Thesis Title : Dynamics of Cellular Suspensions in Bioengineered Microfluidic Confinements: Perspectives from Physiology-On-Chip to On-Chip Medical Diagnostics

ABSTRACT

The dynamics of cells through the micro-vasculature networks in human body is an important physiological indicator of health and disease. However, it is almost impossible to be always able to decipher the migratory features of cells in-vivo. This gives rise to the need of developing in-vitro microfluidic devices analogous to human blood vessels which can be extensively used for research related to cellular migration. The study of cellular flow patterns through micro-confinements is not only important to understand the physiological complexities of human vasculature, but also sheds light in the process of designing diagnostic applications for screening of diseases which demonstrate typical cellular migratory features. Although research groups reported several works related to cellular mechanics through microfluidic devices, there is still a wide plethora of unanswered questions that need to be catered in order to develop a sound understanding of the physiological processes related to micro-circulation and efficient designing of microfluidic medical devices involving cellular transport. This thesis describes different aspects of cellular migration through micro-confinements, both from collective motion as well as single cell perspective, specially highlighting on the various complexities and lacunas involved in the process.

For instance, one key factor influencing cellular transport and distribution in micro-confinements is the deformability of the confining structures. In one of the chapters of this thesis, the intrinsic interplay between solid mechanics, hydrodynamics, and rheology is established using a combination of experiments and theoretical modelling. The elastic response of a micro-confinement is studied with fluids of different rheological complexities, starting with simple water and moving onto complex blood-analogue polymer solutions and finally red blood cell (RBC) suspensions. Furthermore, for the very first time, the effect of channel flexibility on the near-wall cell-free layer (CFL) distribution of red blood cells, is also analysed experimentally.

Another factor impacting motion of circulating cells through microchannels is the effect of surface functionalisation which is discussed in details in one of the subsequent chapters. Here functionalisation of the inner walls of the microchannel is carried out with protein layer as well as with human umbilical vein endothelial cells (HUVEC). The functionalisation not only helped to replicate a biomimetic internal micro-environment, but also contributed to the understanding of the effect of surface

chemistry on the adhesive motion of circulatory tumour cells (CTCs) and RBCs through the micro-confinements.

Going forward, this thesis answers another important research question related to the impact of external electrical stimuli on the adhesive rolling of cancer cells through functionalised microchannels. The experimental studies pertaining to this topic demonstrate that an electric field, even restricted to low strengths within the physiologically relevant regimes, can significantly influence rolling adhesion dynamics of the cells, quantified in terms of the voltage-mediated average rolling velocity and the adhesion frequencies. Furthermore, a simple theoretical model is also developed which suitably complements the experimental results by quantifying the change in kinetic rate of bond breakage for different field strengths.

Finally, the dynamics of cellular flow through micro-porous confinements is demonstrated, keeping in mind applications related to porous microfluidic devices for rapid diagnostics. Using simple wicking experiments with whole blood, it is shown how cellular aggregation within the pores of filter paper, shapes the overall wicking characteristics through paper-based devices used in point-of-care diagnostics. An important feature in this aspect is the liquid redistribution phenomenon due to limited sample volume of blood, which is studied thoroughly in this thesis using simple experiments and analytical scaling arguments. In addition to this, wicking behaviour of samples with abnormal aggregability conditions is also investigated by using RBC suspensions in dextran-infused buffer. A phenomenon of phase separation between the liquid and cellular matter could be observed during wicking of RBC suspensions through paper, which was strongly influenced by the combined interplay of cellular volume fraction, erythrocyte aggregability, membrane deformability of the cells and the degree of confinement. These phase separation regimes establish important connections between the physics of blood transport and physiological indicators like tissue oxygenation, for normal as well as hyper-aggregability conditions. The thesis is eventually concluded with a summary of the key findings, potential application landscape and possible future scope.

Keywords: micro-confinement, microfluidics, vasculature-on-a-chip, cell-free layer, aggregation, functionalisation, adhesive dynamics, phase separation, point-of-care diagnostics, paper-based microfluidics