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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