CELL BIOLOGY

Signal Transduction—Receptors, Mediators, and Genes

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The 2008 annual meeting of the Signal Transduction Society covered a broad spectrum of topics, with signaling in immune cells as the special focus of the meeting. Many of the immune signaling talks concerned B and T lymphocytes in particular; the role of inflammatory cytokines in cancer progression was also addressed. Neoplastic development was also discussed with regard to aspects of cell cycle control, aging, and transformation. Topics extended to signaling pathways induced by bacteria, viruses, and environmental toxins, as well as those involved in differentiation, morphogenesis, and cell death. This international and interdisciplinary scientific gathering induced lively discussions and close interactions between participants.

A report on the 12th Joint Meeting of the Signal Transduction Society, Weimar, Germany, 28 to 31 October 2008.

Introduction

The 12th Joint Meeting of the Signal Transduction Society was held from 28 to 31 October 2008 at the Leonardo Hotel in Weimar, Germany. This meeting was organized by the Signal Transduction Society (STS) together with the study groups of the German Society for Immunology (Deutsche Gesellschaft für Immunologie, DGfI), the German Society for Cell Biology (Deutsche Gesellschaft für Zellbiologie, DGZ), and the Society for Biochemistry and Molecular Biology (Gesellschaft für Biochemie und Molekularbiologie, GBM). The meeting is annually organized as an interdisciplinary event with more than 200 scientists representing a broad spectrum of expertise from immunology and tumor biology to nonmammalian and mathematical models for signal transduction (Fig. 1). There were eight workshops at this year's meeting, with signaling in immune cells as the special focus topic of the conference. This Meeting Report summarizes the oral presentations from each workshop, in which one talk was given by an invited speaker (with the exception of the focus, where four speakers were invited), and all other speakers were selected from the submitted abstracts. Although not highlighted here, the meeting also included a large number of posters, which were presented in a "1-minute, one-transparency" format with a subsequent intensive discussion session.

Transcription Control in Cells and Tissues

The first workshop spanned topics from transcriptional regulation controlling development of the nervous system to regulation of T cell survival and B cell activation. Kerstin Krieglstein (University of Freiburg) gave the first keynote presentation. She discussed the role of transforming growth factor–β (TGF-β) signaling in nervous system development, highlighting signaling through SMAD family transcription factors and the ERK (mitogen-activated protein kinase) MAPK (extracellular signal–regulated kinase) cascade (*1*).

Several talks concerned the NFAT (nuclear factor of activated T cells) family of transcription factors. Andrea Tuettenberg (University of Mainz) showed some special characteristics of the gene expression of human regulatory T cells (T_{reg}): NFAT is present in low abundance in the nuclei, and galectin-10 is a T_{reg}-specific protein that contributes to T_{reg}-mediated immune suppression. Hanna Bendfeldt (German Rheumatism Research Centre, Berlin) continued the discussion of NFAT, presenting her work on the regulation of the A and C isoforms of NFATc1 in human T cell survival and apoptosis. Production of NFATc1A is induced by the p38 MAPK and is important for cell survival, whereas NFATc1C has a proapoptotic effect. Friederike Berberich-Siebelt (University of Würzburg) presented data showing that SUMOylation of NFATc2 and NFATc1C guides these molecules to heterochromatic nuclear territories where they can suppress transcription of target genes by binding to HDACs (histone deacetylases) (*2*). Dirk Mielenz (University of Erlangen) shifted the focus to B cell activation, describing how TFG (TRK-fused gene) and Carma1 (also known as caspase recruitment domain 11, or CARD 11) interact with IKK (inhibitor of κB kinase) to influence nuclear factor–κB (NF-κB) signaling. In B cell activation, CARMA1 is recruited by TFG to the plasma membrane, which results in enhanced activity of the IKK β subunit and therefore increased NF-κB signaling.

Receptor-Triggered Pathways

This workshop highlighted therapeutic targeting of receptor tyrosine kinases, mapping phosphorylation sites on receptor-associated adaptor proteins, and unexpected functions of a death receptor. Arne Östman (Karolinska Institute, Stockholm) opened the workshop by describing how low-molecular-weight inhibitors and antibodies specific for receptor tyrosine kinases are potential targets for cancer treatment. He also discussed stromal-targeted cancer drugs that act on cells that are not themselves malignant, such as cancer-associated fibroblasts, but support the growth of the tumor by releasing growths factors and other cytokines, as well as chemokines (*3*). Heike Hermanns (Rudolf Virchow Center, Würzburg) showed that signaling by the proinflammatory cytokine oncostatin M

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through the MAPK and STAT (signal transducers and activators of transcription)–dependent pathways differentially regulates chemokine expression in primary human dermal fibroblasts (*4*). MAPK signaling prolongs the half-life of chemokines CCL1, CCL7, and CCL8 mRNA by inhibiting the RNA-binding protein tristetraprolin, whereas STAT5 negatively regulates CCL1 transcription. Maren Paulsen (University of Kiel) changed the focus to the FAS ligand, a prominent regulator of cell survival. She showed that the FAS receptor not only induces apoptosis in T cells, but, under certain circumstances, functions in T cell development and selection (*5*).

