Response to cautious use of platelet as relevant inducer of liver regeneration following partial hepatectomy in patients with metastatic hepatic carcinoma

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we want to point out that, platelets may play adverse roles in the remnant liver of HCC and metastatic hepatic carcinoma (MHC) patients.

Firstly, thrombocytopenia plays a very valuable role in the occurrence of hepatic cirrhosis, which is a crucial risk factor of HCC but not MHC. It indicates that the effects of platelet in the formation of the two kinds of liver carcinomas may be different. On the one hand, low level of platelets is recognized as a determining factor of HCC occurrence in patients with chronic hepatitis. On the other hand, a growing body of research suggests that platelets facilitate tumor metastasis in several solid tumors. A recent retrospective study showed that high platelet level was associated with an increased risk of MHC in rectal cancer patients.2

Secondly, apart from the adverse effects in tumorigenesis, platelets also produce adverse influence in the prognosis of HCC and MHC. Numerous epidemiological studies have shown that preoperative thrombocytopenia is an unfavorable prognostic factor of HCC. However, in MHC patients, preoperative thrombocytosis is found to be independently associated with worse overall and disease-free survival.3

The adverse effects of platelets in HCC and MHC may be partially due to several platelet-derived factors. Among them, platelet-derived thrombospondin-1 (TSP-1) is an endogenous inhibitor of hepatocyte growth and LR. It is reported that high expression of TSP-1 is a prognostic marker of poor outcome in HCC.4 However, TSP-1 has also been used as a relevant suppressor of angiogenesis and tumor growth and low expression is found to be a poor prognostic factor in MHC patients.5

In conclusion, the effect of platelet in HCC may be opposite to that in MHC. In HCC, platelet-increasing therapy could improve LR. However, in MHC patients, platelet should be used with caution as a relevant inducer of LR following partial hepatectomy.

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Pang and coworkers comment on our paper on mechanisms of platelet-mediated liver regeneration in healthy mice that underwent a 70% partial hepatectomy.1 Although platelets are increasingly recognized as contributors to liver regeneration, molecular mechanisms involved are incompletely understood.2 Knowledge of these mechanisms might lead to the development of therapeutic interventions aimed at stimulating liver regeneration which may not only be relevant in patients that underwent partial liver resection for primary or secondary liver tumours but also for patients undergoing liver transplantation with a partial liver graft (ie a split liver or a living donor transplantation). We have previously argued that platelet transfusion is likely unsuitable as a therapeutic option because of a likely unfavourable risk/benefit ratio,2 but mechanistic insight may lead to development of more targeted therapy.

I fully agree with Pang and coworkers that although the stimulating effect of platelets on regeneration are beneficial, platelets may also stimulate growth of remaining tumour cells in the liver remnant of patients that underwent a partial liver resection for cancer. Indeed, whereas preoperative high levels of serotonin within platelets decreased the risk of post-operative morbidity in patients that underwent...
a partial hepatectomy for (metastatic) malignancies, patients with high serotonin levels had an increased risk of cancer recurrence. These results suggest platelets to drive both regeneration of the liver remnant and cancer recurrence. In those patients with a high risk of failure of liver regeneration who may benefit from therapy aimed at stimulating platelet-mediated liver regeneration, treatment with platelet inhibitors following initial platelet-promoting therapy may be indicated to decrease risk of recurrence, although such a strategy requires clinical study.

I disagree with the statement that the effect of platelets may be opposite in primary (cirrhosis-related) HCC, and metastatic disease. Although platelet count and concentration of tumour-directed molecules within platelets is clearly different in patients with primary and secondary HCC, and regeneration may be decreased in patients with cirrhosis, platelets are likely to contribute to tumour growth in both primary and secondary HCC. A recent study in Liver International demonstrated thrombocytosis to be associated with increased metastatic risk following a partial liver resection with curative intent in patient with primary HCC. The previously reported association between thrombocytopenia and survival in these patients may therefore be more a reflection of severity of liver disease rather than indicating direct effects of platelets on tumour growth as also discussed by Lee and coworkers in their recent paper.

**REFERENCES**