Cholangiocarcinoma: State-of-the art knowledge and challenges

Jesus M. Banales[1], Vincenzo Cardinale[1], Rocio I.R. Macias[1], Jesper B. Andersen[1], Chiara Braconi[1], Guido Carpino[1], Domenico Alvaro[1], Diego F. Calvisi[2*]

[1]European Network for the Study of Cholangiocarcinoma (ENS-CCA) Steering Committee; [2]Guest Editor, Special Issue on Cholangiocarcinoma

*Correspondence to: Diego F. Calvisi, Institute of Pathology, University Clinic Regensburg, Franz-Josef-Strauß-Allee 11, 93053 Regensburg, Germany; phone: 0049 9419446651; e-mail: diego.calvisi@klinik.uni-regensburg.de

Cholangiocarcinoma (CCA) is a group of malignant tumors originated from the biliary tree. Depending on the anatomical location, CCA must be classified as intrahepatic (iCCA), perihilar (pCCA) and distal (dCCA). The use of term extrahepatic will be soon eliminated from every classification. Besides the anatomical location, CCAs are heterogeneous also in terms of etiological, histopathological, and molecular features. Regardless of the type of CCA, these tumors are universally characterized by clinical aggressiveness and limited treatment options. Due to limited symptoms in the initial/pre-invasive stages of the disease (*silent* disease), CCA is most often diagnosed at advance stage (inoperable or metastatic), when potentially curative treatments such as surgical resection cannot be applied. Furthermore, after surgery, high recurrence rate (up to 50% within first 12 months) applies for early stage patients as well. In addition, the efficacy of systemic treatments is very limited and, thus, novel agents are highly needed for this fatal disease. This body of clinical evidence, together with the epidemiological observation of an increasing trend of incidence and mortality, indicates CCA as a major health concern worldwide.

To improve significantly the prognosis of patients affected by CCA, a better understanding of its molecular pathogenesis is necessary. Over the last decade, the advent of sequencing, transcriptomic, proteomic, and metabolomic technologies has substantially increased the investigative potential of scientists on most cancer types, including CCA. As expected, these large scale, high-throughput studies significantly deepened our knowledge on the molecular events occurring in CCA. However, this breath of information have further unveiled the remarkable molecular complexity of these tumor entities. The observed CCA heterogeneity is presumably the result of the interaction and combination of distinct often unknown causal events, diverse risk factors and a myriad of genetic and epigenetic modifications. Thus, it is clear that several and substantially diverse CCA subsets exist, with peculiar characteristics. Consequently, it is not surprising that targeted therapies that have been proven successful in other tumor types showed either limited or no efficacy in CCA. To overcome this gloomy scenario, several aspects of CCA biology should be better defined. For instance, the functional consequences of specific molecular alterations and their eventual crosstalk should be elucidated using appropriate *in vitro* and *in vivo* models. Furthermore, the mechanisms of drug resistance to targeted therapies and conventional

chemotherapy should be identified, and reliable biomarkers should be discovered and validated to allow the identification of patients at risk as well as the selection of those who presumably may benefit from a given therapy. Also, a further improvement in conventional therapies as well as their combination with targeted treatment should be established.

In the present Special Issue, the current knowledge on the various aspects of CCA has been summarized by key international experts on hepatobiliary biology and malignancy in a collection of review articles. The authors of the book provide a detailed and up-to-date overview of the genetic and epigenetic features of CCA, the experimental models developed to study the disease, the role of the micro-environment in cholangiocarcinogenesis, the established and emerging pathways associated with hepatobiliary tumors, as well as their interplay. A detailed outline of the state-of-the-art diagnostic procedures and therapeutic strategies is also provided to the readers. Thus, in a comprehensive, yet concise way, the Special Issue emphasizes the challenges, barriers, and suggested solutions that have been, or are going to be, brought forward to enable translation of the knowledge into improving health care.

We would like to underline that the present Special Issue is the result of the concerted work of the members of the European Network for the Study of Cholangiocarcinoma (ENS-CCA: www.enscca.org / www.cholangiocarcinoma.eu). ENS-CCA was founded in 2015 as a pan-European multidisciplinary collaborative group, which was created with the scope to investigate various aspects of this dismal disease, ultimately leading to an improvement of patients' outcome. This network has been supported by the European Association for the Study of the Liver (EASL) for the creation of a dedicate patients' registry, and has been recently granted by the prestigious COST Association (Action CA18122 - *EURO-CHOLANGIO-NET*).

Finally, we cordially thank all the experts that contributed to this collection of review articles on CCA, the Editor-in-Chief of Liver International, Prof. Mario Mondelli, for proposing the topic of this Special Issue, and the highly efficient Editorial Board of the journal for helping us in realizing the importance of this information. In particular, we are grateful to Dr. Sarah Bremner for the extraordinary editorial support throughout the preparation of the Special Issue.