

**Tumor Biology and more:  
Highlights of the 10<sup>th</sup> Joint Meeting  
'Signal Transduction: Receptors, Mediators and Genes'**

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The "STS Meetings Signal Transduction: Receptors, Mediators and Genes" have become a widely acknowledged event within the scientific year. From November 2 to 4, 2006, we witnessed the 10<sup>th</sup> issue of the now definitely "traditional" interdisciplinary conference. As scientists from various fields of biomedical research met at the Weimar Hilton Hotel for attend the anniversary Meeting which, as its predecessors, was organized by the Signal Transduction Society. As in the years before, other scientific organizations supported the Meetings, such as special interest groups of the German Societies for Cell Biology (DGZ), Immunology (DGfI) and Biochemistry/Molecular Biology (GBM).

Throughout the three days of the Meeting, five sessions covered a wide spectrum of signal transduction research, among them special workshops on "Receptor-triggered pathways", "Viral and Bacterial Pathogens", "Adhesion Molecules" and "Structural and Functional Compartmentalization". Keynote lectures within these sessions were given e.g. by Rudi Balling from the Helmholtz Centre for Infection Research in Braunschweig and Doris Wedlich from the University of Karlsruhe, and Roland Eils from the German Cancer Research Center in Heidelberg. R. Balling provided an overview on current efforts to better understand bacterial infections by employing extended mouse mutant analysis. A most interesting take home lesson concerned results from studies on "humanized" mice. They allow researchers now to realize and consider differences between "mice and men", which are particularly evident within the immune system.

The contribution by D. Wedlich was devoted to recent concepts on cadherin function in cell-cell adhesion, R. Eils spoke on the emerging power of *in silico* simulation of cellular signaling.

An approved constituent of recent years' STS-Meetings was the "special feature" topic. A particular focus of the Anniversary Meeting was on signal transduction in tumor biology and medicine. The remainder of this report will highlight a couple of issues treated in this context.

Survival rates for various kinds of cancer have significantly improved over the last two decades. This progress is to a large extent due to better diagnostics, surgery, chemo- and radiotherapy. However, rapid progress in the understanding of mis-regulated signal transduction in cancer has helped to develop novel therapeutical strategies that specifically target components of tumor-related signalling pathways. Cancer is the consequence of defects in cellular signaling processes involved in the control of cell growth, survival, division and differentiation. The annual Meeting of the Signal Transduction Society (STS), held in Weimar, Germany from Nov. 1-4, 2006 and traditionally devoted to a wide spectrum of research, this year had a focus on "Molecular and Clinical Tumor Biology". Novel concepts with regard to cancer-related signaling from receptors via cytoplasmic mediators to gene regulation were discussed. The common theme of all contributions was to define critical switch points whose malfunction is involved

in malignancy. Here, we briefly summarize some highlights of keynote presentations on Cancer at the STS Meeting (for details see [www.sigtrans.de](http://www.sigtrans.de) ).

Cloning of the EGF receptor and its oncogenic counterpart HER-2/neu by Axel Ullrich (now at the Max-Planck-Institute of Biochemistry in Martinsried, Germany) and colleagues led to the development of “Herceptin”, an inhibitory antibody directed to the receptor which represents the first FDA-approved drug specifically targeted to an oncogene product. Herceptin is now successfully administered in many cases of metastatic breast cancer. Since the first description of HER-2/neu’s tumor-promoting properties, various other receptor tyrosine kinases have been implicated in cancer, mostly identified by means of genomic analysis strategies. Axel Ullrich and colleagues discovered the RTKs IGF1R, Axl/Ufo and Flk-1/VEGFR2 as critical signaling elements in tumor progression and devised them as attractive targets for drug development. A successful approach to blocking oncogenic receptor activity was applied to Flk-1/VEGFR2, an RTK mediating the function of Vascular Epithelial Growth Factor (VEGF). Flk-1-dependent angiogenesis is crucial for tumor growth and can be efficiently ameliorated by small molecule drugs. VEGFR blockers provide interesting lessons on the multifaceted issue of kinase inhibitor specificity in cancer therapy: SU5416 is highly selective for the Flk-1/VEGFR2, is an anti-metastatic, efficacious drug in mouse cancer models, but showed sub-optimal pharmacological properties in clinical trials. SU11248, on the other hand, also inhibits Flk-1 by interfering with its phospho-transfer function, but is a multi-targeted kinase inhibitor that also interferes with other RTKs such as the PDGF receptor and Kit. However, it proved a beneficial drug with relatively mild side-effects and is as “SUTENT” now in clinical use now for the treatment of Gleevec-resistant gastrointestinal tumors and renal carcinoma.

