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Endotrophin: Nominated for best supporting actor in the fibro-inflammatory saga

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As the population ages, more individuals are at risk of developing age-related chronic diseases, often leading to death. Identifying individuals most at risk for developing multiple co-morbidities could help tailor health care strategies in this growing population. Fibrosis and inflammation are key biological processes involved in the development and progression of a myriad of diseases, including chronic kidney disease, diabetes and cardiovascular diseases.

In an article in EBioMedicine [1], Morten Karsdal and colleagues report the association of circulating levels of a recently described collagen VI cleavage product, referred to as endotrophin, with chronic disease incidence and death in an observational, prospective cohort of elderly Danish women. Participants in this Prospective Epidemiological Risk Factor Study provided fasting blood samples at baseline (n=5,602) and at follow-up (2,094) timepoints. The authors measured the association between serum endotrophin levels and 17 inflammatory and fibro-proliferative chronic diseases that commonly occur in the elderly. Chronic kidney disease demonstrated the strongest association with endotrophin levels, followed by diabetes and cardiovascular diseases. However, it is difficult to know if the elevated serum endotrophin levels in patients with chronic kidney disease are the result of impaired kidney function or a reflection of an actual increase in kidney fibrosis. The authors compared the endotrophin levels with a number of concurrent morbidities. The authors found that the number of chronic diseases increased as endotrophin levels rose, independent of age and BMI. Finally, the authors evaluated the relationship between endotrophin and all-cause mortality up to 1 year after the endotrophin measurements were obtained. They showed that a two-fold increase in endotrophin levels predicted all-cause mortality at baseline (HR = 4.66) and follow-up (HR = 3.53), and they proposed endotrophin as a novel surrogate biomarker for fibroblast activity and progression of chronic disease.

As adipose tissues become dysfunctional, the altered physiological state of obese adipose tissue holds the key to enhanced pathologic sequelae across the board [2]. Adipose tissue that is forced to expand experiences stress at multiple levels. The size of individual adipocytes increases (referred to hypertrophy) prior to the recruitment of additional new adipocytes (referred to as hyperplasia) that help neutralize the excess lipid burden in the system [3]. Adipose tissue undergoes dramatic changes in the process of expanding its size. One of the key factors as to how well adipocytes handle the expansion process is how successfully the reshaping of the extracellular matrix (ECM) occurs [4]. ECM constituents and the machinery that modifies the ECM plays a critical role in this process. A critical mediator of the ECM in adipose tissue is endotrophin. Endotrophin is the carboxy-terminal cleavage product of the alpha3 chain of collagen VI [5]. Collagen VI is ubiquitously expressed, but highly enriched in adipose tissue. Importantly, collagen VI expression and endotrophin are upregulated in obese adipose tissue. Furthermore, immuno-histochemically, we find high endotrophin accumulation in human and rodent tumors, with increased expression in breast cancers, hepatocellular carcinoma, colon and ovarian cancers [6,7]. Selective overexpression of endotrophin leads to significantly increased mammary tumor growth, enhanced infiltration of tumors with endothelial and immunoinflammatory cells into the tumor stroma, enhanced fibrosis and dramatically enhanced metastatic growth. In contrast, neutralizing anti-endotrophin antibodies significantly reduce tumor growth and local infiltration of immune- and endothelial cells [6]. Endotrophin is therefore an excellent candidate linking obesity-associated adipose tissue dysfunction with increased tumor incidence, growth, and metastatic spread. Even though endotrophin acts mostly in the local microenvironment where it is produced, some of it escapes into circulation and can be measured as a biomarker [8]. Significant correlations of plasma endotrophin have been found with a wide array of disease conditions, all of which include fibrotic and inflammatory read outs. These include a) breast cancer; b) association with mortality and cardiovascular events in patients with atherosclerosis; c) renal fibrosis; d) steatohepatitis; e) glycemic regulation in diabetics; f) as predictor of disease progression in patients with chronic kidney disease; and g) as a predictive marker for the response to antidiabetic PPARγ agonists [9]. Based on these reports, it is clear that circulating

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endotrophin levels are meaningful predictors of a multitude of different disease states.

The data that Morten Karsdal and colleagues present add to previous animal and human studies that demonstrate that endotrophin could play a key role in the progression of age-related fibro-inflammatory diseases [10]. Cross-sectional biomarker studies, such as this one, require less cost and time commitment than longitudinal studies and can measure multiple biomarkers and disease states simultaneously, but this work is correlational and not meant to imply causality. Even though many preclinical studies have provided evidence for causality, determining the biological relevance of endotrophin in disease development in the clinic remains to be shown and findings need to be confirmed in different populations. Future work should attempt to examine the utility of endotrophin as a predictive marker for susceptibility to the development of chronic disease, or to monitor its progression. As the fibro-inflammatory saga continues to unfold, endotrophin is rapidly securing its position as a supporting actor in the pathogenesis of age-related morbidities.

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Contributors

PES and OTG performed the literature search and wrote the manuscript.

Declaration of Competing Interest

Olga Gupta, MD: Zealand Pharmaceutical - consultant on neonatal hypoglycemia. KJT - consultant on pharmacotherapy for childhood obesity. Rhythm Pharmaceutical - consultant on childhood obesity. Novo Nordisk - consultant on pharmacotherapy for childhood obesity (completed 2019). Philipp Scherer, PhD: Sponsored research agreement with Merck (ongoing). Sponsored research agreement with NovoNordisk (completed 1 year ago).

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