specificity · Asymmetric subunit expression · Glycogen synthase kinase 3 beta (GSK3β) · Epithelial-to-mesenchymal transition (EMT) · Zinc finger protein Snail1 · Forkhead box protein C2 (Foxc2) · Homeobox protein SIX1 · Hallmarks of cancer

Introduction

Protein kinase CK2 shares a quaternary structure composed of catalytic and regulatory subunits with few other protein kinases. Two catalytic subunits (α or α′) associate with a dimer of regulatory β subunits, which do not share homology with any other regulatory subunit of protein kinases [1, 2]. CK2 is a multifunctional, ubiquitously expressed, protein kinase with the unusual ability to phosphorylate serine, threonine, and tyrosine residues within clusters of acidic residues [3, 4]. It has been estimated that this kinase might be individually responsible for the generation of a substantial fraction of the eukaryotic phosphoproteome [5]. At the molecular level, CK2

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participates in hierarchical phosphorylation signaling as either a priming or primed protein kinase for the phosphorylation of key protein substrates (reviewed in [6]). Although a few studies have shown that extracellular stimuli can modulate CK2 activity [7–10], most of the data suggest that this kinase is acting as a "lateral signaling player" on numerous signaling pathways that are critical for cell proliferation, differentiation, and apoptosis. This means that cellular responses such as proliferation, growth, and survival will be potentiated by CK2, while a death signal will be dampened. Following a brief overview of what is known about the contribution of CK2 to several aspects of transformation and cancer, we discuss the biological consequences of the multi-subunit structure of CK2 and consider the pivotal role of its regulatory CK2β subunit in targeting specific protein substrates. Building on this, we focus our discussions on recent evidence that shows the critical role played by CK2β and the dramatic consequences of its perturbation in the regulation of epithelial cell plasticity. Finally, we discuss how unbalanced expression of CK2 subunits in breast carcinoma could participate in the molecular circuits propagating the tumor phenotype.

Protein kinase CK2 and the "hallmarks of cancer"

Historically, a large number of growth-related proteins have been identified as CK2 substrates, suggesting their role in growth-related functions [11–16]. Accumulating observations also support the view that CK2 is a component of regulatory protein kinase networks that are involved in several aspects of transformation and cancer illustrating the extreme complexity of CK2 functions. These data have been widely reviewed in the literature [2, 17, 18]. Despite the demonstration in transgenic mouse models of a causative role of CK2α overexpression in hematopoietic and mammary oncogenesis [19–23], CK2 does not conform to the definition of oncogene since there is no evidence of point mutations in CK2 giving rise to tumors. However, a recent study revealed that mutated CK2α in association with 34 other mutated genes confers cancer resistance to immune attack [24]. Furthermore, other studies have also pointed out the frequent copy-number alteration of all CK2 genes in several malignancies [25]. Yet, there is a wealth of evidence that CK2 plays a major role in tumorigenesis, by enhancing the transforming potential of oncogenes and acting as an antiapoptotic molecule [14, 26–28]. Accordingly, elevated CK2 expression associated with high activity is a common denominator in the majority of cancers and is associated with aggressive tumor behavior [29–32]. The reliance of malignant cells on CK2 functions, which underlines a phenomenon defined as "non-oncogene addiction" [33], has been thoroughly reviewed by Ruzzene and Pinna [14]. How CK2 alterations contribute to cancer development is an important and challenging question. Although beyond the scope of the present article, it is noteworthy that a review of the literature discloses that CK2 participates to the regulation of many of the same cellular responses that characterize the "hallmarks of cancer" originally described by Hanahan and Weinberg [34, 35]. Indeed, CK2 both activates and alleviates the expression of a number of proteins essential for proliferation [9, 11, 13, 18, 28, 36–45]; evading growth suppressors [39, 41, 46–57]; avoiding immune destruction [58, 59]; enabling replicative immortality [8, 60–66], tumor-promoting inflammation [67–74], invasion, and metastasis [22, 23, 29, 31, 56, 66, 72, 75–95]; inducing angiogenesis [29, 96–106]; regulating genome instability and mutation [25, 40, 57, 107–142]; resisting cell death [26, 30, 108, 143–160]; and deregulating cellular energetics [161–166], all relevant for cancer progression (Fig. 4). Therefore, it is conceivable that modest alterations in CK2 activity and/or protein levels can influence the acquisition and maintenance of the emerging cancer hallmarks in several different ways. In light of these observations, CK2 has evidently emerged as an attractive candidate for molecular targeted cancer therapy. Numerous publications in this area have been summarized in several reviews [2, 12, 167]. Importantly, an orally available small molecule inhibitor of CK2 (CX-4945) that promotes an anti-proliferative and anti-angiogenic response in mouse cancers has recently entered Phase II clinical trials as a potential anticancer drug [168–170].