A trigger for angiogenesis is hypoxia, a link investigated by Jacques Pouyssegur and colleagues from the Institute of Signaling, Developmental Biology and Cancer Research in Nice, France. Hypoxia-Inducible Factor-1 (HIF-1) is a transcription factor that governs the adaptation of cells to low oxygen tension. The activity of HIF-1 relies on the concentration of its alpha subunit whose rate of degradation depends on the availability of oxygen. Recent work revealed an important role of an oxygen sensing protein named Factor Inhibiting HIF-1 (FIH-1) which also participates in the control of HIF-1 activity. Interestingly, HIF-1 alpha has two transcriptional transactivation domains (TADs), governing the expression of distinct sets of genes. A picture emerges in which the attenuator protein FIH-1 dictates the respective activity of the two HIF-1 TADs in a differentiated manner, depending on the actual oxygen tension. These findings may explain the observation that HIF-1 has dual effects and can induce either cell survival or cell death.

Cancer is a developmental disease, i.e. gene regulatory networks that control normal development can be subverted and evoke cancer upon mutational dysregulation. A striking example for such a double-faced signaling system with important functions in both development and cancer is the c-Met receptor and its cellular effectors. Walter Birchmeier and colleagues from the Max-Dellbrück-Center for Molecular Medicine in Berlin, Germany have studied the receptor tyrosine kinase c-Met and its major cytoplasmic substrate Gab1 for many years. c-Met is the receptor for Hepatocyte Growth Factor (HGF) and can, together with the the large adaptor protein Gab1, trigger metastatic behavior of many types of cancer cells if hyperactive. Physiologically, c-Met and Gab1 are determinants of morphogenesis, in particular of tubular structures. Recent work on conditional mutant mice by Birchmeier’s group showed that the Met signalling system is not important for normal skin generation and maintenance, but is crucial for skin regeneration in wound healing. Studies on mice expressing various mutants of docking protein Gab1 correlated for the first time Gab1-triggered downstream pathways with in vivo functions, e.g. signaling from

Gab1 to tyrosine phosphatase Shp-2 with migration of muscle precursor cells into the limbs.

Another example of a signal transduction system with essential functions in both development and cancer is the JAK/STAT pathway triggered by cytokine receptors. JAK-STAT signaling is unique in that STAT proteins, upon dimerization, immediately link receptor-induced signals generated at the plasma membrane to transcriptional events in the nucleus. Physiologically, STATs control proliferation and differentiation in hematopoiesis and immune defense and, at least for STAT3 and STAT5, developmental and migratory processes throughout organogenesis. Given these fundamental functions, it is not surprising that aberrant JAK/STAT signaling is frequently associated with cancer. As discussed by Richard Moriggl from of the Ludwig Boltzmann Institute for Cancer Research in Vienna, Austria, tumor cells can gain independence from external signals by autocrine production of cytokines or through inappropriate activation of intracellular key signaling molecules, resulting in persistent STAT activation. An only recently recognized oncogenic feature of a STAT factor relates to the tertiary structure of the protein: STAT5 tetramers were found to accumulate in excess compared to dimers in various human leukemias, leading to the notion that STAT5 tetramer formation is associated with leukemogenesis.

