Red blood cell membrane functionalized electrochemical biosensor for detection of fibrinogen

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Abstract:

In recent years, blood coagulation monitoring has become crucial to diagnosing causes of hemorrhages, developing anticoagulant drugs, assessing bleeding risk in extensive surgery procedures and dialysis, and investigating the efficacy of hemostatic therapies. In this regard, advanced technologies such as microfluidics, fluorescent microscopy, electrochemical sensing, photoacoustic detection, and micro/nano electromechanical systems (MEMS/NEMS) have been employed to develop highly accurate, robust, and cost-effective point of care (POC) devices. These devices measure electrochemical, optical, and mechanical parameters of clotting blood. Which can be correlated to light transmission/scattering, electrical impedance, and viscoelastic properties. In this regard, this paper discusses the working principles of blood coagulation monitoring, physical and sensing parameters in different technologies. In addition, we discussed the recent progress in developing nanomaterials for blood coagulation detection and treatments which opens up new area of controlling and monitoring of coagulation at the same time in the future. Moreover, commercial products, future trends/challenges in blood coagulation monitoring including novel anticoagulant therapies, multiplexed sensing platforms, and the application of artificial intelligence in diagnosis and monitoring have been included. The circulating blood inside our bodies has many functions including transporting O_2, CO_2, and delivering nutrients to the cells. This circulating blood is also a significant source of information on *in vivo* coagulation parameters, hypercoagulability, and alterations in fibrinolysis. Blood coagulation involving a blood fluid to become a solid clot is critical to stop bleeding when an injury occurs inside or outside of the body. However, abnormalities in blood coagulation such as hypercoagulability can cause excessive blood clots and vein blockage, leading to stroke. Cancer , infectious diseases such as HIV and hepatitis, trauma, diabetes, and retinal vein occlusion etc. affect the coagulation stages and create serious complications, as well. For example, the tumor cells can cause thromboembolic complications due to activation of blood coagulation by producing procoagulants such as tissue factor (the primary activator of blood coagulation), releasing soluble factors such as thrombin that induce platelet activation, aggregation, expressing proteins regulating the fibrinolytic system and causing impairment in plasma fibrinolytic activity. Therefore, accurate measurement and understanding of hemostasis including blood coagulation and fibrinolysis is highly demanded to study defects from sensing parameters in different disease models. Blood coagulation and fibrinolysis are complex processes in which platelets, fibrins, enzymes, and a series of complex chemical reactions play a role. With the advancements in artificial intelligence (AI) and machine learning, algorithms that can track multiple parameters simultaneously throughout a treatment/diagnosis and find out patient specific patterns that can aid in pinpointing proper treatment or underlying causes will become one of the biggest developments in coagulation measurement technologies in the upcoming years. Especially with the challenges set by the novel anticoagulant technologies for the current measurement techniques and the validity and applicability of diagnostic parameters such as INR, simultaneous observation of multiple parameters or complicated patterns within them may be necessary for proper observation of patients with special needs. For these special cases, AI and machine learning based algorithms may very likely find place within future novel POC blood coagulation measurement technologies in the upcoming years. Since red blood cells (RBCs) also have significant functions in blood clotting and its disorders , the RBC rheology in different disease conditions has been widely studied. Blood coagulation monitoring with high level of accuracy and reliability for anticoagulant drug dose adjustments (e.g., for heparin and warfarin), studying effects of the drugs, and checking the risks in surgeries for the patients is highly demanded. Viscoelastic assessments, optical (scattering and fluorescent imaging), and electrical impedance measurement are frequently used for both evaluating pharmacological treatments and diagnosing the blood coagulation abnormalities. Electrochemical biosensors embedded inside microfluidic chips facilitate multiplexed sensing of different parameters such as pH, oxygen, glucose, lactate, and chloride. In addition, microfluidic centrifugal technology has enabled miniaturization of typical laboratory processes such as blood plasma separation and enzyme-

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linked immunosorbent assay. In this regards, combining these novel platforms with microfluidic viscometers lead to the development of multiplexed microfluidic chips for blood coagulation monitoring and other blood tests. Moreover, different fluorescent probes provide monitoring of different blood coagulation factors such as thrombin. Multiplexed sensing for both blood coagulation analysis and other biochemical parameters is promising for developing low cost and multiplexed blood assessments. Recent advances in microfluidic technology has enabled the researchers to simulate the blood coagulation process in physiological conditions and study the events in the molecular level. Moreover, the fluorescent imaging and targeting different particles with fluorescent probes in microfluidic channels facilitate understanding of the interactions and origin of defects with a remote, accurate, and multiplexed manner. Other platforms like centrifugal microfluidic devices can be used for future multiplexed analysis of blood as it facilitates the separation of different blood components. Moreover, we discussed different nanostructured materials for the detection and treatment blood coagulation purposes which helps developing future monitoring and control of hemostasis at the same time in *in vivo* condition. In this paper, we covered different technologies for coagulation sensing and their working principle, some recent commercial devices, and possibilities of continuous *in vivo* hemostasis monitoring.

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