CK2 as an atypical protein kinase

The CK2 holoenzyme can exist in $\alpha_2\beta_2$, $\alpha\alpha'\beta_2$, or $\alpha'_2\beta_2$ configurations and has a low dissociation constant around 4 nM, which is a characteristic of strong heterocomplexes [171]. Unlike many signaling protein kinases, CK2 is constitutively active, independent of second messengers or phosphorylation events, and there is not yet a recognized potential model to explain how this kinase is regulated within cells. However, mounting evidence suggests that it can be regulated through mechanisms such as local recruitment into complexes or intracellular compartmentalization [142, 172, 173]. In addition, the individual CK2 subunits might also play independent functions on their own [20, 45, 174–176]. In the early 1990s, Stigare et al. [177] first reported in an epithelial *Chironomus* cell line that most of the catalytic α-subunit was tightly bound to nuclear structures in the absence of its β-subunit counterpart. In addition, free monomeric CK2α is relatively common in plants, and several reports have

provided evidence for an unbalanced expression of CK2α and CK2β subunits in different mammalian tissues [178–180]. The dynamic properties of the molecular interaction between CK2 subunits were first revealed in living cells, by the observation of individual CK2 subunits on a short timescale using live-cell fluorescent imaging [45]. This study provided evidence of the independent movement of CK2α and CK2β in cells, showing that the majority of the two subunits are not present in a permanent holoenzyme. This apparent difference in mobility was also evident at the level of their nuclear translocation: each CK2 subunit enters the nucleus as distinct subunits rather than as a preassembled holoenzyme. Cellular and structural data configure the CK2 holoenzyme either as a strong transient or permanent complex [171]. Dissociation of the tetrameric CK2 complex in living cells has been postulated. However, the presence of noninteracting CK2 subunits within cells cannot result from the spontaneous dissociation of the complex. Rather, it can be hypothesized that at any one time, CK2 subunits can interact with each other and/or with specific partners to participate in the transient formation of distinct multimolecular complexes. In this scenario, CK2 activity may be subtly modulated by a variety of interchangeable partners. Accordingly, the CK2β subunit was characterized as a regulatory binding partner of several important protein kinases, including A-Raf, c-Mos, p90rsk [178], PKCζ, the checkpoint kinase Chk1 [181], the cell cycle Wee1 kinase [182], and the activin receptor-like kinase ALK1 [98]. Together, these data supported the view that CK2β may act as a scaffold to coordinate the regulation of kinases distinct from CK2, offering intriguing new prospects for understanding its implication in different signal transduction pathways [175].

A protein kinase on the move

As a signaling protein, CK2 appears as a moving enzyme that could be rapidly recruited to target specific nuclear proteins in response to different stress stimuli such as heat shock [183], ionizing radiation [184], hypoxia [104–106], DNA breaks [142, 172], viral infections [185–188]. Importantly, compelling evidence accumulate showing that alterations in the subcellular localization of CK2 subunits contribute to cancer development and are correlated with clinicopathological parameters. This is especially the case in prostate and colorectal cancers where enhanced nuclear localization of CK2α has been reported to correlate with poor prognostic factors [76, 189, 190]. Early immunocytochemical studies have shown that CK2 is mostly detected both in the cytoplasm and the nucleus of most cells. However, there are also evidence that CK2 can be targeted to plasma membranes to regulate ion channel activity [191–193] and the phosphorylation of various membrane-bound proteins [194–196]. JAK family tyrosine kinases bind to cytokine receptors and are activated upon cytokine binding. Activated JAKs are crucial in transmitting signals through activation of the key downstream transcriptional effector STAT3. However, activating mutations in JAK2 are frequently observed in the majority of patients with myeloproliferative disorders, with the most common mutation being V617F, resulting in constitutive activation of the JAK-STAT signaling pathway. Zheng et al., provided the first evidence that CK2 binds to JAK2 and is critical for activation of the JAK2-STAT pathway in response to cytokine stimulation and also for constitutive activation of JAK2 in cells expressing JAK2 V617F [70]. Importantly, pharmacological CK2 inhibition decreases proliferation and induce apoptosis in cells expressing JAK2 V617F raising the possibility that CK2 inhibitors might be potent inhibitors of constitutively activated JAK2 V617F and downstream pathways.

Critical role of CK2β in targeting specific CK2 substrates

Unlike the regulatory subunit of other hetero-oligomeric kinases, the CK2β subunit is not required for the activity of the catalytic subunits. Both the isolated CK2α subunits and the holoenzyme are endowed with constitutive activity. However, binding of the regulatory subunit to CK2α results in the phosphorylation of a range of substrates that are not or are only weakly phosphorylated in its absence. In contrast, a limited number of protein substrates are phosphorylated by the noncomplexed catalytic subunit but not by the holoenzyme [197, 198] (Fig. 1). Interestingly, it has been reported that the tight association between CK2 and some of its substrates is often bridged by the CK2β dimer [2, 39, 78, 80, 122, 199–201]. This means that any change in CK2β expression might lead to a shift in the balance of phosphorylated CK2α- and holoenzyme-specific substrates. Furthermore, since CK2 substrates localize in many different subcellular compartments, a dynamic rather than a static interaction of the CK2 subunits may help adjust the kinase specificity to ensure that the relevant form of the catalytic subunit is present at each of these locations. To fine-tune these activities, it is likely that cells have developed specific mechanisms to actively segregate the CK2 subunits or to differentially downregulate their expression. Very little is known about the kinetics of the assembly of CK2 subunits into intact cells, a process that could be controlled by interactions with other cellular proteins. This raises the possibility that CK2α could be locally and transiently recruited into multimolecular complexes in which the CK2β dimer serves as a scaffold or a

