Editorial

Antiangiogenic Agents

Angiogenesis has been described as one of the hallmarks of cancer, playing an essential role in tumor growth, invasion and metastasis. Antiangiogenic therapy was initially perceived as a "magic bullet" that could eventually be used for the treatment of any type of cancer. For this reason inhibition of angiogenesis has become a major challenge in the development of new anticancer agents, with a countless number of antiangiogenic strategies being tested in preclinical and clinical trials.

Recent progress in combining antiangiogenic drugs, mainly acting on the VEGF/VEGFR (Vascular endothelial growth factor/ Vascular endothelial growth factor receptor) pathway, with chemotherapy and other conventional therapies are discussed in this issue. Strategies for the optimization of combination therapy and the selection of appropriate treatment regimens are examined. As new drugs are entering clinical trials, reliable biomarkers are needed to stratify patients for antiangiogenic therapy, to identify resistant patients and to monitor response to treatment.

Moreover, recent experimental findings suggest that some antiangiogenic drugs could promote tumor invasiveness and metastasis. The success in the discovery and pharmacological development of future generations of angiogenesis inhibitors will benefit from further advances in the understanding of the mechanisms involved in human angiogenesis.

There is a need of more molecules to be tested on and a special chapter dealing with recent developments in high-content screening (HCS) technologies, that represents an attractive alternative for anti-angiogenic drug discovery, is reported in the issue. HCS integrates high-throughput methodologies with automated multicolor fluorescence microscopy to collect quantitative morphological and molecular data from complex biological systems are also presented.

The complex role of oxidative stress and redox signaling in cancer neovascularization have been reported on a process without which the tumor is unable to grow beyond few millimeters in size. Reactive oxygen species and nitric oxide affect cell responses to hypoxia, a major trigger of angiogenic switch in tumors and are important upstream regulators as well as downstream mediators of action of the most potent proangiogenic factor - vascular endothelial growth factor.

Modulation of redox species production, signaling and metabolism and/or manipulating cellular antioxidant responses represents a multitargeted therapeutic approach which may possibly overcome the limitations of single-agent antiangiogenic treatments and potentiate effects of standard methods.

The role of chemokines has been also discussed together with the chemokine stromal cell-derived factor-1 (SDF-1)/CXCL12 represents the single natural ligand for the chemokine receptor CXCR4. CXCL12 possesses angiogenic properties and is involved in the outgrowth and metastasis of CXCR4-expressing tumors and in certain inflammatory autoimmune disorders, such as rheumatoid arthritis.

Here, we discuss the different aspects of CXCL12/CXCR4 biology as well as the development and anti-cancer/stem cell mobilizing activity of CXCR4 antagonists.

In this issue, we indicate some key examples showing how alternative splicing decision may induce a switch from anti-angiogenic to pro-angiogenic functions and reciprocally. For some of these splicing events, the molecular mechanisms that trigger alternative splicing toward one or the other direction start to be elucidated. The emergence of strategies enabling to regulate alternative splicing opens new routes for anti-angiogenic therapies.

We also add to the issue some interesting concepts on vascular smooth muscle cells (VSMC) respond to arterial wall injury by intimal proliferation and play a key role in atherogenesis by proliferating and migrating excessively in response to repeated injury, such as hypertension and atherosclerosis. In contrast, fully differentiated, quiescent VSMC allow arterial vasodilatation and vasoconstriction. Exaggerated and uncontrolled VSMC proliferation appears therefore to be a common feature of both atherosclerosis and hypertension.

Attention is focused on subfamilies of MAPKs (Mitogen-activated protein kinases), the extracellular signal regulated kinases (ERKs). An overview of the work on ERKs 1 to 2, emphasizing when possible their biological activities in VSMC proliferation, is presented in this issue. It is clear from numerous studies, that ERK1/ERK2 pathway has an important role in VSMC proliferation induced by insulin (INS) and thrombin, even if thrombin regulation of VSMC's proliferation remains poorly understood.

A chapter dedicated to Pim1 is also considered in this issue together with Human Pim1 (proviral integration site for Moloney murine leukemia virus) kinase is a 313-amino acid serine-threonine kinase that possesses several biological functions in cell survival, proliferation and differentiation, and its overexpression has been observed in a number of human cancers.

This chapter is a clear example how the use of molecular modeling techniques is largely used for the identification and optimization of proteins inhibitors. This data collection, which to the best of our knowledge was not previously reviewed in such detail, could offer a useful tool for medicinal chemists working in the field of small molecule kinase inhibitors.

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