Microfluid Nanofluid (2013) 15:519–532
DOI 10.1007/s10404-013-1172-2

RESEARCH PAPER

Pneumatic mold-aided construction of a three-dimensional hydrogel microvascular network in an integrated microfluidics and assay of cancer cell adhesion onto the endothelium

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Received: 9 September 2012 / Accepted: 5 March 2013 / Published online: 2 April 2013

Abstract A pneumatic microchannel network (PμCN) fabrication method for producing a three-dimensional microvascular system in an integrated microfluidic device is described. The spatial dynamics of the PμCN profile is systematically characterized and quantitatively analyzed. A microvessel network-embedded hydrogel scaffold is constructed using in situ pneumatic actuation of the PμCN and collagen polymerization. The endothelium-containing microvasculature, which has high cell viability and typical vascular features, was formed by seeding and cultivating human umbilical vein endothelial cells (HUVEC-C). Furthermore, a quantitative investigation of the adhesive interactions between breast cancer cells and endothelial cells was performed with vascular tissue-mimicry in the hydrogel-supported endothelial network using human breast cancer cells (MDA-MB-231) and HUVEC-C cells. The results show signal-promoted and region-preferred adhesion of cancer cells in the established microvascular network. The PμCN can be applied as an active microfluidic molding component for convenient and robust reproduction of microvasculature in vitro. PμCN application can be valuable in monitoring and investigating blood vessel-involved physiologic/pathologic processes. Moreover, this method will facilitate controllable parenchymal tissue organization and construction for tissue engineering as well as subsequent applications for clinical medicine.

Keywords Microvasculature · Pneumatic membrane · Microfluidics · Cancer cells · Endothelial cells

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Electronic supplementary material The online version of this article (doi:10.1007/s10404-013-1172-2) contains supplementary material, which is available to authorized users.

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1 Introduction

Mammalian microvascular networks, including arterioles, capillaries, and venules, are pervasive, interconnected, highly branched, and hierarchically organized microchannels that are the primary units of oxygen/nutrient delivery and waste removal of normal tissue metabolism and functions in vivo (Herbert and Stainier 2011). In addition, numerous pathologic events such as inflammation and tumor metastasis develop via functionally vascular systems, and are always accompanied by a series of interactions, e.g., leukocyte–endothelium and cancer cell–endothelium interactions (Nathan and Ding 2010; Grivennikov et al. 2010). Investigating and understanding the temporal and spatial dynamics of these biological networks and their endothelium-involved interactions are of fundamental importance in tissue biology because of specifically happening foci (Hendrix et al. 2003). Conventional studies using biologically relevant animal models have already revealed the physiologic features of the microvasculature (Iadecola and Nedergaard 2007; Muradashvili et al. 2012; Sasaki et al. 2006). However, controllably manipulating and studying intravascular microenvironment in vivo is difficult (Nelson and Tien 2006). In addition, conventional methods using animal models are time-consuming,