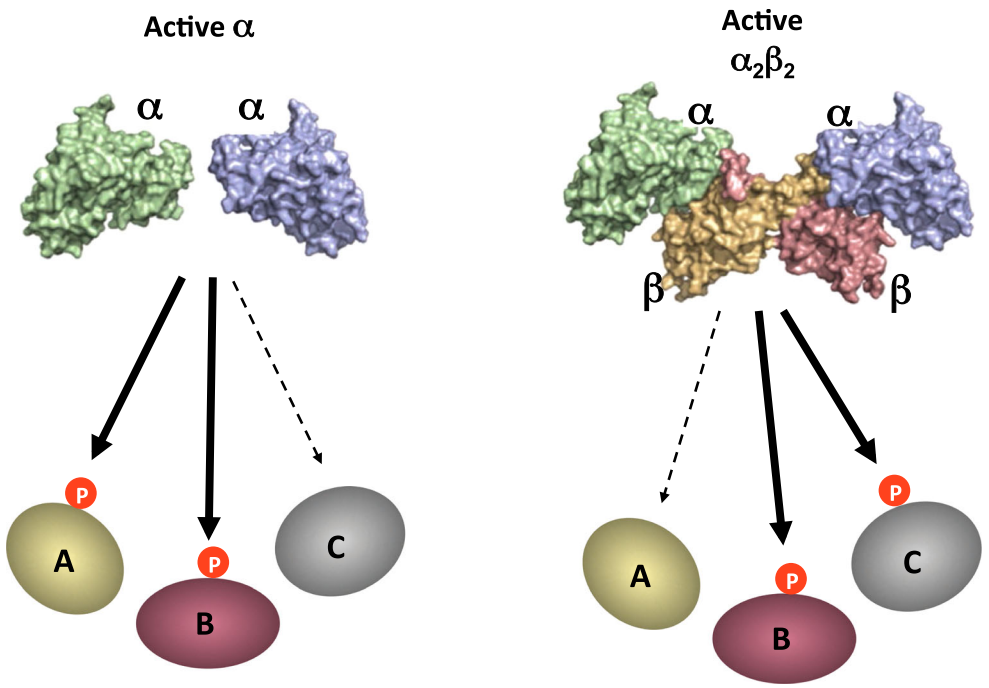

Fig. 1 Role of CK2β in targeting CK2 substrates. CK2 substrates can be phosphorylated by the noncomplexed CK2α subunits (e.g., substrate A). Binding of the regulatory CK2β subunit to CK2α results in the phosphorylation of a range of substrates that are not, or are only weakly, phosphorylated in its absence (e.g., substrate C), whereas other proteins can be equally phosphorylated by the isolated CK2α subunits or by the holoenzyme (e.g., substrate B). This model suggests that any change in CK2β expression may lead to a shift in the balance of phosphorylated CK2α- and holoenzyme-specific substrates

docking subunit through high-affinity interactions with substrate or non-substrate protein partners [174, 198, 200]. Alternatively, it has been suggested that upon activation of Src family kinases, a pool of CK2α not associated with the β-subunits becomes tyrosine phosphorylated with a resultant increase in its activity toward a subset of specific substrates [202]. Altogether, it can be predicted that such mechanisms might be crucial in the control of the many cellular processes that are governed by this pleiotropic kinase.

Dysregulation of CK2 in mammary tumorigenesis

Early studies postulated that CK2 could contribute to breast cancer carcinoma development because enforced overexpression of CK2α in the mammary gland of transgenic mice promotes hyperplasia and neoplasia in this organ [82, 203]. Moreover, upregulation of CK2 protein and activity was observed during the development of DMBA-induced mammary tumors [204]. In mouse models, CK2 cooperatively promotes oncogenesis and tumor progression with overexpression of oncogenes such as c-myc [205] or with loss of tumor suppressors such as p53 [19, 21, 206]. Later on, studies have shown that human breast cancer tissues contain high CK2 catalytic activity usually correlated with CK2 overexpression, suggesting a pathologic relationship between CK2 expression and mammary tumorigenesis [82]. Because of the importance of subgroup classification based on a tumor's biology and clinical behavior, Giusiano et al. evaluated the prognostic significance of CK2α expression in association with various clinicopathological parameters in a large cohort of breast tumor patients. This study demonstrated a strong association between CK2α overexpression and breast tumor aggressiveness, highlighting this kinase as an adverse prognostic marker [29]. Furthermore, at the mRNA level, both CK2α and CK2β are elevated and associated with a poor survival prognosis [25, 30]. This is consistent with two studies that have identified CK2 as a component of an "invasiveness gene signature" predictive of metastasis and poor survival in breast cancer [32, 88]. Clinically, breast tumors have been categorized into three basic therapeutic groups: oestrogen receptor (ER+), ERBB2 expressing (HER2+) and triple-negative breast cancers (TNBCs) lacking expression of ER, progesterone receptor (PR) and HER2. A recent analysis of transcript expression for CK2 subunits revealed significant levels of both CK2α and CK2β overexpression but strong CK2α′ underexpression in all breast cancer subtypes, features that were correlated with lower survival rates [30]. Although a correlation between transcript and protein deregulation remains to be addressed, these data suggest

that deregulated CK2 gene transcript expression may be a mechanism underlying the increased CK2 activity and protein levels detected in specific breast tumor subtypes.

