

Hepatobiliary cancer is a major health concern worldwide, being the second most common cause of cancer-related death and the fifth most frequent tumor entity globally. Hepatobiliary cancer comprises a group of highly aggressive tumors, with heterogeneous etiological and histopathological features. The differences in the etiology are presumably the major factor responsible for the diverse incidence trend characterizing these malignancies. Indeed, while the most frequent forms of primary liver cancer, namely hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA) are rapidly rising in incidence and mortality in the world, extrahepatic cholangiocarcinoma (eCCA) shows a progressively decreasing tendency. Due to the paucity of specific symptoms, most hepatobiliary tumors are identified at advanced stage and only a small percentage of patients can be subjected to tumor resection at the time of diagnosis. For patients with inoperable disease, treatment options are inadequate and mostly ineffective. In particular, only the multikinase inhibitor Sorafenib has shown some limited anti-tumoral activity in advanced HCC in terms of patients' survival, whereas the other targeted therapies employed so far in hepatobiliary tumors have been proven unsatisfactory.

In order to significantly improve the prognosis of patients affected by hepatobiliary cancers, a better understanding of their molecular pathogenesis is highly required. In recent years, the advent of sequencing, transcriptomic, and proteomic technologies has substantially increased the investigative potential of scientists on hepatobiliary cancers. On the one hand, these high-throughput analysis approaches have significantly improved our knowledge on the molecular events occurring in these malignancies. On the other hand, these technologies have revealed the remarkable complexity and the assorted molecular features underlying these tumor entities. Such heterogeneity is presumably the consequence of the functional interaction among genetic and epigenetic alterations, risk factors, and causative events. In light of these findings, it is clear that numerous and highly diverse hepatobiliary tumor subsets exist, with peculiar molecular characteristics. Thus, it is not surprising that molecularly-targeted therapies against hepatobiliary tumors have been largely unsuccessful to date.

To significantly improve their effectiveness, several aspects of tumor biology should be better clarified. For instance, comprehensive investigations should be conducted to elucidate the functional consequences of specific molecular alterations and their eventual crosstalk. In addition, mechanisms of drug resistance to targeted therapies cannot be excluded and should be identified. Furthermore, reliable biomarkers should be discovered and validated in order to allow the selection of patient subsets who will presumably benefit from a given treatment.

In the present book, the opinions of a number of key international experts on hepatobiliary cancers are reported. These detailed opinions focus on various aspects of the molecular pathogenesis of these highly malignant diseases. By commenting on recently published landmark research articles on this topic, the authors of the book provide a detailed and up-to-date overview of both the established and emerging pathways associated with hepatobiliary tumors, their interplay, and the effect of their inhibition in experimental *in vitro* and *in vivo* models. In particular, the role and the mode of action of newly-discovered oncogenes and tumor suppressor genes in hepatobiliary malignancies are described and thoroughly discussed. Suggestions on future experiments to be conducted are also given to the readers. Moreover, the possible therapeutic implications of innovative drugs are critically analyzed and evaluated. Thus, the book overall covers important topics of hepatobiliary carcinogenesis, ranging from the molecular bases of the disease to their clinical repercussions. In a comprehensive, yet concise way, the book in fact emphasizes the challenges, barriers, and solutions that have been, or are being, brought forward to enable translation of the current knowledge into health care.

Together with providing a broad landscape of the molecular features of hepatobiliary cancers, the present book drives the readers to the selection of the specific genes and/or molecular events whose suppression or reactivation might be deleterious for the growth and survival of distinct subsets of hepatobiliary tumors. Thus, the book ultimately envisages the implementation of "Precision Medicine" ("an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person"; Precision Medicine Initiative, US National Institutes of Health) to hepatobiliary cancers.

Although preliminary, I believe that the body of information provided by the present opinion collection is an invaluable source for the elucidation and understanding of the molecular pathogenesis of hepatobiliary cancers and may indeed contribute to the design of innovative, effective and tailored therapies against these deadly diseases.

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