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Preview

A microfluidic approach for early prediction of thrombosis in patients with cancer

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Li and colleagues have made a notable advancement in predicting cancer-associated thrombosis with a microfluidic device that monitors circulating platelet activity.[1] This tool could improve the management of thrombotic events in patients with cancer, guiding timely treatment and potentially reducing mortality.

Patients with cancer face a significantly higher risk of thrombosis—including venous thromboembolism (VTE) and arterial events—than the general population, with VTE occurring in approximately 15% of cancer cases, contributing to substantial mortality.[2] Thrombotic events not only increase mortality risk but also promote cancer progression. Because platelet activation plays a crucial role in the correlation between cancer and thrombosis, a reliable method to monitor tumor-associated platelet activity would help to predict and prevent thrombotic events in patients with cancer. In the current issue of *Cell Reports Methods*, Li et al. present a device aimed at addressing this need.

The device developed by Li and colleagues is a microfluidic-based "chromatograph" designed to analyze circulating platelets. It leverages the interaction between platelets and a fibrin matrix, a crucial component of blood clots, to assess platelet activation. The device incorporates microchannels filled with a stationary phase matrix. When platelets flow through these microchannels, their interaction with the fibrin matrix is tracked via high-sensitivity fluorescence microscopy.

Notably, Li and colleagues have strived to ensure their model's physiological relevance. Unlike many other existing techniques, this microfluidic device aims to recapitulate the bio-rheological conditions that platelets face within the living vessels, accounting for variables such as pressure, flow, and shear stress. By doing so, it enhances the physiological applicability of the obtained data.

Li and colleagues demonstrated the effectiveness of the microfluidic device by detecting changes in platelet activity in tumor-bearing mice and patients with cancer. Their findings revealed a strong correlation between platelet activation status and tumor progression, with an increased risk of thrombosis observed in lung, breast, and liver cancer as the disease advanced. Follow-up studies conducted over 6 months on patients with advanced lung, breast, and liver cancer further supported the link between platelet activity level and thrombus occurrence rate, highlighting the device's predictive potential.

Interestingly, the device's predictive capacity appeared to surpass that of conventional blood coagulation parameters, such as activated partial thromboplastin time (APTT), thrombin time (TT), and prothrombin time (PT). This suggests that the device could serve as a more reliable prognostic marker for cancer-associated thrombosis.

The study conducted by Li and colleagues represents a significant advancement in the field of cancer-associated thrombosis. Their innovative device offers valuable insights into the dynamic changes in platelet activity associated with tumor progression. However, several important questions still need to be addressed to fully comprehend its implications. For instance, the reproducibility of the device's performance across diverse patient populations and its integration with existing diagnostic protocols are essential considerations. Furthermore, identifying the specific platelet activation markers that the device is sensitive to could provide deeper insights into the molecular mechanisms underlying cancer-associated thrombosis. Answering these critical questions will be pivotal in harnessing the device's full potential.

Microfluidic, or lab-on-chip, technologies have rapidly advanced across various disciplines, including chemistry, physics, biology, medicine, and clinical fields. Although certain applications have gained commercial success, the potential to accelerate cancer-associated thrombosis research has been largely overlooked. However, several studies, like Li et al., suggest emerging development in this area. For instance, Zhao et al. presented the CVS-on-a-chip (Vein-Chip), which mimics the venous geometry of patients with cerebral venous sinus thrombosis (CVST).[3] By reconstructing patient-specific 3D vascular geometries, the Vein-Chip provides a personalized and cost-effective platform, bridging the gap between cerebrovascular imaging diagnostics and patient-specific blood clot testing. This approach has the potential to enhance diagnostic platforms, facilitate cardiovascular patient monitoring, and advance personalized antithrombotic therapies.

Other recent developments have allowed for the coculture of multiple cell types and the construction of *in vitro* blood vessels/tissues, such as the 3D spheroid-microvasculature-on-a-chip