CK2 contribution to the epithelial phenotype

Epithelial cells usually exist as sheets of immotile, tightly packed, polarized cells with distinct apical, basal, and lateral surfaces. Remarkably, these cells can dramatically alter their morphology, losing their epithelial apicobasal polarity to become motile, fibroblast-like mesenchymal cells in a process of epithelial–mesenchymal transition (EMT). In the early steps, aberrant reactivation of EMT in cancer epithelial cells may facilitate the dissemination of tumor cells and the generation of cancer stem cells, fueling both initiation and metastatic spread [207–210].

There is compelling evidence for the multiple functional contributions that CK2 makes to maintain the epithelial phenotype and polarity [211–213]. In particular, studies have suggested its implication in the regulation of the actin cytoskeleton via phosphorylation of the Wiskott-Aldrich syndrome protein (WASP) [214]. CK2 is also required for proper microtubule organization to facilitate neurite outgrowth in neuroblastoma cells [215], documenting the potential role of CK2 in the regulation of cell polarity and morphology. Although CK2α activity and expression were found to be upregulated in breast tumors, the contribution of CK2β to this dysregulation has not been explored [29, 82]. A differential expression of CK2 subunit transcripts was observed in Basal and Luminal A molecular subtypes. Interestingly, Luminal A were depleted for CK2β transcripts while higher expression of all three subunits was observed in Basal subtype [25]. Analysis of CK2 subunits at the protein level in breast tumor samples showed that whereas most samples expressed equivalent amounts of catalytic and regulatory subunits, their ratio was unexpectedly deviant in a subset of samples. Importantly, these clinical breast tumor samples displayed high concordance between CK2β underexpression and EMT markers, emphasizing the coupling between an asymmetric expression of CK2 subunits and EMT in vivo [80].

Mechanistically, EMT appears to be a dynamic process, resulting from the execution of several interconnected cellular programs that controls epithelial plasticity [216–218]. A plethora of pathways including the RTK, TGFβ, Notch, Wnt, and BMP pathways are able to induce EMT [219–223]. These pathways signal through intracellular kinase cascades to activate EMT transcription factors (Snail1) ([224, 225], Snail2 [226], Twist [227], Zeb1 [228], Zeb2 [229], Foxc2 [230], and others), which together with the loss of E-cadherin transcription are considered important hallmarks of the process [217]. In breast tumors, Snail expression precedes the expression of other factors [231–233]. Snail1 expression seems to be required for EMT initiation, whereas other EMT inducers are required to maintain late EMT [232, 234]. Thus, a temporal hierarchy in the activation of the EMT transcription factors may lead to the sequential repression of the epithelial phenotype, the acquisition of mesenchymal traits, extracellular matrix (ECM) remodeling and the appearance of invasive properties associated with acquired multidrug resistance [235]. Late recurrence in breast cancer associated with tumor dormancy is common and is associated with very poor outcomes. Interestingly, it has been recently reported that a high degree of epithelial–mesenchymal plasticity in primary breast tumors is strongly associated with late recurrence, as opposed to the conventional classification based on expression status of HER2, ER and PR. These findings suggest that in primary tumor, an EMT-related gene signature that is independent of disease subtype could predict the transition of tumor cells to a dormant phenotype with potential outgrowth as recurrent disease [236]. Since low CK2β expression is associated with an EMT-related gene signature and ECM remodeling, this molecular alteration is likely a common phenomenon applicable to all breast cancer subtypes.

Linking CK2β to SNAIL1

Analysis of clinical breast tumor samples exhibiting a wide range of CK2α expression levels showed that Snail1 expression was significantly increased in low CK2β-expressing tumor samples. This suggests that CK2β underexpression may be associated with EMT, which is a common feature of aggressive human breast tumors. Furthermore, downregulation of CK2β in MCF10A mammary epithelial cells clearly promoted EMT [80]. This is in accordance with previous observations showing that Snail1 expression is elevated in highly aggressive breast tumors of the basal-like phenotype [237].

Snail1 is a labile zinc finger protein and its turnover is tightly controlled by the E3 ligase-mediated proteasome degradation process [238]. Snail1-mediated EMT confers cellular plasticity by regulating genes involved in cell death and stem cell maintenance [239]. As a transcriptional repressor, Snail1 interacts with several corepressors and epigenetic remodeling complexes to directly repress specific target genes such as the E-cadherin gene [240].

