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HOT OFF THE PRESS: BASIC

Circulating Extracellular Vesicles in Normotension Restrain Vasodilation in Resistance Arteries

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DOI: 10.30824/2003-6

Extracellular vesicles (EVs) are particles naturally released from a cell that are surrounded by a lipid bilayer and lack replicative capacity [1]. In recent years they have received significant attention as both biomarkers and mediators of intercellular signaling. In particular, circulating populations of large extracellular vesicles (i.e. microparticles or microvesicles) are elevated in conditions of vascular injury, strongly correlated with measures of vascular health, and predictive of future adverse cardiovascular events [2]. Our laboratory, and others, have also shown that large EVs can serve as vectors for intercellular communication leading to endothelial injury [3].

Interestingly, while there has been considerable interest in the impact of various cardiovascular conditions on circulating EVs, the impact of hypertension has been comparatively understudied. In the January issue of Hypertension work from the laboratory of Dr. Uta Erdbrügger addresses this critical gap in knowledge [4]. Good et al examined levels of circulating EVs in plasma from spontaneously hypertensive rats (SHR) and normotensive Wistar Kyoto Rats (WKY). At 12 weeks of age they observed significant increases in levels of circulating large EVs arising from endothelial cells as well as leukocytes. More importantly, they provided the first functional analysis of the impact of hypertension on the bioactivity of circulating EVs.

First, they observed that large EVs isolated from normotensive rats reduced vasodilation in isolated resistance arteries. This observation was consistent with previous reports from Brodsky et al. [5] and others. Most interestingly however was the observation that this impairment in vasorelaxation is absent in large EVs isolated from hypertensive rats. This was also true for EVs isolated from normotensive vs hypertensive human subjects. The authors also

confirmed that this alteration in EV bioactivity is not seen in SHR prior to blood pressure elevation: EVs from 6 week SHRs (normotensive) are capable of impairing vasorelaxation but EVs from 12 week SHRs (hypertensive) lose this ability. Thus, as the authors state, "alteration of EV function occurs during or after the development of hypertension in SHR animals".

The precise mechanisms responsible for this alteration are unclear, but the authors did report that delipidation of SHR EVs restored their ability to impair vasorelaxation. They speculate that the lack of an effect on vasodilation may be an adaptive response to the hypertension whereby the EVs are rendered less antivasodilatory.

It is interesting to note that this effect is somewhat different than that seen in other systems. Work from Jansen et al. [6] and our group [3] has shown that the antivasodilatory effects of endothelial-derived large EVs is increased when formed under high glucose conditions. Thus these effects appear to be quite disease-specific and further study is clearly needed to understand how EVs are altered by cardiovascular disease and the impact of this on in vivo endothelial function.

There are a number of limitations to this work which are well highlighted in the associated editorial for the article and need not be discussed here [7].

However one pressing question that I think merits investigation is whether antihypertensive treatment has any impact on EV bioactivity and if there differences between antihypertensive agents.

This would appear to be a logical next step for this work. Nevertheless this study represents a critical advance in understanding the impact of hypertension on EVs and the role of EVs in regulating vascular function in health and disease.

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