EDITORIAL

CARDIO(BLOOD-LYMPH)VASCULAR GENOMICS: NEED FOR A TERMINOLOGY ADJUSTMENT

In a recent Genomics in Medicine review on Cardiovascular Disease in the New England Journal of Medicine (1), consideration was given only to cardio(blood)vascular disease; (lymph)vascular genomics was omitted. This represented an untimely deficiency. Aside from the chromosomal aneuploidies commonly associated with lymphatic anomalies and even fetal demise (2-4), specific genes have now been identified for three monogenic lymphedema-angiodysplasia conditions, and loci have been mapped for several others (Figure).

Furthermore, there are close to 40 distinct familial lymphedemas, most OMIM-listed or cross-referenced, affecting the lymphatic segment of the “vasculature.” An article by Northup et al in this issue of the Journal presents a syndromic classification of these hereditary lymphedemas along with an atlas of characteristic phenotypic features (5).

Mutations have been identified in: endothelial receptor VEGFR-3 for lymphatic growth factor VEGF-C (6) in a subpopulation of Milroy syndrome of lymphatic hypoplasia; winged helix transcription factor FOXC2 (7) uniformly in hundreds of patients with Lymphedema-distichiasis (LD) syndrome with a hyperplastic lymphatic system; and transcription factor SOX18 (8) in 2 families with autosomal recessive Hypotrichosis-lymphedema-telangiectasia syndrome. Interestingly, the genetically engineered haploinsufficient (+/-) Foxc2 mouse (9) exhibits a double row of eyelashes and hyperplastic lymphatic phenotype like human LD, and the knockout (-/-) mouse displays aortic arch anomalies and interventricular septal defect (mimicking Tetralogy of Fallot), cleft palate and bony abnormalities spanning the clinical spectrum in severe LD. Clearly, the lymphatic system is an integral, interacting component of the “vasculature” and the “blood-lymph circulatory loop.” Moreover, as pointed out in our earlier editorials (10,11) and reviews (12-14) in Lymphology, more precise inclusive and exclusive terminology should be used when referring to either the blood- or lymph-containing vessels or both, and the commonly used expression “the vasculature and the lymphatics” should be abandoned altogether since it perpetuates a fundamental misconception. Thus, a “terminology adjustment” is needed to facilitate future discussion of the similarities and differences between the blood vasculature and the lymph vasculature in general and specifically for thoughtful exploration of the genomics of cardiovascular [i.e., cardio(blood-lymph)vascular] disorders.

REFERENCES

Fig. Genomics of lymphedema-angiodysplasia syndromes displaying mutation of known genes for familial Milroy lymphedema subpopulation (VEGFR-3 at chromosome 5q34-35), lymphedema-distichiasis (FOXC2 at chromosome 16q24), and hypotrichosis-lymphedema-telangiectasia (SOX18 at chromosome 20q13) and linkage locations for Agenaes syndrome (chromosome 15) and Noonan syndrome (chromosome 12). In addition, aneuploidies and rearrangements involving other chromosomes are associated with additional lymphedema-angiodysplasia syndromes.


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