A wide range of signaling pathways have been found to activate Snail1 expression including TGFβ [241, 242], Notch [243, 244], and Wnt pathways [245]; reactive oxygen species [246]; and hypoxic stress [247–249]. The central role of Snail1 in the regulation of EMT has been linked to its subcellular location and functions through

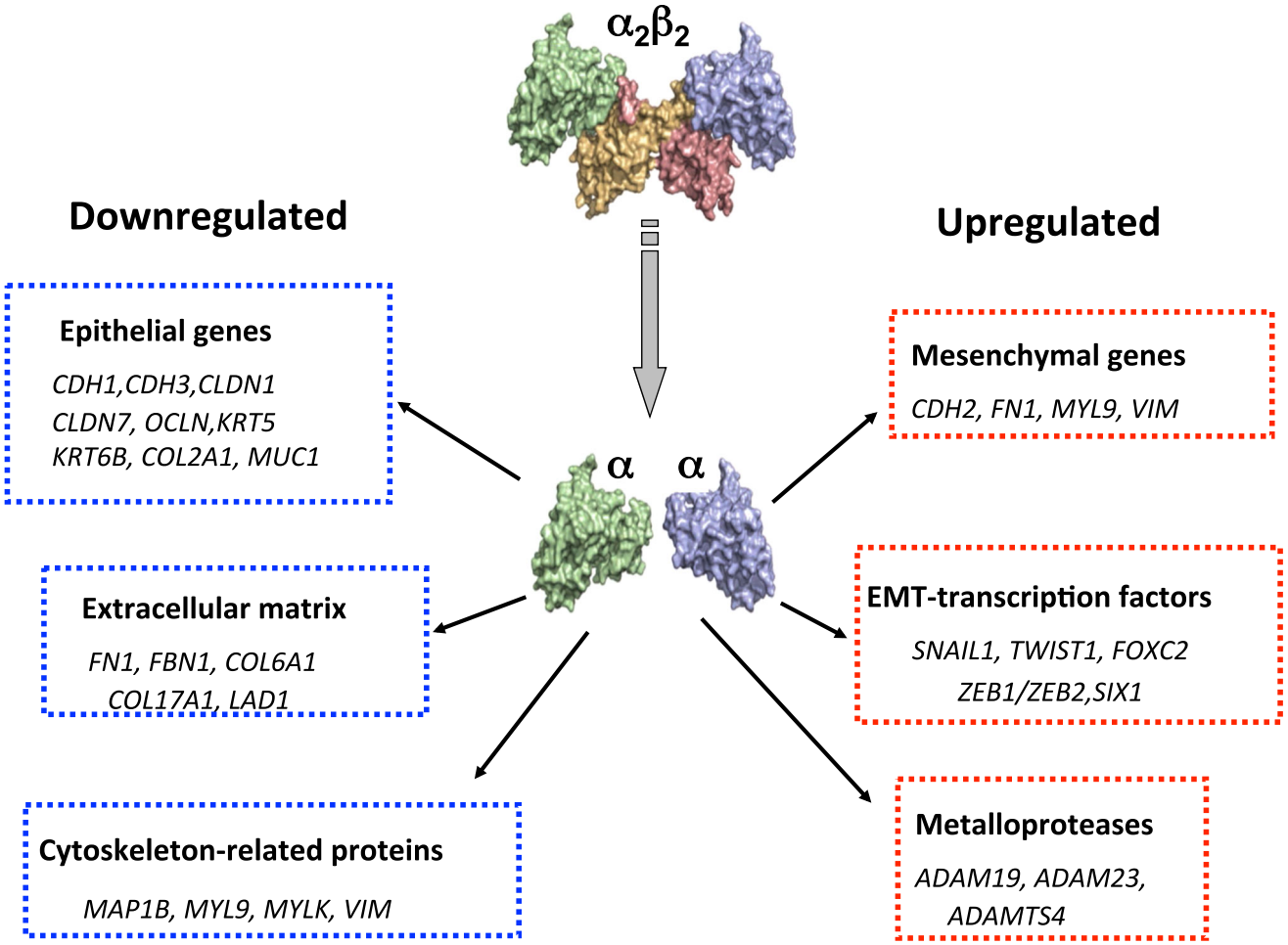

Fig. 2 Selected transcripts modulated in CK2β-depleted MCF-10A mammary epithelial cells. Downregulated and upregulated genes are in *blue* and *red*, respectively. Microarray data were deposited in the Gene Expression Omnibus (GEO) public database at NCBI, under Accession number GSE28569

different phosphorylation events. There are at least five kinases that can phosphorylate Snail1 on five distinct regions for regulating Snail1 protein transcriptional activity, nuclear location, and protein stability. For example, the p21-activated kinase (PAK1) phosphorylates Snail1, promotes the accumulation of Snail1 in the nucleus and subsequent Snail1-mediated transcriptional repression of target genes [250]. In contrast, GSK3β phosphorylates two Ser residues on Snail1, one of which targets Snail1 for ubiquitination and degradation [251, 252]. Snail1 is also phosphorylated by CK2 on Ser92 [81]. Importantly, CK2β is required for CK2-mediated Snail1 phosphorylation, and pull-down assays using MCF10A cell lysates revealed that Snail1 binds the CK2 holoenzyme through its CK2β subunit [80]. CK2β-dependent phosphorylation had a cumulative positive effect on GSK3β-mediated Snail1 phosphorylation, showing that both kinases can negatively regulate Snail1 stability through its hierarchal phosphorylation. Strikingly, Snail1 silencing was sufficient to prevent the EMT phenotype induced in response to CK2β attenuation, highlighting the key role of CK2 in Snail1-mediated EMT [80].

