HHS Public Access

Author manuscript

Arterioscler Thromb Vasc Biol. Author manuscript; available in PMC 2022 October 01.

Published in final edited form as:

Arterioscler Thromb Vasc Biol. 2021 October ; 41(10): e493–e495. doi:10.1161/ATVBAHA.121.316810.

Response by Jung et al to Letter Regarding Article, "Sustained Activation of Endothelial YAP1 Causes Epithelioid Hemangioendothelioma"

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In 1981, two pathologists, Sharon Weiss and Franz Enzinger, identified 26 patients with a novel tumor epithelioid hemangioendothelioma, characterized by an "epithelioid" or "histiocytoid" endothelial cells arising from medium-sized or large blood vessels[1]. This pioneering study demonstrated that histologically verified epithelioid hemangioendothelioma filled the blood vessel lumen and expanded the vessel wall in a centrifugal fashion (Figure 1 of reference 1)[1]. Patients in Weiss and Enzinger's study often suffered symptoms relating to occlusion of the blood vessels, including pain and swelling, and exhibited fusiform expansion of grossly intact blood vessels[1]. During the last four decades, multiple clinical reports and studies from investigators across the globe have reported large occlusive intravascular epithelioid hemangioendothelioma in major blood vessels, including the aorta and vena cava of human patients[2–10]. Similarly, intravascular epithelioid hemangioendothelioma of the pulmonary vessels, first described as intravascular broncho-alveolar tumor in 1976, promotes severe narrowing or total occlusion of the vessel lumen[1, 11–13]. Taken together, multiple lines of evidence in human patients refutes Seavey C.N. et al's misleading statement that "human epithelioid hemangioendothelioma does not present as large occlusive intravascular growth…"

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Disclosures: None.

Conflict of interest: The authors have declared that no conflict of interest exists.

Over half of epithelioid hemangioendothelioma cases exhibit intravascular endothelial growth[1], yet the underlying pathogenesis driving intravascular endothelial cell proliferation, and thus occlusion of the vessel lumen remains largely unknown. To limit cell proliferation and organ size, the core kinases of the highly conserved Hippo pathway LATS1/2 phosphorylate the transcriptional co-activators YAP1 and its homologue WWTR1, which in turn promotes its cytosolic retention and proteosomal degradation. Failure of YAP1/WWTR1 degradation, and thus sustained activation of YAP1/WWTR1 signaling, is frequently associated with a variety of human cancers. Consistent with this, cytogenetic analyses of patients with epithelioid hemangioendothelioma identified a highly stable, nuclear, and constitutively active YAP1 or WWTR1 fusion genes[14, 15], suggesting sustained activation of YAP1/WWTR1 signaling.

Hence, the goal of our study[16] as stated: “Despite the potential importance of dysregulated Hippo/YAP signaling in epithelioid hemangioendothelioma, it has remained unclear whether YAP1 activation alone is sufficient to drive the formation of epithelioid hemangioendothelioma in vivo.” Endothelial cell specific activation of YAP1 alone (YAP^{5SA}) in adult mice resulted in formation of occlusive intravascular tumors arising from the endothelium of the pulmonary artery, the aorta, and the right atrium that histologically resembled epithelioid hemangioendothelioma, including features of epithelioid or spindled endothelial cells with cytoplasmic vacuoles, embedded in a myxohyaline stroma (Figure B-C)[16]. Consistent with our observations, a recent elegant study[17] from Duojia Pan’s laboratory demonstrated that endothelial cell specific activation of WWTR1 alone (TAZ^{4SA}) or WWTR1-CAMTA1 fusion in mice promotes the formation of occlusive intravascular tumors arising from the endothelium of the pulmonary artery that histologically resembled epithelioid hemangioendothelioma, including epithelioid or spindled endothelial cells with cytoplasmic vacuoles (Figure 1, 2, 4, Supplementary figure S1)[17]. In addition, WWTR1 alone (TAZ^{4SA}) or WWTR1-CAMTA1 fusion activates expression of the YAP1 target gene signature in highly proliferative endothelial cells forming intravascular epithelioid hemangioendothelioma (Figure 4, 6, Supplementary figure S3)[17]. Consistent with Duojia Pan’s study[17], we observed enrichment in the YAP1 target gene signature, upregulation of the vast majority of mitotic cell cycle genes, and expression of known epithelioid hemangioendothelioma markers in endothelial YAP1-expressing intravascular epithelioid hemangioendothelioma lesions (Figure D-F)[16]. We also observed highly mitotic $Cdh5^{+}$ endothelial cells in intravascular epithelioid hemangioendothelioma lesions, suggesting a cell autonomous role of YAP1 in endothelial cell proliferation (Figure E-F)[16]. These studies[16, 17] support a model in which endothelial cells expressing stable and active YAP1/WWTR1/WWTR1-CAMTA1 give rise to a highly mitotic form of intravascular epithelioid hemangioendothelioma in the large vessels, like the pulmonary artery, leading to severe deep vessel occlusion – a clinical phenomenon first described by Weiss-Enzinger[1] and Dail-Liebow[12]. Taken together, our study[16] demonstrates that sustained activation of endothelial YAP1 signaling in mice recapitulates human intravascular epithelioid hemangioendothelioma at genetic, histologic, and clinical levels.

The surgeons examining the fusiform expansion in patients of Weiss and Enzinger’s study suggested the possibility of an organizing thrombus, however, microscopic analyses revealed intravascular growth of rounded or slightly spindled eosinophilic endothelial

cells with prominent cytoplasmic vacuolization attached to the blood vessel wall[1]. Intraluminal tumors, including intravascular epithelioid hemangioendothelioma, are often misdiagnosed but provide an uncommon explanation of vessel thrombosis, a common clinical presentation[18–21]. Our retrospective analysis of pathologic lung tissue with intravascular occlusive tumors arising from endothelial cells of the pulmonary artery revealed round and oval cells with abundant pale eosinophilic cytoplasm and prominent cytoplasmic vacuolization (Figure A)[16], consistent with Weiss and Enzinger's[1] description of intravascular epithelioid hemangioendothelioma.

Further, Seavey C.N. et al's comparison of a study utilizing the NIH3T3 cell line is inappropriate for two reasons: first, the NIH3T3 cell line, cultured ex vivo in a 2-dimensional environment, does not recapitulate the complex 3-dimensional environment of intravascular epithelioid hemangioendothelioma, and second, NIH3T3 is not a relevant cell type to study endothelial cell biology in a tumor environment. Similarly, we clearly stated in our manuscript[16] that "this model may not phenocopy all aspects of human YAP1-TFE3 fusion protein–associated epithelioid hemangioendothelioma, as TFE3 also regulates several cellular processes."

Cardiac epithelioid hemangioendothelioma is extremely rare and only a handful of case reports have been recorded in the literature[22–25]. This has likely hampered studying the genetic drivers of epithelioid hemangioendothelioma at this anatomic location. Our study[16] warrants future studies to address this knowledge gap.

Acknowledgments:

UMass Medical School IACUC and IRB approved all animal and human samples use protocols, respectively.

Sources of Funding:

C.M.T is supported by National Institutes of Health grant HL141377.

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