This workshop focusing on receptor triggering also included talks on identifying phosphorylation sites on adaptor proteins. Tilman Brummer (University of New South Wales, Sydney) reported on a proteomics-based study to create a phosphorylation map of GAB2, which is a proto-oncogene and adaptor protein involved in signaling through a variety of growth factor, hormone, antigen, cytokine, and cell matrix receptors. Brummer and colleagues found new PI3K (phosphoinositide 3-kinase) phosphorylation sites in GAB2 that are recognized by 14-3-3 proteins and, thus, may represent a regulatory mechanism with implications for diverse tyrosine kinase signaling systems (*6*). Henning Urlaub (University of Göttingen) identified phosphorylation sites in the SH2 domain–containing leukocyte adaptor protein SLP-65. He described SLP-65 as a key regulator for B cell receptor–dependent MAPK activation and of activator protein–1 (AP-1)– regulated gene transcription.

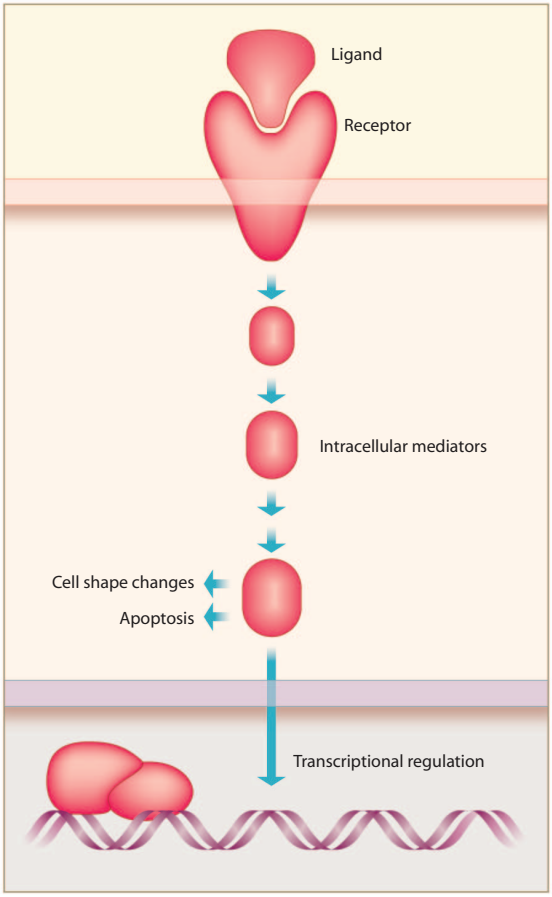

Fig. 1. The annual meeting of the Signal Transduction Society considered cellular signaling in every aspect, including seminars on ligand-receptor interactions, adaptor proteins and other intracellular mechanisms of signal transduction, and targets of signaling. Speakers addressed the roles of signaling in various contexts, including immunology, cancer biology, differentiation, cell death, and cellular morphology.

Tumor Biology and Cancer Therapy

This session highlighted advances in targeting therapeutics to receptors and adaptor proteins and identifying prognostic indicators for breast cancer. Götz von Wichert (University of Ulm) continued discussion of the topic of clinical aspects of cancer biology introduced by Arne Östman in the previous workshop, presenting several translational studies and new concepts for the treatment of gastrointestinal tumors, particularly in regard to the inhibition of epidermal growth factor (EGF) receptors and vascular endothelial growth factor (VEGF) receptors. He also pointed out limitations of these potential approaches; for example, patients with colorectal cancers bearing mutations in K-RAS might have an even poorer prognosis if given an EGFR inhibitor than if given no treatment. Britta Eiz-Vesper (Hannover Medical School) introduced a new approach to cell-based immunotherapeutics. Her group applied an RNA interference (RNAi)–based approach to permanently suppress the presence of the NKG2A-CD94 heterodimeric receptor on natural killer (NK) and T cells, which resulted in enhanced lysis of these cell types.