A comparative genome-wide characterization of CK2β-regulated mRNA expression could identify an EMT core signature consisting upregulation of mesenchymal genes (CDH2, FN1, MYL9, VIM, SNAIL1, TWIST1, ZEB1/ZEB2, SIX1), genes involved in the regulation of the extracellular matrix (FN1, FBN1, COL6A1, COL17A1, LAD1), the cytoskeleton (MAP1B, MYL9, MYLK), the metalloproteases (ADAM19, ADAM23, ADAMTS4), and downregulation of epithelial genes (CDH1, CDH3, CLDN1, CLDN7, OCLN, KRT5, KRT6B, COL2A1, MUC1) (Fig. 2). This is in accordance with the observations that CK2β downregulation in epithelial cells induces dramatic changes in cell adhesion and migration [213].

Linking CK2β to FOXC2

The forkhead box proteins, Foxc1 and Foxc2, belong to the forkhead family of transcription factors, which are important in regulating the expression of genes involved in cell growth, proliferation, and differentiation [253–255]. It has been reported that Foxc2 is maintained in the cytoplasm of injured renal cells where it promotes an epithelial phenotype, suggesting that this protein may have regulatory functions independent of its nuclear transcriptional activity [256]. In contrast, nuclear Foxc2 localization is implicated in EMT induction and plays causal role in metastatic dissemination [230]. Recently, Golden and Cantley provided strong evidence that a CK2-mediated phosphorylation of Foxc2 at serine 124 promotes cytoplasmic retention of this transcription factor in normal epithelial cells [78]. In agreement with the mechanism already observed for CK2-dependent phosphorylation of Snail1 [80], the authors found that CK2β is also required for CK2-mediated phosphorylation of Foxc2. Consistent with these findings, nuclear localization of Foxc2 was correlated with decreased expression of CK2β and upregulation of EMT markers in breast metastatic tumor cell lines. Phosphorylation of Snail1 and Foxc2 by the CK2 holoenzyme alters their stability and subcellular localization, respectively. Therefore, the CK2β threshold level is critical in governing Snail1 and Foxc2 fate. This is consistent with a model in which increased CK2β expression may impinge upon Snail1 and Foxc2 functions to reinforce epithelial integrity [78, 80]. These findings also illuminate CK2β as a key regulatory protein that acts as a substrate-dependent modulator of CK2α activity.

