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Primary cilia as biomechanical sensors in regulating endothelial function

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ABSTRACT

Depending on the pattern of blood flow to which they are exposed and their proliferative status, vascular endothelial cells can present a primary cilium into the flow compartment of a blood vessel. The cilium modifies the response of endothelial cells to biomechanical forces. Shear stress, which is the drag force exerted by blood flow, is best studied in this respect. Here we review the structural composition of the endothelial cilia and the current status of knowledge about the relation between the presence of primary cilia on endothelial cells and the shear stress to which they are exposed.

Most cells in our body can bear monocilia or primary cilia, depending on e.g. their proliferative status. Cilia on the epithelial cells of the collecting ducts in the nephron are a classical example of monocilia (reviewed in (Rodat-Despoix and Delmas, 2009)). A decade ago attention in the developmental biology field was drawn to cilia by the groups of Hamada and Brueckner (Nonaka et al., 2002; Essner et al., 2002) who showed that the endodermal epithelial cells of the embryonic organizing center utilized a combination of motile and primary cilia to generate and sense nodal flow. This has an instrumental role in breaking the symmetry of the embryo. Since endothelial cells (ECs) comprise a specialized population of epithelial cells which are continuously exposed to fluid flow and are highly responsive to hemodynamic forces it is not surprising that these cells can bear primary cilia as well (reviewed in (Van der Heiden et al., 2011)). To date, there are no reports of ECs bearing motile cilia which have functions in blood vessels, but ciliary protrusions on ECs have been described for over 40 years (Mollo et al., 1969; Bystrevskaya et al., 1988; Gallagher, 1980). It is now clear that endothelial cilia truly belong to the subpopulation of primary cilia since they are composed of a 9+0 bundle core of microtubule doublets, and extend from the basal body of the cell (Fig. 1). Through the basal body they connect to the cytoskeletal microtubules of the cells (Fig. 1G,H). They are present on many types of endothelial cells, like Human Umbilical Vein Endothelial Cells (HUVECs) (Iomini et al., 2004; Geerts et al., 2011), mouse aorta ECs (Van der Heiden et al., 2008), and embryonic ECs from various species (Nauli et al., 2008; Hierck et al., 2008; Van der Heiden et al., 2006). Depending on the species and the location in the cardiovascular system the typical length of endothelial cilia varies between 1 and 5 μm, making them significantly shorter than cilia on other (epithelial) cells. A video which shows that, despite their short length, fluid flow is able to bend the endothelial cilium is available and accompanies the electronic version of this manuscript. To access this video component, simply click on the image visible below (online version only). A selection of still pictures from this video is shown in Fig. 1A. A cilium typically protrudes from the luminal side of the cell into the lumen of the vessel although it sometimes appears to protrude from the basal side into the basement membrane and underlying extracellular matrix (Fig. 2A). Interestingly, many cells found on the ventral luminal side of the embryonic aorta present primary cilia (Fig. 2B). These cells most probably represent endothelium-derived hematopoietic stem cells (Boisset et al., 2010). Functional consequences of the presence of cilia on these cells are yet unclear. Nauli and colleagues first demonstrated that primary cilia are necessary for calcium and nitric oxide signaling in ECs (Nauli et al., 2008). In contrast to ciliated cells, ECs without a cilium were not able to translate mechanical stimulation of the cilium into an intracellular calcium transient. This function depends on the presence of Polycystic Kidney Disease (PKD) proteins which are localized in the cilium. This is very interesting since it adds a vascular component to the large spectrum of ciliopathies which often present with various variants of cystic kidney diseases (reviewed in (Van der Heiden et al., 2011; Tobin and Beales, 2009; Nauli et al., 2011)).

Endothelial cells are highly responsive to (changes in) blood flow. In fact, they are able to sense the friction force or drag which is exerted on the cells of the vessel wall by the blood flow. This force is called shear stress and it depends on the viscosity and velocity profile of local blood flow. The unit of shear stress is Pascal (Pa) although it is often represented in dyne/cm^2 (10 dyne/cm^2=1 Pa). Blood flow and shear stress play decisive roles in, e.g., the development of the cardiovascular system (Hierck et al., 2008; Henning et al., 2011). Rapidly changing geometries are intricately related to changes in shear stress patterning. High shear stress,

