We here summarize the current view of molecular mechanisms involved in the dissemination process of colorectal cancer cells to the liver as deduced from preclinical models. We focus on molecular aspects of the current understanding of the biology of liver metastases formation and survival, both being crucial for identification and validation of possible therapeutic targets and review the latest findings elucidating some features of the liver as a metastatic niche. In more detail, we outline the role of proteases and of major pathways such as asc-MET signaling and its modulation by factors such as MACC1 and TIMP1, as well as Notch and TGFβ signaling. The relevance of these signalling pathways during tumor-stroma interactions in this context will be addressed. In addition, the functional role and validation of targets such as PRL3, Trop-2, L1CAM, S100A4, S100P, CD133, LIPC, and APOBEC3G are summarized.