ABSTRACT

We present a multi-scale theoretical model for the endothelial glycocalyx (EG) and the associated endothelial surface layer (ESL). This is a macromolecular-level model that accounts for the self-assembly of the ESL from macromolecules present in the plasma and on the endothelial cell surface, and for the dynamic exchange of ESL constituents with macromolecules in the plasma. Results of non-equilibrium molecular simulations and numerical analysis of coarse-grained models of ESL formation, deformation, and disruption under plasma flow conditions will be presented. We will show that the dynamic and transient nature of the ESL is a crucial feature controlling its structure and function. Our model predicts that the apparent ESL thickness is a decreasing function of plasma flow rate and depends on the concentration of associating macromolecules in the plasma, in qualitative accord with several experimental studies. An analysis of the hydrodynamic shear stress transmitted by the ESL to the EG and the resulting chain tension induced in individual surface-bound EG macromolecules will also be presented.

INTRODUCTION

The endothelial glycocalyx is a layer composed of glycoproteins and proteoglycans bound to the extracellular surface of the endothelium. On the luminal endothelial surface, this layer serves as the scaffolding for the adsorption of serum proteins, allowing for the development of an extended gel-like macromolecular network on the capillary wall. Collectively, the glycocalyx and adsorbed protein layer are known as the endothelial surface layer (ESL) [1]. The glycocalyx and ESL are believed to play an important role in capillary permeability [2,3] by creating a selective steric barrier for molecular and cellular transport to the cell surface and intercellular junctions and also serve as a medium for cell signaling via mechanotransduction [4,5] and growth factors [6]. The ESL can be considered to function as a molecular filter that is capable of limiting or, in some cases excluding, blood-borne solutes, based on size and charge, from reaching the endothelial surface [7,8].

Experimental studies indicate that the ESL is a dynamic structure that changes in response to inflammation, and to changes in plasma composition and flow conditions. It is well known that components of the glycocalyx, such as the syndecan family of heparan sulfate proteoglycans, are actively shed during inflammation, which likely affects ESL function. In addition to inflammation, other conditions may predispose the ESL to breakdown. For example, certain cardioplegia solutions used clinically have been reported to cause a loss of ESL [9] and an analysis of plasma hemodilution by a variety of clinically utilized fluids suggests that some fluids promote a dissolution of the ESL [10]. Also, reactive oxygen species can damage the ESL whether generated via epi-illumination [11], oxidation of LDL [12] or during ischemia-reperfusion injury in vivo [13].

Continuum models can account for a number of the mechanical and transport properties of the ESL [5,14,15]. However, macromolecular-level models are necessary for theoretical studies of the kinetics of ESL formation, the dynamic microstructure and transport properties of the ESL, and the detailed mechanisms of cell signaling via mechanotransduction. The purpose of this contribution is to introduce such a macromolecular model and present results obtained for the formation of the ESL and the response of the ESL and glycocalyx to plasma flow and composition.

MODEL

We have developed a bottom-up, multi-scale approach to modeling the endothelial glycocalyx (EG) and the ESL. The starting point is the construction of structural models for key macromolecular constituents of the EG, including the syndecan-1 and glypican-1 proteoglycans, and the associating plasma constituents (e.g. albumin and hyaluronic acid) that form the ESL. The luminal EG is modeled as a grafted layer of the branched polyelectrolyte EG constituents, and established theories of solvated grafted polymers [16] have been adapted to determine the intrinsic EG layer properties (thickness, mass...
distribution, compressibility, and shear modulus) and the interaction of the glycocalyx with extracellular macromolecules that form the ESL. One key role of the EG is to provide a selective, compliant substrate for the self-assembly of the relatively thick ESL layer and for transmission of mechanical tension from the ESL to the endothelium. Our model for the ESL is based on the theory of associating polymers [17], polymers with distributed binding sites that self-assemble into transient gel networks. In addition to their intrinsically transient behavior, associating polymer models exhibit characteristic mechanical properties observed in the ESL. For instance, in response to shear flow of solvent such networks can relax, leading to plastic deformation and partial dissolution of the network.

RESULTS

We have used our multi-scale model to gain macromolecular level insight into the impact of plasma composition and flow properties on the structure and mechanics of the EG and ESL. Non-equilibrium molecular simulations and numerical analysis of coarse-grained models were used to study ESL deformation and disruption and the transmission of stress to the underlying EG layer under various plasma flow conditions. We will show that the dynamic and transient nature of the ESL is a crucial feature controlling its structure and function; the macromolecules that form the ESL are not permanent constituents but rather are in dynamic equilibrium with macromolecules in the plasma. In particular, our model predicts that the apparent ESL thickness is a decreasing function of plasma flow rate, and depends sensitively on the concentration and type of associating macromolecules in the plasma, in qualitative accord with several experimental studies [1]. We also present an analysis of the hydrodynamic shear stress transmitted by the ESL to the EG and the resulting chain tension induced in individual surface-bound EG macromolecules, a potentially important parameter for models of mechanical signal transduction.

REFERENCES