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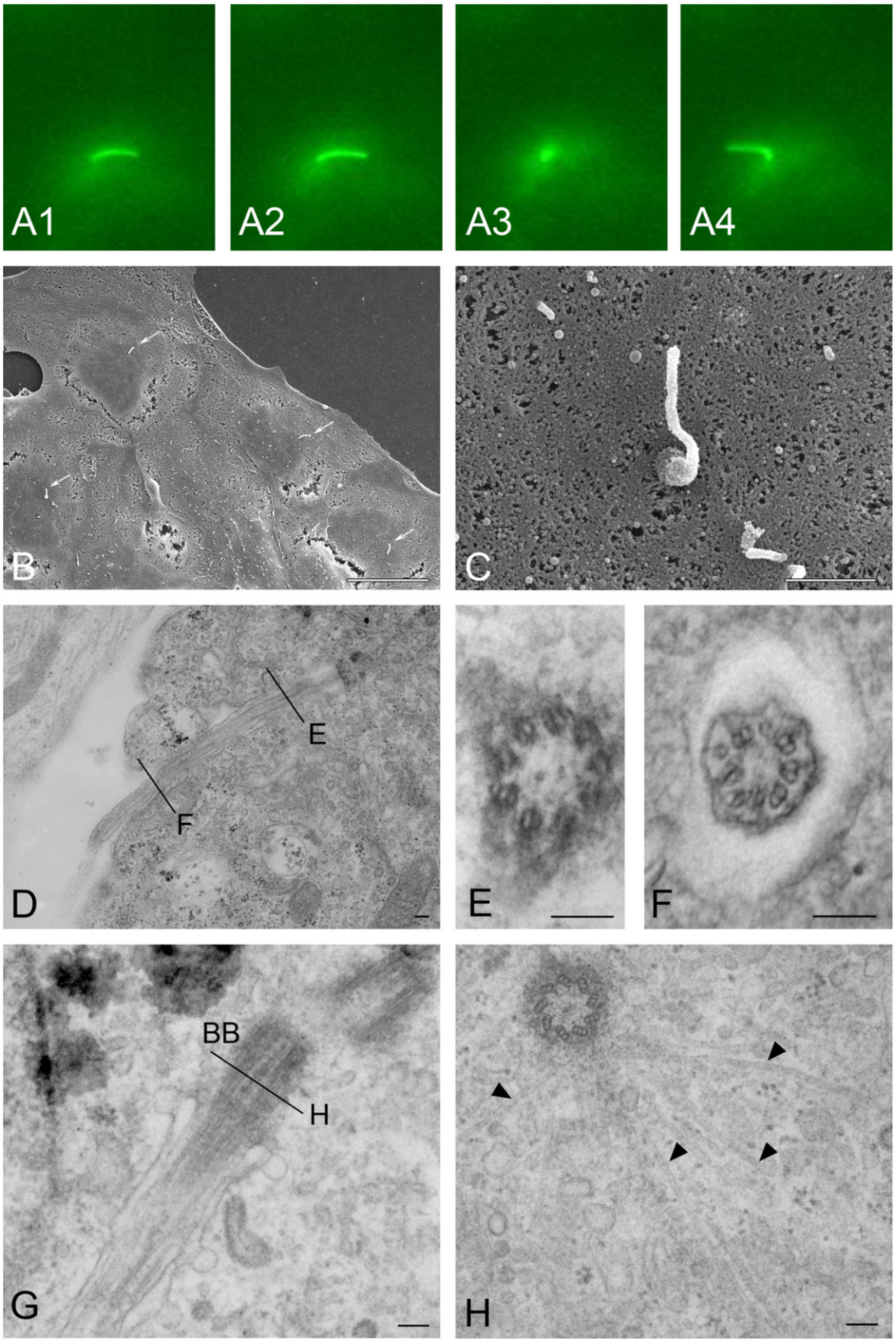

Fig. 1. Structural characteristics of the endothelial primary cilium. Panels A1 to A4 show fluorescent micrographs of a time series of ECs which are stably transfected with a tubulin-eGFP fusion construct and are exposed to oscillatory flow. Note that the fluorescent fusion protein localizes to the cilium which bends from right to left into the flow. Panels B and C show field emission scanning electron micrographs of primary cultures of chicken embryonic endothelial cells. The arrows (B) point to the primary cilia which show a typical perinuclear localization. Transmission electron micrographs (D–H) show longitudinal (D,G) and cross sections (E,F,H) through the cilium. Endothelial cilia are 1–5 μm in length and 200 nm in diameter. They protrude from the surface (A–D), have a 9+0 configuration of microtubules in their core (E,F), and are connected through the basal body (BB, G) to the microtubular cytoskeleton (arrowheads in H). Scale bars: B=10 μm, C=1 μm, D–H=100 nm.