UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title

Metabolic dysfunctions and hepatocellular carcinoma: depicting a new scenario for liver cancer therapy

2)Abstract (max 500 words)

Hepatocellular carcinoma (HCC) is usually the result of a chronic hepatic insult that can be ascribed to different causes, the most common being chronic liver diseases of different etiologies. The role of the etiology in the clinic decision-making for HCC therapies, if any, is still debated. Often, HCC patients have been segregated in two groups (viral or non-viral etiology of the tumor) to assess eventual differences in therapy outcome, but the evidence collected in this field remains unconclusive. Among the non-viral etiologies, growing attention is devoted to *metabolic dysfunction-associated steatotic liver disease* (MASLD), a condition often associated with other metabolic dysfunctions, including Type 2 Diabetes Mellitus (T2DM) and obesity. More than 25% of the global population is estimated to suffer from MASLD, and the incidence of its complication *metabolic dysfunction-associated steatohepatitis* (MASH) is projected to increase by up to 56% in the next 10 years. Accordingly, MASLD/MASH is already the fastest growing cause of HCC, and the prevalence of MASLD-related HCC is likely to increase concomitantly with the growing obesity epidemic. Although the incidence of MASLD-related HCC is lower than that of HCC of other etiologies, such as for example hepatitis C, more people have MASLD than other liver diseases. Furthermore, it is well known that, although MASH with advanced fibrosis is an important driver of HCC, recent evidence indicates that HCC is increasingly observed in non-cirrhotic, often obese, patients affected by MASLD. MASH-HCC has unique molecular and immune traits compared with other etiologies. However, also in this etiology, immunity plays a pivotal role in cancer development since emerging evidence indicates that reduced immune surveillance and increased gut inflammation are potential key steps in MASLD/MASH-related tumorigenesis. Nevertheless, some clinical evidence reported that MASH-HCC patients are less responsive to immunotherapy that patients with HCC derived from other etiologies, although this issue is still controversial. Indeed, the progressive accumulation of exhausted and unconventionally activated T cells has been reported in the livers of MASH patients, and preclinical observations in animal models of MASH-HCC indicated that anti PD-1 therapeutic immunotherapy, although expanding activated CD8+PD1+ T cells within tumors, did not lead to tumor regression, thereby indicating that tumor immune surveillance was impaired by other mechanisms.

In the light of these consideration, this PhD project aims at

1) understanding how metabolic dysfunctions impair immunosurveillance in the liver, leading to an increased risk of cancer development and therapy failure.
2) exploiting novel strategies, by testing molecules of natural and synthetic origin, to avoid the transition from MASH to HCC and/or promote the immune response against liver cancer cells.

To reach this goal, the PhD candidate will take advantage of complex in vitro models (e.g., co-cultures, multicellular spheroids) and in vivo immunocompetent mouse models of HCC.