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Editorial
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Prokineticin 2 as a Biomarker

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Editorial

Biomarkers can be used to determine cancer prognosis and monitor disease status, recurrence, or response or progression to therapy.

Prokineticin 2 (PK2) is a novel chemokine originally discovered as a stimulator of smooth muscle contractility and now known to be an important player in many pathologies with inflammatory/neuroinflammatory components [1,2]. During inflammation, Prokineticin 2 (PK2) is strongly upregulated under the influence of Granulocyte Colony-Stimulating Factor (G-CSF) in inflammatory cells, especially neutrophils [3].

It is well known that inflammation is a critical component of tumor progression and that neutrophils are the major immune-infiltrating cancer cells that trigger the release of a variety of growth factors, cytokines, and chemokines that promote inflammatory states [4].

Prokineticin 2, which binds and activates two G-protein-coupled receptors, Prokineticin Receptor 1 (PKR1) and Prokineticin Receptor 2 (PKR2), is involved in all steps of tumorigenesis, growth, progression, and metastasis [5]. PK2 acts as a chemokine on the tumor microenvironment and influences cancer cell migration, invasion, and angiogenesis, and is now indicated as a new potential prognostic factor in various cancers.

In Colorectal Carcinoma (CRC), one of the most common and malignant tumors, PK2 has been shown to regulate angiogenesis in both preclinical and clinical studies.

In vivo experiments showed that mice subcutaneously injected with cell lines transfected with the PK2 vector exhibited greater mass and neovascularization, suggesting that PK2 promotes tumor growth and metastasis [6]. Examination of six human colorectal cancer cell lines revealed that three of them showed an increase in PK2 levels. was evident. Colorectal cancer cell line, that expressed low PK2 mRNA level, once transfected with PK2 gene and injected in mice induced significant increase of angiogenesis and tumor growth compared to the cell line with the control vector.

Conversely, colorectal cancer cell line, that expressed high PK2 mRNA level, once transfected with of PK2 siRNA and injected in mice induced significant decrease of angiogenesis and tumor growth compared to the cell line with the control vector [7]. In patients, PK2 expression was significantly related to lymphatic invasion, lymph node metastasis, clinical stage, and postoperative liver recurrence rate [7]. Prokineticin receptor 2 expression was also associated with a higher incidence of vascular invasion, lymph node metastasis, liver metastasis, and hematogenous metastasis, as shown by immunohistochemical analysis. PKR2 expression increases with advancing tumor stage and correlates with a negative prognosis [8].

PK2 also appears to play a role in Lung Cancer (LC), another malignant tumor that causes death worldwide. In the lung cancer mouse model obtained by implanting murine Lewis Lung Carcinoma cells (LLC-1) into granulocyte-deficient and Growth factor-independent-1 (Gfi1) mice and normal littermates, a significant increase in LLC-1 tumors was observed in control mice compared with Gfi1-null mice, which do not express PK2 because granulocytes are the major source [9].

In Neuroendocrine Neoplasms (NEN) [10], a group of rare and highly vascularized tumors of the neuroendocrine system, and in prostate cancer [11], angiogenesis plays a key role in tumor growth and metastasis, as demonstrated by the efficacy of pharmacological therapies based on antiangiogenic drugs. Indeed, the anti-VEGF (Vascular Endothelial Growth Factor) bevacizumab (Avastin) represents a valid therapeutic approach in advanced-stage NEN. However, because refractoriness or resistance to anti-VEGF is a limiting factor that may lead to treatment failure, the use of anti-PK2 antibodies in combination with anti-VEGF could be a potential clinical strategy to avoid anti-VEGF resistance. This is supported by *in vivo* observations by Ferrara, who showed

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that in mice with Chemically Induced Colitis (CIC), which had highly elevated serum levels of G-CSF, the main trigger of PK2 expression in myeloid cells, the combination of anti-PK2 or anti-GCSF with anti-VEGF antibodies significantly reduced tumor progression (CRC) [12]. Recently, a prospective case-control observational study measured circulating PK2 levels in pulmonary and Gastroenteropancreatic (GEP) NEN, which are rare epithelial neoplasms arising from pluripotent endocrine cells of the gastrointestinal tract and pancreas. The authors demonstrated that PK2 levels were significantly higher in patients with progressive disease than in control subjects, suggesting that PK2 is a potential prognostic marker for NEN [13].

In human prostate, analysis of PK2 mRNA and protein expression showed that in primary cultures of epithelial cells from normal and malignant prostate, the expression of prokineticin's and their receptors increased with prostate malignancy. This may suggest that PK2 is involved in prostate carcinogenesis and regulates angiogenesis confirming PKs as a target for prostate cancer treatment [14].

Breast cancer and cervical cancer are the most common cancers in women worldwide. The involvement of PK2 in breast cancer has been demonstrated in breast cancer models of mice implanted with cell lines with different metastatic properties. PK2 was found to promote the migration of metastatic tumor cell lines without affecting non-metastatic cell lines, suggesting that inhibition of PK2 may be a therapeutic strategy against metastasis [15]. In human cervical cancer cell lines, high mRNA and protein expression of PK2 was found to promote cell migration and invasion, and this high expression positively correlated with shortened patient survival, suggesting that PK2 may be a potential prognostic biomarker and therapeutic target for this type of tumor [16].

Gliomas are the most common type of central nervous system tumors, and most histologic findings of gliomas are malignant [17]. Although the diagnosis and treatment of gliomas have progressed, the overall prognosis of glioma patients remains poor. Correlations between clinical information and prokineticin expression were analyzed using logistic regression. Multivariate analysis revealed that upregulated PK2 expression was an independent prognostic factor for poor survival [18]. Glioblastoma, the most malignant form of glioma with a poor prognosis, is characterized by extensive vascularization and strong upregulation of both VEGF and VEGF receptors, favoring anti-angiogenic therapy based on VEGF suppression [19]. PK2 has been shown to play a role in glioblastoma. In a mouse xenograft model obtained by subcutaneous or intracranial inoculation of human glioma cancer cells into nude mice, administration of the PKRs antagonist PKRA7 reduced tumor mass by decreasing blood vessel density. These effects were enhanced when PKRA7 was administered in combination with temozolomide and gemcitabine, the standard chemotherapeutic agents. This demonstrates the potential role of PK2 antagonists as components of combination therapies [19]. Many anticancer drugs are highly effective in cancer treatment. However, they trigger clinically significant cardiovascular morbidity and, in some cases, mortality. Recently, high plasma PK2 levels were shown to be associated with the risk of cardiotoxicity after cancer treatments. This was the first demonstration that PK2 is a potential biomarker for identifying patients who are susceptible to cardiotoxicity [20].

Conclusion

Considering the important role that prokineticin's play in cancer, numerous groups are searching for new molecules that can act as agonists and antagonists [21]. Biomarkers are playing an increasingly important role in the diagnosis, treatment, and management of cancer patients. The development of new non-invasive biomarkers with higher sensitivity and specificity is essential in clinical practice to identify patients with favorable prognosis who can safely avoid overtreatment.

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