Preface: Advances in Molecular Targets for Therapeutics in Resistant Cancers

Medical therapy of cancer has achieved considerable progress in the course of time, largely due to the progressive introduction of novel conventional and molecularly targeted agents. However, this special issue deals with the status of some cancers for which prognosis in the advanced stages remains paradigmatically poor. These tumors are very difficult to treat due to characteristics which must be better defined and understood. Clearly, many efforts are directed toward the primary prevention of cancer, together with a very early diagnosis, which facilitates curative interventions. At the same time, research should identify special vulnerabilities of these tumors to be exploited for proper pharmacological treatments.

Hepatocellular carcinoma (HCC) has these exceedingly malignant characteristics, which are thoroughly described by Maurizio Soresi et al. in "Epidemiology, diagnosis and non-pharmacological treatment of HCC" in this issue. With the increasing advent of HBV vaccination in highly endemic countries and the availability of the new direct-acting drugs against HCV, HCC frequency and mortality will hopefully slip from its current place at the top of the list of such cancers to a lower level in the near future.

In "The role of Hsp70 in the diagnosis of HCC," Lydia Giannitrapani and Gabriele Multhoff note that reliable tumor biomarkers to detect asymptomatic precursor lesions in early HCC are still lacking. They explore the impact of heat-shock protein 70 as a molecular tumor biomarker for the detection of HCC and its potential use as a tumor-specific target for future anticancer therapies in HCC. In their article "From targets to targeted therapies in hepatocellular carcinoma," Melchiorre Cervello et al. discuss the most important studies on the signaling pathways implicated in the pathogenesis of HCC, as well as the most promising drugs, apart from sorafenib, which may have a potential application for new therapeutic interventions in this neoplasia.

In "Druggable targets in pancreatic adenocarcinoma," Stefania Nobili et al. consider the main hallmarks of the unique biology of the highly lethal pancreatic ductal adenocarcinoma (PDAC) in its microenvironment, in cancer-driving proliferative pathways, and in growth suppression loops. They further investigate how PDAC evades the immune system surveillance and provide insight into the molecular aspects of each feature. They also present the main preclinical and clinical results of targeted interventions developed on the basis of such biological rationales, underscoring the existence of novel promising approaches for the treatment of PDAC.

The current standard systemic therapy of triple-negative breast cancers (TNBCs) remains based on cytotoxic drugs because TNBCs are not amenable to targeted therapies. In "Mechanisms of Raf-1 kinase inhibitor protein dysregulation in triple negative breast cancers and identification of possible novel therapeutic approaches for these tumors," Natale D'Alessandro et al. consider an altered expression of the oncosuppressor Raf-1 kinase inhibitor protein (RKIP) that is frequent in TNBCs as a determinant of their aggressive biology. Interestingly, the analysis of the possible mechanisms of RKIP downregulation in TNBCs allows the identification and recapitulation of different possible approaches, including epigenetic modulation and NF-κB inhibition, for the therapy of TNBCs.

The special issue is completed by two appraisals concerning aspects more generally relevant to different cancers. The inflammatory milieu is critically associated with cancer progression and angiogenesis in several tumors, and strong evidence indicates that cyclooxygenase-2/microsomal prostaglandin E synthase-1/prostaglandin E2/E Prostaglandin type receptor (COX-2/mPGES-1/PGE2/EPs) signaling supports epithelial tumor aggressiveness, promoting cell growth, epithelial-mesenchymal transition and stemness. Further, PGE2 modulates pro-oncogenic and pro-angiogenic pathways such as those mediated by EGFR and FGFR-1. Such roles of PGE2 and its partner factors are examined in "Targeting PGE2 signaling in tumor progression and angiogenesis"

2151-8017/14/$35.00

by Sandra Donnini et al. Integrins, present on the surface of tumor and stromal cells, including endothelial cells, have a profound impact on the ability of cells to survive, expand, migrate, invade, and metastasize. Moreover, they facilitate tumor cell malignancy and/or stemness and drug resistance. Thus, understanding how integrin expression and function are regulated during the progression of tumor malignancy is imperative. In "Targeting integrins in cancer" Chiara Pazzagli and Sandra Donnini review the association of integrins and their network of partner proteins with cancer. The last two reviews also present the major therapeutic advances related to COX-2/mPGES-1/EPs and integrins that have been made over the past few years in targeting tumorigenesis and angiogenesis.

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