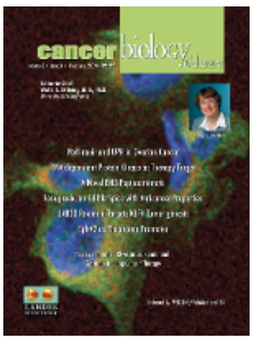

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Commentary

Pyk2 and Cyr61 at the cross-road of cAMP-dependent signalling in invasiveness and neuroendocrine differentiation of prostate cancer

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Key words: Pyk2, Cyr61, prostate cancer, integrins, differentiation, invasiveness, proliferation

In this issue of *Cancer Biology & Therapy*, Kisslinger et al. demonstrated for the first time that Proline-rich tyrosine kinase (Pyk2) and cAMP interact in regulating prostate cell functions and in "keeping" prostate identity.[1] In EPN cells, a line of non-transfomed epithelial cells derived from human normal tissue, cAMP potently inhibits growth (~90% after eight days) and preserves prostate differentiation through Pyk2 phosphorylation. The antiproliferative effect mediated by Pyk2 activation seems to be a consequence of abolishing AKT1 phosphorylation. While in EPN-PKM3 cells, an EPN clone bearing a Pyk2 kinase-negative mutant, cAMP incubation induces a moderate inhibition in cell proliferation (-35%), the remaining AKT1 was still activated for up to 72 hours and shifted prostate cells towards a neuroendocrine phenotype. In fact, analysis of the expression of the HOX gene network revealed that Pyk2 function alone did not affect HOX gene expression, but cAMP stimulation induced a modulation of HOX D and C genes, which are involved in neuroendocrine differentiation.

Pyk2 is a non-receptor tyrosine kinase of the focal adhesion kinase (FAK) family, involved in several cellular functions such as adhesion, motility, anchorage independence, cell proliferation, apoptosis and the G_1 to S phase transition of the cell cycle.[2,3] Pyk2 seems to have a main role in the tumorigenesis, differentiation and invasiveness of prostate cancer. In fact, Pyk2 is functionally expressed in both normal and neoplastic prostate tissue. The expression of this tyrosine kinase is inversely correlated to the degree of prostate malignancy. Pyk2 progressively decreases as the grade of the adenocarcinoma increases until disappearing in anaplastic, undifferentiated cancer.[4,5] This suggests that in the prostate Pyk2 may play the role of an oncosuppressor gene, while its expression or lack of expression could reflect the state of differentiation of the tumor. In addition, a decrease in the expression of Pyk2 resulted in a MAP kinase-dependent decrease in the proliferation of prostate cells, while the loss of Pyk2 kinase activity in EPN-PKM3 cells correlated with increased cell motility and migration.[6,7] However, most of these data were obtained in non-transformed epithelial cells, while several studies on prostate cancer cells suggest an involvement of Pyk2 activation in invasion processes.[8,9] Therefore, an inverse role of Pyk2 in cancer cells cannot be excluded; where signal transduction pathways are deregulated and the normal interactions and feed-back loops between proliferative and growth suppressing pathways are lacking due to multiple mutations acting at several levels.

In most cases Pyk2 is involved in integrin-mediated signal transduction. Pyk2 is activated after integrin clustering in response to various extracellular matrix components, such as fibronectin and by a number of growth factor receptors, including ErbB tyrosine kinases. After activation, Pyk2 undergoes multiple phosphorylations and engages in protein-protein interactions with a variety of proteins including cytoskeletal proteins, such as paxillin; tyrosine kinases, such as Src and C-terminal src-kinase; serine/threonine kinases, such as integrin-linked kinase and p21-activated kinase; and modulators of small GTPases of the Rho family. These multiple interactions have been established as critical regulators of early cell invasion signalling, promoting cancer cell migration and the initiation of metastasis formation.[3] In EPN-PKM3 prostate cells the loss of Pyk2 activity upregulates expression of the α5-integrin subunit, which mediates adhesion to fibronectin.[7] Expression of α5-integrin correlates with the resistance of prostate cancer cells to undergo apoptosis.[10,11] In the human prostate cancer cell line PC-3, upregulation of α5-integrin is associated with increased adhesion to the extracellular matrix protein fibronectin, thereby facilitating colonization of the bone matrix where these cells preferentially metastasize.[12,13] Therefore Pyk2 plays a central role in the mechanisms that regulate cell-cell and cell-substrate interactions. The lack of Pyk2 kinase activity induces normal prostate cells to acquire a malignant, invasive, highly proliferating and migrating phenotype.

