THE GENETIC BASES OF LYMPHEDEMA

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Background: Lymphedema, caused by dysfunction of lymphatic vessels, leads to disabling swelling that occurs mostly on the extremities. Lymphedema can be either primary (congenital) or secondary (acquired). Familial primary lymphedema commonly segregates in an autosomal dominant or recessive manner. It can also occur in combination with other clinical features. Nineteen mutated genes have been identified in different isolated or syndromic forms of lymphedema. However, the prevalence of primary lymphedema that can be explained by these genetic alterations is unknown. We have investigated systematically eleven of these putative genes.

Methods: We screened 112 index patients from **families** with inherited primary lymphedema and 328 patients with **sporadic or unknown origin** primary lymphedema. A targeted next generation sequencing panel for IonTorrent (Personal Genome Machine, PGM) was designed. We included coding regions of *FLT4, VEGFC, KIF11, FOXC2, SOX18, CCBE1, PTPN14, GATA2, IKBKG, GJC2* and *GJA1*.

Results: We discovered 44 mutations explaining 39% of the **inherited** cases. In addition, 49 mutations were found in **sporadic or with unknown origin** patients, explaining 15% of the cases. We are currently performing co-segregation analyses and more detailed clinical phenotyping for those patients with a more likely pathogenic nucleotide change.

Discussion: The genetic cause of primary lymphedema remains unexplained in 61% of patients with a family history and 85% of sporadic or with unknown origin cases. Identification of those genes is important for understanding of etiopathogenesis, stratification of treatments and generation of disease models. Interestingly, most of the proteins that are encoded by the genes mutated in primary lymphedema seem to act in a single functional pathway involving VEGFR3 signaling. This underscores the important role this pathway plays in lymphatic development and function, and suggests that the unknown genes may also have a role in the same pathway. We use whole exome sequencing (WES) to unravel those genes.

FROM MOLECULAR GENETICS AND BIOLOGY TO EFFECTIVE TREATMENTS OF LYMPHATIC DISORDERS

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In 1971, Judah Folkman proposed the concept of anti-angiogenic tumor therapy [1]. 12 years later, Harold Dvorak isolated the responsible growth factor VEGF [2]. Nine years later, Napoleone Ferrara reported the generation of neutralizing monoclonal antibodies against VEGF. Another five years later, Phase I trials started with the humanized version of one of the monoclonals: bevacizumab. Since 2004, when it received FDA approval, it has been marketed under the brand name Avastin [3].

The translation of basic biomedical research into tangible benefits for patients appears sometimes agonizingly slow. The public has been promised much by hyped scientific breakthroughs [4]. Scientific journals and scientists have played along in over-hyping scientific breakthroughs in the hope of impact factors and citations in order to secure and justify funding and fame [5]. Not surprisingly, practitioners ask when the discoveries from basic research will finally improve the standard of care for their patients.

Lymphatic research is no exception. Practitioners are largely still limited to symptomatic treatment and there seems to be still an invisible, but perceptible divide between those who do the molecular biology research and those who treat patients. The Avastin story is a plea for basic research: it might be complicated and it might take time, but it eventually does pay off. How is the lymphatic research community doing concerning the translation of research results into treatment options? Examples of lymphatic research in or shortly before the clinical trial stage include:

– Growth factor enhanced lymph node transplantation to treat secondary lymphedema [6]
– Utilizing the Schlemm channel's lymphatic character in glaucoma treatment [7]
– Anti-angiogenic tumor treatment with anti-lymphangiogenic agents [8]

Treatment of primary lymphedema with VEGF-C has been proposed [9]. However, our understanding of the physiological process of lymph vessel development is far from complete [10], despite significant recent progress in our understanding of developmental lymphangiogenesis [11,12] and first attempts at tissue-engineering lymphatic vessels [13].

If the results from high throughput cancer profilings are predictive of lymphatic conditions, then many patients will feature very individual, multifactorial disease profiles [14]. Even more challenging than the identification of such causes will be the development of treatment regimens that rapidly can be tailored to such individual needs.

Bibliography

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