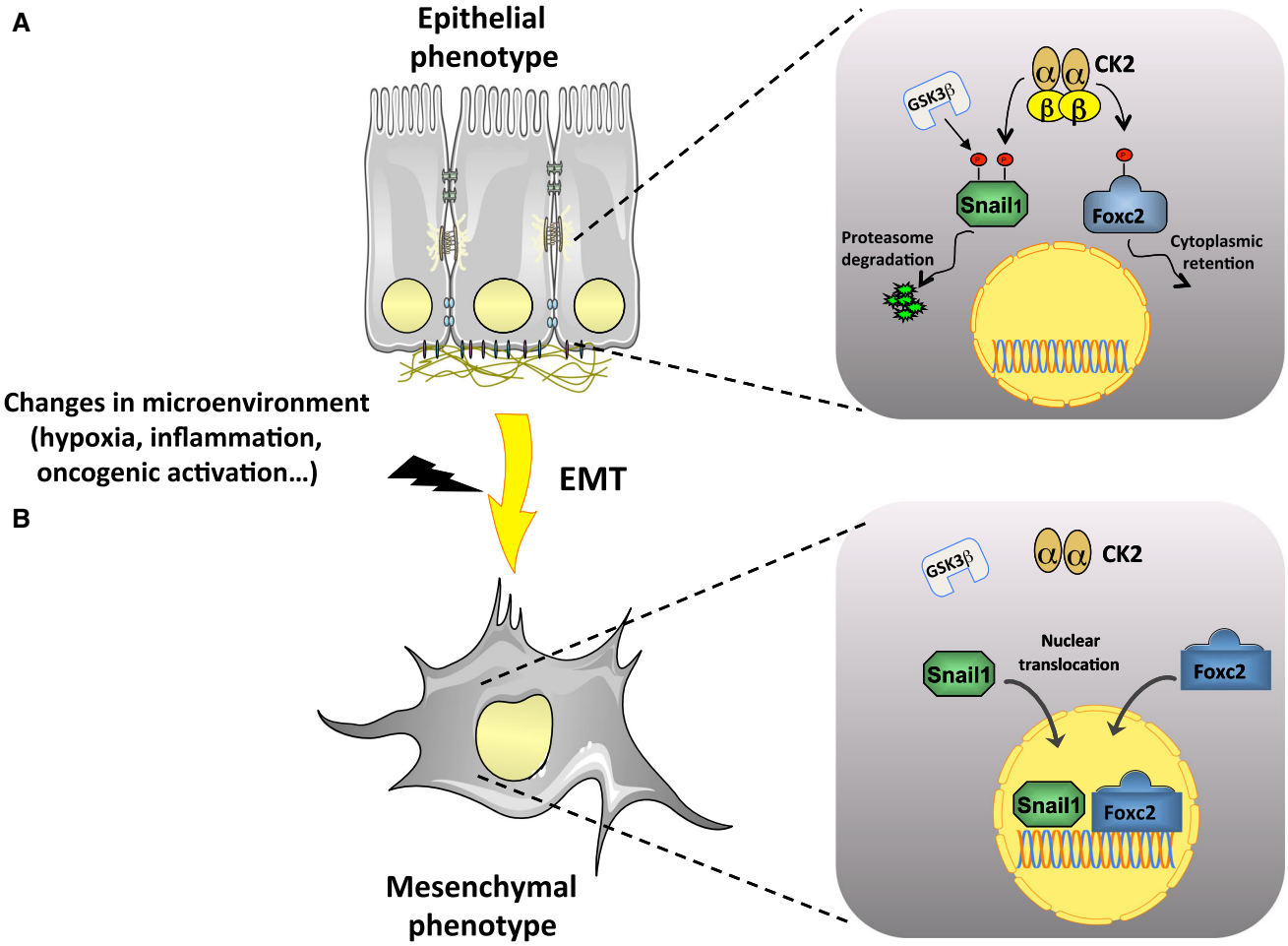

Fig. 3 A hypothetical model in which CK2β is at center stage in the regulation of epithelial plasticity. **a** Snail1 and Foxc2 are master transcription regulators that trigger the formation of a signaling network responsible for establishing and maintaining mesenchymal cell phenotypes. In epithelial cells, both GSK3β and CK2 can negatively regulate Snail1 stability through its hierarchal phosphorylation. CK2-mediated phosphorylation of Foxc2 promotes its cytoplasmic retention. Importantly, CK2-dependent phosphorylation of both transcription factors is mediated by the holoenzyme and thus requires the presence of CK2β. **b** Silencing of CK2β or unbalanced expression of CK2 subunits in response to changes in the microenvironment leads to inefficient phosphorylation of Snail1 and Foxc2, thereby leading to their nuclear translocation and to EMT induction associated with enhanced migratory potential and acquisition of apoptosis resistance

SIX1 is overexpressed in CK2β-depleted cells

The SIX1 homeoprotein has been implicated in both tumor initiation and tumor progression in many human cancers [257–262]. Overexpression of SIX1 mRNA was observed in 44 % of primary breast cancers and 90 % of metastatic lesions. Recently, several studies provided evidence that SIX1 both participates in TGFβ signaling in mammary cells [262, 263] and induces EMT to promote tumor development [264].

It has been reported that CK2 phosphorylates SIX1 and this phosphorylation negatively affects its DNA binding activity [115]. Interestingly, we found that in vitro, SIX1 was not phosphorylated by CK2α alone, whereas optimal phosphorylation was observed in the presence of the CK2 holoenzyme. Furthermore, a potential negative impact of this phosphorylation on SIX1 expression is suggested by the observation that in MCF10A cells, SIX1 is upregulated both at the mRNA and protein levels in CK2β-depleted epithelial cells. In contrast, forced expression of exogenous CK2β in these cells downregulated SIX1 mRNA expression [213].

Conclusions

As the complexity of the cellular CK2 signaling network unfolds, it becomes increasingly important to put individual CK2 protein substrates and partners into context and understand their dynamics in normal versus cancerous

