The 528th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H21.10.13)

Inflammation and cancer: molecular targets and opportunities

Raymond N. DuBois
(M.D. Anderson Cancer Center, Vice President)

It is now clear that long-term use of NSAIDs leads to a 40%-50% reduction in risk for colorectal cancer and some other malignancies. How do these "anti-inflammatory" drugs act to reduce cancer risk? NSAIDs effectively target inhibition of prostaglandin synthesis by the cyclooxygenase enzymes (COX-1 and COX-2). Prostaglandins, such as PGE2, regulate the expression of several downstream effector genes, some of which regulate pro-inflammatory pathways. These bioactive lipids signal via G protein-coupled receptors, which in turn can transactivate growth factor receptors and regulate cell proliferation, migration, angiogenesis and cell survival. Prostaglandin E2 (PGE2) has been shown, in some reports, to directly activate components of the canonical Wnt signaling system. Additionally, PGE2 can transactivate the epidermal growth factor receptor (EGFR) in colorectal carcinoma cells via a c-Src dependent mechanism that regulates cell proliferation and migration. The pathway which regulates degradation of prostaglandins, namely 15-PGDH, is also regulated by EGFR signaling. We also found that PGDH (as well as certain prostaglandin transporters) may serve as a tumor suppressor in colorectal cancer and provide a possible COX-2-independent way to target PGE2 to inhibit cancer progression. Several large clinical trials have been completed demonstrating that selective COX-2 inhibitors are effective in preventing adenoma regression and prolonging survival in humans with colorectal cancer.

The 537th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H22.2.22)

VEGF receptor signal transduction

Lena Claesson-Welsh
(Uppsala University, Professor)

Signal transduction by vascular endothelial growth factors (VEGFs) through their cognate VEGF receptor tyrosine kinases follows the consensus scheme for receptor tyrosine kinases. Thus, binding of ligand induces receptor dimerization and activation of the tyrosine kinase through transphosphorylation between receptor molecules, leading to initiation of intracellular signal transduction pathways. Certain signal transduction pathways are shared with most, if not all, receptor tyrosine kinases, whereas some may be unique (e.g., transduced only by VEGF receptors). Indications that such unique signaling pathways may be discerned only when VEGF receptors are expressed in their proper context (i.e., in endothelial cells of microcapillary origin). In this talk, I present a number of methods for the study of signal transduction in endothelial cells. I mention how to isolate and examine endothelial cell lines together with the embryoid body model representing vasculogenesis and angiogenesis, the procedure for subcutaneous Matrigel plugs, and, finally, how to construct gene-targeted mouse models. I emphasize the need for validation of in vitro data in more complex models, where endothelial cells reside in their proper three-dimensional context.

The 539th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H22.3.18)

Novel basic and therapeutic insights in angiogenesis

Peter Carmeliet
(Vesalius Research Center (VRC), Professor)

Understanding the molecular basis of the formation of blood vessels (angiogenesis) is of great medical relevance. Indeed, insufficient angiogenesis leads to tissue ischemia, and an excess of angiogenesis promotes cancer, inflammation and other disorders. In the last years, an antibody targeting an angiogenic growth factor has been approved as the first clinical anti-angiogenic agent and successfully used to treat colorectal cancer, lung and breast cancer patients. Additional anti-angiogenic agents with a complementary mechanism and broad safety profile are thus needed to increase the overall efficacy and overcome resistance to anti-angiogenic treatment. Supply of oxygen is one of the most ancestral functions of the vascular network, vessels should possess mechanisms to sense and re-adapt oxygen supply and, hence, perfusion in case of oxygen shortage. These are critical processes, since an abnormal leaky and misshaped endothelial lining, as occurs in tumor vessels, impair perfusion and oxygenation. The resultant tumor hypoxia represents a strong stimulus for tumor malignancy and metastatic tumor cell spreading. Since we have recently shown that endothelial cell specific deletion of one PHD2 allele suffices to induce endothelial cell normalization, we also hypothesize that improving the normalization of neo-vessels in ischemic tissues might improve perfusion and oxygenation and thereby improve therapeutic angiogenesis.