Cyr61, a member of growth factor-inducible immediate-early genes belonging to the CCN family, plays an important role in cell proliferation, adhesion and differentiation of prostatic stromal and epithelial cells and in the processes of tumorigenesis and invasiveness of prostate cancer.[14-16] These biological properties are mainly modulated by interactions with cell surface integrins because Cyr61 functions as a bridge between cell membrane integrins and

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extracellular matrix components (i.e., fibronectin). In PCa, a prostate cancer cell line, Cyr61 regulated the level of activated Rac1 as well as its downstream targets, including phosphorylated JNK, E-cadherin and p27(kip1), which are key molecules involved in cell growth, migration and invasion.[16] In other tumor models it has been shown that CYR61 cooperates with integrins to promote metastasis, peritoneal disseminations, tumour proliferation and resistance to apoptosis.[17-20]

It is interesting to observe that as for Pyk2, Cyr61 is regulated through the cAMP signal transduction pathway. In fact, cAMP responsive element-binding protein (CREB) positively regulates the expression of Cyr61 in response to hypoxia in vitro and activates Cyr61 gene expression in correlation with hypoxic regions in tumors in vivo.[21] Therefore, cAMP increases the expression of both Cyr61 and Pyk2. It will be important to check the interaction between Pyk2 and Cyr61 in these experimental models and their correlations with the cAMP-dependent pathway, cell proliferation, neuroendocrine differentiation and tumor invasiveness (Fig. 1). The interaction between components of the machinery involved in the control of cell adhesion and motility could have a pivotal role in the regulation of both proliferation and cAMP-mediated commitment to neuroendocrine differentiation. In this view, a series of potential proteins for stromal signaling and the bladder or prostate differentiation program including cathepsin L, follistatin-related protein, neuroendocrine convertase, tumor necrosis factor receptor and others was recently identified. The prostate stromal/epithelial signaling may be accomplished through activation of the interaction between extracellular matrix molecules and receptors, complement and coagulation cascades, focal adhesion and cell adhesion pathways (including Pyk2).[22] In conclusion, the data by Kisslinker et al.[1] may provide a new class of targets that can be used for the design of new strategies in prostate cancer treatment.

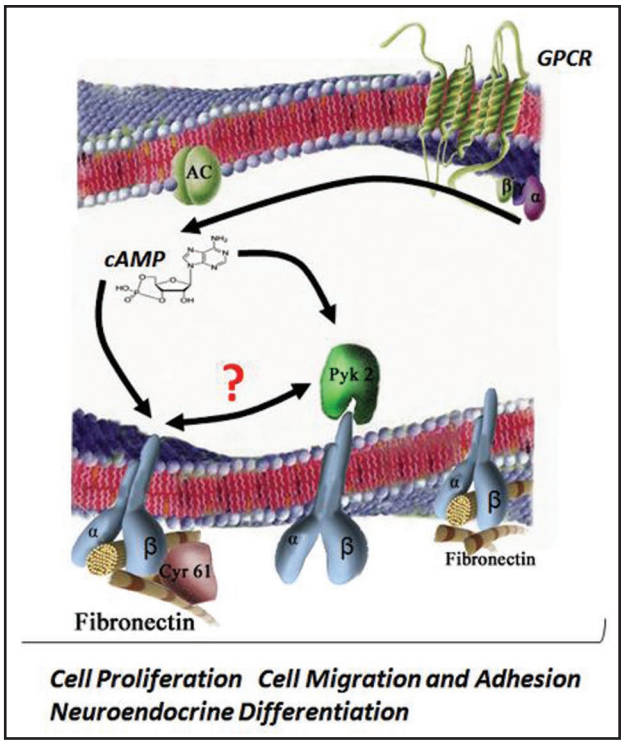

Figure 1. Hypothesis of the interaction between Pyk2 and Cyr61 under the control of the cAMP-dependent pathway in the modulation of cell proliferation, neuroendocrine differentiation and tumor invasiveness in prostate cancer.

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