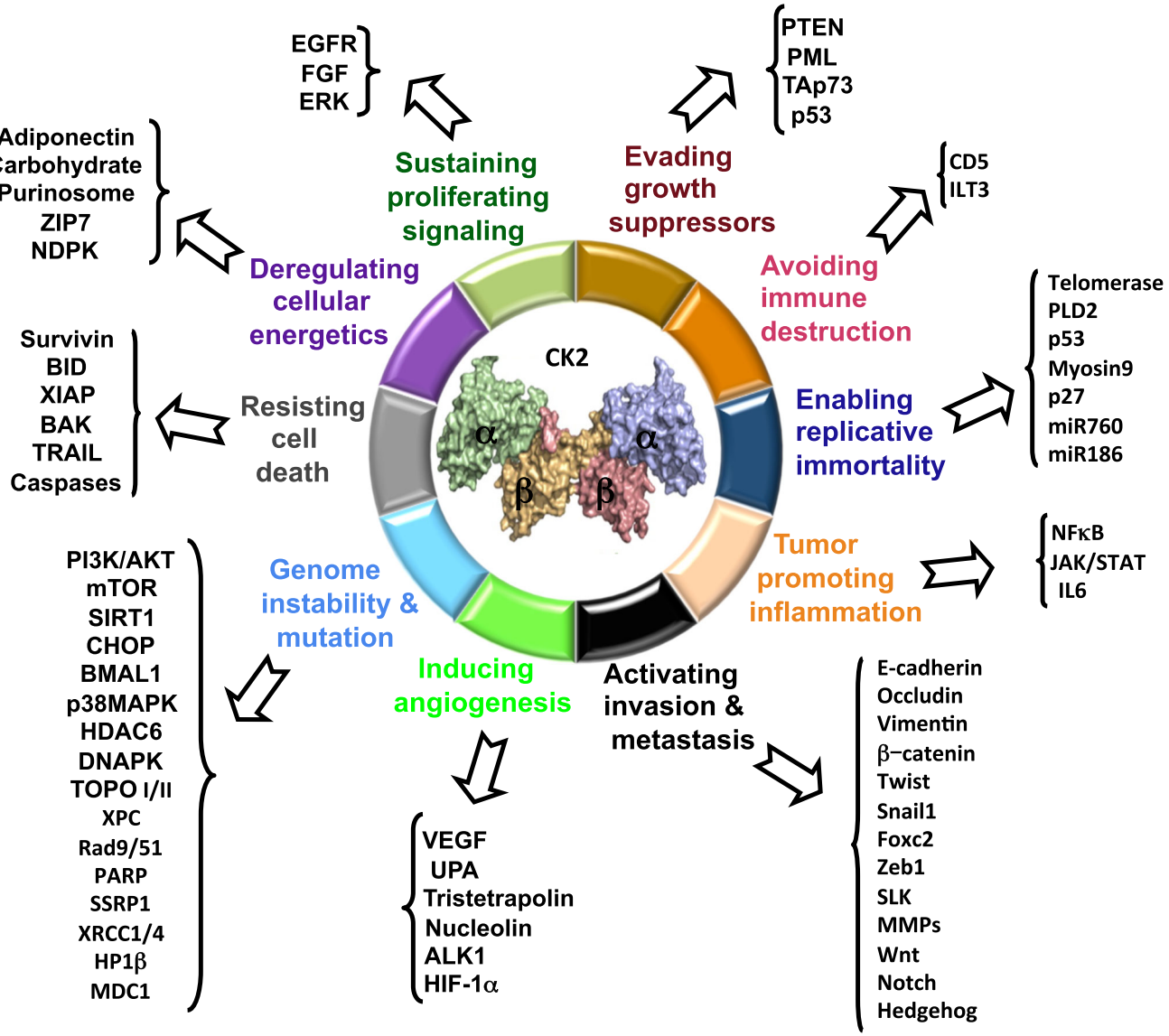

Fig. 4 Selected targets and/or interactors of CK2 that contribute to the "hallmarks of cancer"described by Hanahan and Weinberg [34, 35]. At each phase of tumorigenesis, high CK2 activity may reinforce the progression of the disease through promotion of the hallmarks

cells. The recent research discussed in this review describes the contribution of the deregulated expression of CK2 to cancer development and highlights CK2β as a gatekeeper of epithelial differentiation. CK2β appears to be a key factor that tips the balance in favor of epithelial cell differentiation through the coordinated negative regulation of key EMT-inducing transcription factors. Therefore, the CK2 holoenzyme, through stoichiometric expression of its two subunits, is critical to maintain a normal epithelial morphology. In this situation, CK2β may target CK2α to specific proteins (Snail1, Foxc2, SIX1, and others) whose phosphorylation is highly dependent on the presence of CK2β. However, this cellular mechanism can be overcome in specific conditions such as a low ratio of CK2β to CK2α expression. In this setting, the inefficient CK2-mediated phosphorylation of these key proteins may lead to their stabilization/activation and to consequent disruption of the epithelial phenotype (Fig. 3). Therefore, reduced CK2β may be a novel molecular alteration during malignant tumor progression. How the relative abundance of CK2 subunits is regulated in response to the activation of specific signaling pathways remains a challenging question. Recent data suggest that the kinase activity of the CK2 catalytic subunits is implicated in the regulation of their own gene expression [265]. Intriguingly, miR-125b, whose expression is downregulated in breast tumors, was found to perform its tumor suppressor function via the direct targeting of the 3′-UTRs of CK2α [266]. Conversely, no effector modulating CK2β expression is known, although a link between hypoxia and CK2 was aptly revealed by the demonstration that under hypoxic conditions, the CK2 holoenzyme is dissociated, allowing free CK2α to induce stabilization of the HIF-1α protein [106]. Moreover, it has been observed that tumor samples expressing low levels of CK2β had upregulated HIF-1α expression, suggesting that CK2β underexpression may be associated with the hypoxic conditions found in human breast tumors [80]. Although traditionally considered to be the regulatory subunit of CK2, it appears that this highly conserved protein also has cellular functions that are independent of CK2, reinforcing the importance of delineating its regulation. Therefore, we can anticipate that the identification of new partners for CK2β will certainly tease out additional mechanistic insights on the multiple functions of CK2 during tumorigenesis (Fig. 4). While there are many unanswered questions with regard to how differential levels of CK2β regulate distinct proteins involved in normal versus cancerous cells, the potential for CK2 to be an efficacious target in treating cancer patients remains high.

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