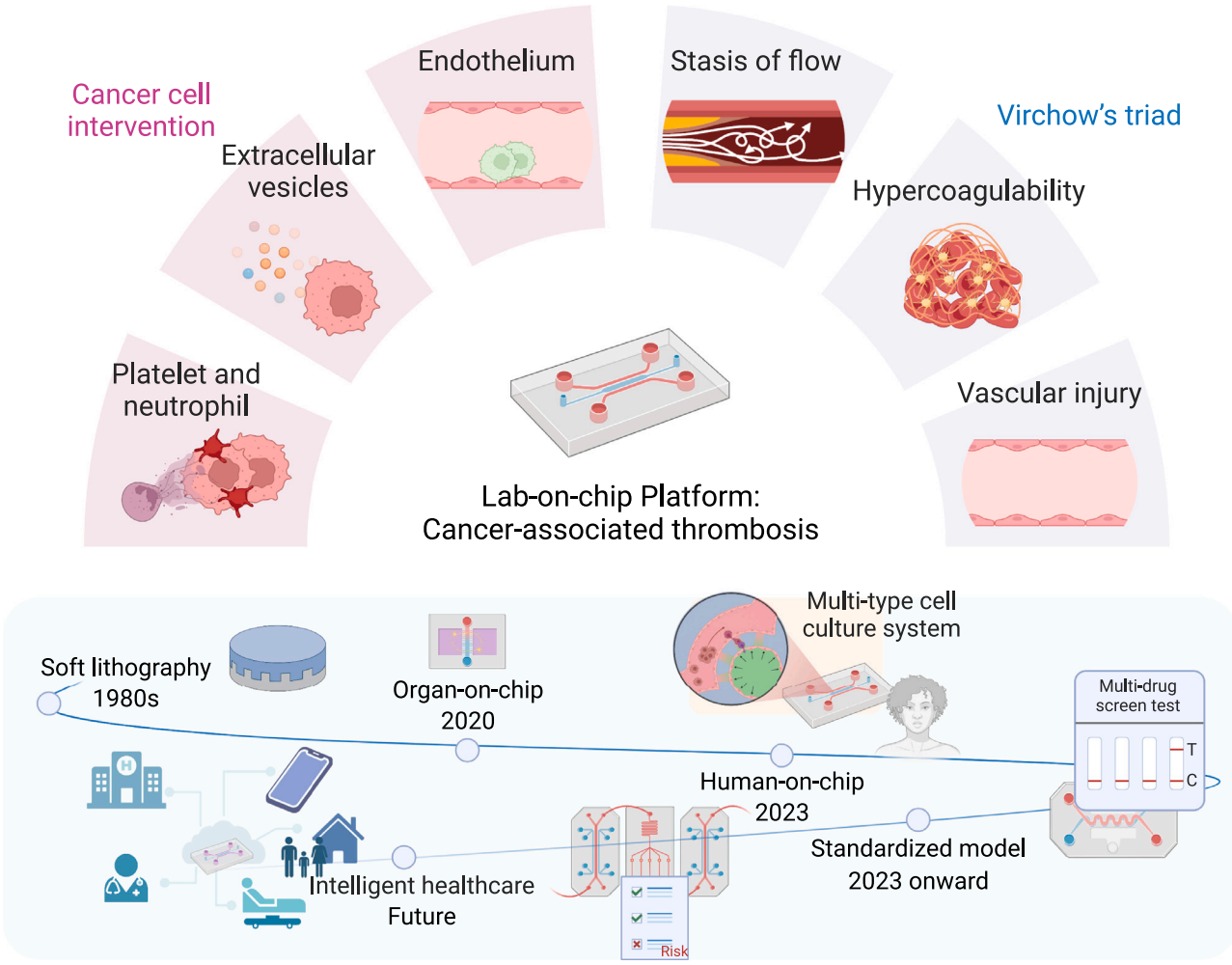

Figure 1. A blueprint of lab-on-chip platform for healthcare of patients with cancer-associated thrombosis

Lab-on-chip platforms can perform factor-separated investigations and assessment of patient-specific Virchow's triad for a better understanding of cancer-associated thrombosis, potentially developing from organ/human-on-chip to standardized models and intelligent healthcare in the future.
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(SMAC) model introduced by Zhang et al. This model offers a controlled hydrodynamic microenvironment and physiologically relevant parameters to study the mechanobiology interplay between tumor spheroids and the endothelium during metastasis.[4] Such techniques provide a valuable platform for investigating cancer-associated interventions with procoagulant properties.

Individual cancer patients exhibit complex and distinct abnormalities in components of Virchow's triad (blood flow stasis, endothelial injury, and hypercoagulability) as well as their hypercoagulable or prothrombotic state. Microfluidics offers accessible modification and testing of these factors. Platforms such as droplet blood tests,[5,6] image-based vessel reconstruction models,[3] and endothelialized microchips[4,7] simplify and personalize testing procedures and have the potential for translation into user-friendly products. The success of point-of-care testing (POCT) in the commercialization of COVID-19 rapid antigen testing demonstrates the impact of POCT on healthcare delivery. Microfluidic-based POCT for cancer-associated thrombosis diagnosis could significantly benefit patients, as anticoagulant therapy is a cornerstone of treatment and necessitates real-time diagnosis and rapid management during critical illnesses.

Building off of the Li et al. design, key areas of development should focus on identification and validation of specific biomarkers that can enable rapid and accurate detection of thrombotic events at the point of care, the optimization of risk assessment that includes the current gold standards of bleeding risk assessment, the discovery of the next-generation anticoagulant drug, and biomedical engineering translation. Integration of multiple assays targeting various aspects of the disease, such as coagulation function and cancer-specific biomarkers associated with thrombosis, could provide a comprehensive assessment of thrombotic risk, facilitating personalized treatment decisions. Translation into miniaturized, portable devices would allow for bedside or outpatient testing, enabling

real-time monitoring and prompt intervention. We hope to see a future for cancer-associated thrombosis POCT that revolutionizes patient care by improving early diagnosis, risk assessment, and management strategies (Figure 1).

DECLARATION OF INTERESTS

The authors declare no competing interests.

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