The 694th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H29.5.31)

Role of lymphangiogenesis and lymphatic vessel microenvironment in metastatic progression

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The lymphatic vasculature is an important pathway for dissemination of most solid tumors and presence of metastases in the lymph nodes remains one of the key prognostic criteria. Despite the apparent clinical significance of lymphatic spread, it is not understood whether the presence of metastases in lymphatics is only an indicator of aggressive disease or whether the lymphatic system directly contributes to metastatic progression. We have demonstrated that the induction of lymphangiogenesis in the primary tumor increases regional and distant metastases. Moreover, induction of lymphangiogenesis at the distant site, in the lung, leads to the colonization of the lung through the pulmonary lymphatics and rapid progression of metastatic disease. Metastases in pulmonary lymphatics exhibit rapid growth and they are not hypoxic despite the absence of angiogenesis. Furthermore, metastases in lymphatics exhibit remarkably low rate of cell death. We have recently discovered that the soluble factors made by lymphatic endothelium protect melanoma and breast cancer cells from death by inducing metabolic adaptations in cancer cells. Lymphatic endothelial cells promoted survival of tumor cells under stress by improving mitochondrial function in tumor cells and by inducing metabolic shift to maintain redox homeostasis and promote cellular energy production. I will present recent advances in our understanding of the mechanisms by which lymphatic vessels, and in particular lymphatic endothelium, impact metastasis.

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Chaperone-dependent S1P signaling

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Sphingosine 1-phosphate (S1P) is a simple lysophospholipid produced from the metabolism of sphingomyelin. Our laboratory cloned the first S1P receptor as an orphan G protein-coupled receptor (GPCR) from vascular endothelial cells in 1990 and de-orphaned in 1998. We now know that five distinct GPCRs (S1P1-5) that are widely expressed mediate most of the actions of this lysophospholipid mediator. Some of the well-studied actions of S1P include its essential roles in vascular development, immune cell trafficking and neuronal development. Indeed, the first S1P receptor inhibitory drug, Fingolimod, is now approved as an oral medication in the treatment of multiple sclerosis. Novel S1P receptor-based therapeutics are being developed to control additional autoimmune diseases such as ulcerative colitis and psoriasis.

We recently discovered that the majority (−65%) of plasma S1P is chaperoned by HDL-bound Apolipoprotein M. Our recent studies suggest that chaperones impart specific biological functions to S1P. In the vascular system, S1P works together with angiogenic factors such as VEGF-A to regulate early vascular development. Indeed, RBC release of S1P is essential for embryonic development. S1P receptors 1, 2, and 3, which have distinct as well as overlapping signaling pathways, cooperate to regulate vascular development. However, postnatally, S1P receptors in the endothelium regulate vascular homeostasis. Dysregulation of S1P receptors influence vascular disease in mouse models of atherosclerosis, pathologic angiogenesis, etc. HDL-bound S1P acts as a biased agonist to suppress vascular inflammation and restore endothelial function. HDL-S1P-dependent signalling via the endothelial S1P receptor-1 is needed for liver regeneration after partial hepatectomy and suppression of fibrosis after liver injury. Thus, S1P signalling is modulated by chaperones and receptors in both physiological and pathological contexts in a wide variety of organ systems.

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(H29.6.6)

Emergency Cesarean Section－A Multinational View of the "30 Minute Rule"

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Cesarean section is one of the most commonly performed surgeries worldwide. Cesarean section rates and response times in conducting emergency cesarean section, however, vary widely from country to country. In 1989, the American College of Obstetricians and Gynecologists (ACOG) committee on professional standards issued a recommendation that US hospitals with obstetric services should be able to begin a cesarean delivery within 30 minutes of the time the decision was made to perform the procedure. This has become known as the "30 minute rule." Similar guidelines have also been adopted in the UK. The rule was intended to expedite delivery in cases such as umbilical cord prolapse, placental abruption, placenta previa with hemorrhage, non-reassuring fetal heart rate tracing and uterine rupture. Interestingly, the "30 minute rule" has become a medical-legal standard for the adequacy of obstetric care in spite of limited published data showing its usefulness in improving outcome.

A benchmark study was conducted in the US to determine the relationship between maternal and infant outcome and emergency cesarean section response times (Bloom SL. Obstet Gynecol 2006; 108: 6-11). This was a large, multi-center trial that prospectively evaluated 2,808 primary cesarean deliveries performed for emergency indications. Of these, 1,814 (65%) began within 30 minutes of the decision to operate. Infants delivered within 30 minutes were more likely to have acidosis and to require intubation in the delivery room, probably attesting to the need for an expedited delivery. In the 994 (35%) of emergency cesarean sections conducted 30 minutes or more after the decision to operate, 95% of newborns did not have adverse outcomes. In this group, however, the most common indication for emergency cesarean section was non-reassuring fetal heart rate tracing, a condition that is widely and subjectively interpreted.

Another important consideration is that all the hospitals in this study were university based with access to "in-house" multidisciplinary coverage. A review of the literature suggests that many hospitals in the US and abroad struggle to meet this rule, especially small or rural facilities with limited resources or personnel. Many argue that a universal standard requiring that all emergency cesarean sections occur within 30 minutes is unrealistic and unsupported by scientific evidence. Most would agree, however, that hospital audits should be conducted to assess timeliness of emergency deliveries in an effort to improve performance standards.