The acquisition of malignancy by tumor cells comprises the potential of autonomous cell division, a striking property that distinguishes them from “normal”, mortal somatic cells. Doubtlessly, dysregulations in signaling events underlying replication and cell cycle progression also contribute to autonomous cell multiplication and tumorigenicity. Ludger Hengst who is now at the the Biocenter of the Medical University in Innsbruck, Austria, was one of the pioneers who defined molecules that limit cell cycle progression. While cyclins and cyclin dependent kinases (CDK) push the cell cycle forward, CDK inhibitor like p27Kip1 can downregulate CDK activity, e.g. in response to antimitogenic signals. However, this inhibitor was found to participate also in activated CDK complexes. Recent work by Hengst's group may contribute to the explanation of this paradoxon. They described an as yet unrecognized link between p27 and oncogenic tyrosine kinases such as the Src family kinase Lyn and BCR-ABL. Tyrosine phosphorylation of p27 impairs its inhibitory function in the complex with CDK2. At the same time it increases kinase activity of CDK2. In consequence, p27 becomes itself phosphorylated by the CDK and this modification renders it susceptible for proteosomal degradation. In the light of these findings it is no longer surprising that p27 is prematurely eliminated in cells transformed by activated tyrosine kinases.

Reduced levels of the cell cycle inhibitors frequently indicate poor prognosis for cancer patients. On top of this, the cell cycle in general is of enormous interest for diagnostic and predictive issues in cancer medicine. Ron Laskey's work at the MRC Cancer Cell Unit Hutchinson in Cambridge, UK, is concerned with the exploitation of DNA replication for cancer diagnosis. He has coined the term “replication licensing” and showed that minichromosome maintenance (MCM) proteins are central players in this process. They are, hence, promising screening markers in early stages of cancer. In addition to this, MCM3 is also a potential novel target for cancer treatment: It is acetylated by the acetylase MCM3AP and, upon acetylation, inhibits the initiation of DNA replication. MCM3AP is upregulated in response to stimulation by cytokines TNF- $\alpha$  and interleukin-6. Most interestingly, this cytokine combination is able to kill many tumor cell lines, but leaves normal human cells unaffected. This observation obviously may open up intriguing perspectives for therapy.

Although ubiquitin, as indicated by its name, is a particularly “common” protein, and attachment of ubiquitin to proteins prone to degradation is a cellular reaction as basic as protein biosynthesis, alterations to the ubiquitin system is associated with inflammatory diseases and cancer. Ivan Dikic from the Institut of Biochemistry of the Frankfurt University Clinic provided examples of disease-related pathways not only regulated by a single ubiquitin and its respective activating, conjugating, and ligating enzymes, but also by a sophisticated cross-talk of different ubiquitin-like modifiers (Ubls) such as SUMO, NEDD8, ISG15 and FAT10. Ubiquitin and Ubls interfere with the function of potentially oncogenic proteins such as p53, NF $\kappa$ B and DNA repair enzymes, which are regulated by ubiquitylation, sumoylation and neddylation. Ubiquitin-related pathways, thus, constitute interesting targets for anticancer drugs. The proteasome inhibitor Bortezomib/PS-341 is already approved for clinical use in multiple myeloma (MM) therapy and affects various growth and survival pathways in MM cells, e.g. by inhibition of NF- $\kappa$ B, impairment of the DNA repair machinery and down-regulation of growth and antiapoptotic signaling pathways. As Dikic pointed out, more specific agents that target the ubiquitin-system are currently being developed, including selective inhibitors of ubiquitin ligases like MDM2. Moreover, deubiquitinating enzymes and the binding interfaces of ubiquitylated proteins and ubiquitin binding domains have emerged as potential drug targets, thereby further extending the spectrum of promising novel options in cancer treatment.

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