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Commentary

Intra-platelet Serotonin as a Biomarker in HCC Recurrence: When Time Matters

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We thank Yang et al. for their attention to our work and concomitant description of their findings. In our investigation, we demonstrated a post-resection depletion of intra-platelet (IP) serotonin (5-HT) concentrations in patients with hepatocellular carcinoma (HCC) [1]. We observed an exhaustive pattern of post-resection platelet kinetics in patients with early HCC recurrence. While the post-resection serum and IP 5-HT levels were significantly depleted in patients with HCC recurrence, the preoperative concentration, although observed a similar tendency, this did not reach statistical significance. Interestingly, Yang et al. observed that the high serum 5-HT, high IP 5-HT and high IP 5-HT per platelet were all associated with poor overall and recurrence-free survival [2]. In accordance with it, Xia et al. reported that a preoperative elevated 5-HT was associated with advanced tumor node metastasis and poor recurrence-free survival and overall survival [3]. Similarly, in another study by Padickakudy et al., higher levels of preoperative IP 5-HT were found to be associated with improved postoperative liver regeneration, and an increase in early tumor recurrence suggesting a bivalent property of IP 5-HT in liver regeneration and post-resection recurrence [4].

Collectively, all the above-mentioned studies monitored the kinetics of IP 5-HT in post-resection cancer recurrence. Although there appears to be only a subtle difference between the designs of the studies, our study has some critical disparities. Our data explicitly refers to a post-resection time point (four weeks after liver resection), while the other studies focused on preoperative time points.

Platelets exhibit a variety of qualitative abnormalities in patients with cancer (before or after surgery) [5,6]. These deviations comprise reduced, elevated or spontaneous platelet aggregation, and hypersensitivity to various platelet agonists. A state of oxidative stress was reported in resting blood platelets obtained from cancer patients [7]. Platelet proteome harbors differentially expressed proteins associated with tumors that were found normalized after tumor resection [8]. Likewise, partial hepatectomy also highly influences platelet functions. A hypercoagulable state elicited as a result of liver resection combined with the active promitogenic effect of platelets in liver regeneration stimulates platelet activation [9]. In this context, identifying an optimum time-point of blood sampling is crucial to aptly translate the prognostic or predictive value of post-resection platelet kinetics in cancer patients. Although our study on post-resection IP kinetics at four-weeks post-resection has not assessed the absolute advantage of this time point, it has technically minimized the biases from the confounding factors including the presence of tumor or immediate post-resection related stresses.

Another issue that needs to be mentioned is the method of platelet preparation. Mussbacher et al. have stressed on a significant heterogeneity among anticoagulants used to prevent unwanted platelet activation [10]. Platelets are highly sensitive to changes in the microenvironment, they are prone to *in vitro* activation during platelet-preparation.

Optimized sample preparation is crucial to investigate platelet granule release and preventing artifacts due to *in vitro* platelet activation. There are also some discrepancies in the analysis of IP 5-HT between different studies; in the study by Shu et al., IP 5-HT was calculated by subtracting the plasma 5-HT level from the serum 5-HT level [3] whereas, in our investigations, although not as optimized as mentioned by Mussbacher et al., we precisely isolated platelets and monitored the IP growth factors in the platelet extracts [1]. Our results showed that along with IP 5-HT exhaustion, there was also exhaustion of platelet counts, which is in accordance with the phenomenon observed by Shehta et al. [11]. Along with IP 5-HT, we also observed similar propensity with other platelet-related growth factors including angiopoetin-1 and platelet-derived growth factor. The potential pathophysiological significance of post-resection platelet exhaustion was not explored in our previous study. Our published (and ongoing) studies indicate that a highly stochastic phenomenon along with the differential secretion of IP growth factor is orchestrated in patients with post-resection HCC recurrence.

In considerations with all these factors, we suggest that the discrepancies observed in these (apparently) similar studies should better be readdressed with full-consideration to the platelets' disease-specific, site-specific and stage-specific response [12]. Taking everything into account, not only IP 5-HT but also all platelet-based growth factors stability should be studied under different conditions to identify the most efficient protocol in-regards to the timing, collection, and handling.

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Competing Interests

The authors have declared that no competing interest exists.

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