Stanley P L Leong

California Pacific Medical Center and Research Institute, USA

Cancer metastasis from the primary site to the sentinel lymph nodes and beyond in relationship to the immune system

Multiple factors are involved in the development of cancer. They may include carcinogens, host genetic risk, chronic inflammation and others, which cause mutations within cellular DNA. The mutant cancer cells flourish in the cancer microenvironment (CM) consisting of fibroblasts, lipocytes, immune cells, lymphatic and vascular vessels and other parenchymal cells. Mutation gives rise to the unique characteristics of cancer heterogeneity with various clones competing to survive within the CM. By evading the host immune surveillance and by its intrinsic proliferative advantages using unique signaling pathways, cancer clones grow by expansion. The cancer cells tend to spread first through the sentinel lymph node (SLN) in over 90% of the time, which serves as a primary gateway for the cancer cells to proliferate and spread further to distant sites. Patients with negative SLNs but subsequently develop distant metastasis during follow-up indicate that their cancer cells have bypassed the SLNs to spread through the vascular system. VEGF-C has been found to induce lymph angiogenesis in the SLNs and facilitate systemic metastasis. The interaction between cancer cells and the immune system varies among different patients and it undergoes continuous dynamic changes. The relationship between the cytotoxic T cells (CTLs) and cancer cells is highly complex and their molecular interactions have been elucidated through the understanding of the CTLA-4 and programmed death (PD-1) pathways. During cancer progression and evolution in the host, the cancer cells have maximized their ability to take advantage of the CTLA-4 and PD-1 pathways to proliferate while causing the CTLs to undergo apoptosis and wither away so that the cancer cells can grow without hindrance. Thus, aggressive cancer clones have achieved the survival advantage as the 'fittest' clones akin to Darwin's survival of the fittest from the influence of natural selection. The CM may exert the selective force to favor the cancer clones to develop, similar to the principles of directed evolution of enzymes and antibodies The molecular relationship between cancer growth and CM as well as the host influence such as the immune system on cancer progression may be studied by using multiplexed microscopy, genomic profiling, microRNA analysis and gene exon sequencing. To date, blockade of the immune checkpoint pathways such as ipilimumab (anti-CTLA-4), pembrolizumab and nivolumab (both anti-PD-1) have resulted in significant tumor responses with subsequent FDA approval of these drugs. The immune system and cancer growth are so complex that perhaps artificial intelligence needs to be developed to elucidate the proliferation of cancer cells in relationship to the structure and physiology of the lymphatic system in a new field, which may be coined as Oncolymphology.

Speaker Biography

Stanley P L Leong is board certified in surgery and is an internationally recognized surgical oncologist with expertise in melanoma. He specializes in sentinel lymph node surgery and immunotherapy for patients with advanced melanoma. He has lectured nationally and internationally on new advances in the treatment of malignant melanoma and the use of selective sentinel lymphadenectomy. As Associate Director of CPMC's Center for Melanoma Research and Treatment, he collaborates with other investigators including Mohammed Kashani-Sabet on a new integrated research program at CPMCRI aimed at developing novel combination therapies for aggressive and metastatic tumors, including melanomas. He is the founding member and president of the Sentinel Node Oncology Foundation. He has chaired and co-chaired the biennial International Cancer Metastasis Congress since 2005 with emphasis in the mechanisms of cancer metastasis through the lymphovascular system.

e: leongsx@sutterhealth.org

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