Changing the focus from receptors to scaffold and adaptor proteins, Stephan M. Feller (University of Oxford) discussed the structural basis for oncogenic signaling of adaptor proteins GRB2 and GAB2 in tumor cells. They discovered two atypical SRC-homology 3 (SH3) domain interaction sites in GAB2 that might be crucial for the binding of the C-terminal SH3 (SH3C) domain of GRB2. Therefore, the SH3C domain might represent a target site for the generation of specific inhibitors. Rafael D. Fritz (University of Zurich) characterized the ability of the scaffold protein CNK1 to influence the invasive potential of breast carcinoma by interfering with the expression of *membrane type 1 matrix metalloprotease* (*MT1-MMP*) (*7*). Shifting the tumor biology discussion from therapy to prognosis, Susanne Steinert (University of Jena) presented data on bone morphogenetic protein 2 (BMP2) as a potential prognostic marker for human breast cancer. BMP2, which is found in small, low-grade breast tumors, was positively correlated with the presence of the anti-apoptotic protein Bcl-2 and other proteins, and so may be useful as a prognostic marker in breast cancer (*8*).

Signaling Induced by Pathogens

Seminars in this workshop addressed the physiological consequences of signaling induced by bacterial and viral pathogens. In the keynote lecture, Klaus Aktories (University of Freiburg) addressed the role of bacterial toxins in modifying cellular RHO guanosine triphosphatases (GTPases). He provided, as examples, toxins from human pathogens that activate RHO GTPases, for example, the cytotoxic necrotizing factors (CNFs) of *Escherichia coli* and *Yersinia* spp., as well as toxins that inactivate RHO GTPases, such as the *Clostridium difficile* toxins A and B (*9*). Aktories stressed the immunomodulatory function of these toxins, given that RHO GTPases play an important role in immune cell signaling, and the mutagenic potential of these toxins. Regarding the carcinogenic potential of bacterial toxins, Katharina F. Kubatzky (University of Heidelberg) presented findings that *Pasteurella multocida* toxin (PMT), which causes atrophic rhinitis in pigs, induces anchorage-independent growth of cultured epithelial kidney cells (*10*). Sina Bartfeld (Max-Planck Institute for Infection Biology, Berlin) compared the ability of *Helicobacter pylori*, a bacterium that may contribute to gastric cancer by causing chronic inflammation, to induce activation of the NF-κB pathway with that of tumor necrosis factor–α (TNFα) and interleukin-1β (IL-1β). With an RNAi-based high-throughput assay, Bartfeld and colleagues identified an

E3 ligase associated with NF-κB activation in response to *Helicobacter pylori*, but not in response TNFα or IL-1β.

Norbert Reiling (Research Center Borstel), who was one of the two recipients of the 2008 STS Science Award, reported an inverse relation between Toll-like receptor (TLR) signaling to NF-κB and Wnt signaling through β-catenin in macrophages after aerosol infection of mice with *Mycobacterium tuberculosis* (*11*). Changing the focus from bacterial to viral pathogens, Eike R. Hrincius (University of Münster) presented data demonstrating that the influenza A virus nonstructural protein 1 (NS1), sequence variation of which determines pathogenicity, binds to the cellular adaptor proteins CRK and CRK-like (CRKL). Therefore, the specific interactions of NS1 variants with cellular adaptor proteins are an important determinant of influenza infection severity.

Differentiation, Senescence, and Aging

Topics addressed in this session ranged from the role of signaling in determining cell fate to the cellular consequences of aging and exposure to ultraviolet (UV) radiation. Peter Herrlich (Leibniz Institute for Age Research, Fritz Lipmann Institute) opened this workshop with a keynote seminar on the role of the GTP-binding protein p21-RAS in determining cell fate. He described the signaling pathway from growth factor receptors through p21-RAS to the ERM (ezrin, radixin, and moesin) complex and F-actin. Ezrin is a binding partner for CD44v6, a splice variant of the cell adhesion molecule CD44 that plays a role in tumor survival and invasion, but MERLIN can counteract ezrin-mediated p21-RAS activation and thus may act as a tumor-suppressor (*12*). Also addressing the role of signaling in cell fate, Guido Posern (Max-Planck Institute of Biochemistry, Munich) described the role of the fusion oncoprotein OTT-MAL in acute megakaryocytic leukemia and its function as a downstream mediator of signaling through RHO GTPases. He gave insight into the complex function of OTT-MAL, which is a transcriptional coactivator of serum response factor (SRF) that can exert antiproliferative and proapoptotic effects or promote proliferation, depending on the tissue in which it is present (*13*).

Two speakers discussed the role of UV radiation in cellular senescence. Joachim Altschmied (Institute for Environmental Medical Research at the University of Düsseldorf) presented work from his group on regulators of the cellular aging process. He showed that telomerase reverse transcriptase (TERT) is exported from the nucleus under conditions of oxidative stress and replicative senescence. Export requires phosphorylation of TERT by SRC kinases and is negatively regulated by the phosphatase SHP2 (*14*). Altschmied also noted that the metalloproteinase MMP-1 plays a role in UV radiation–induced skin aging, and the grainyhead-like 3 (GRHL3) transcription factor may function as an antiaging therapeutic by virtue of its ability to increase nitric oxide bioavailability. Marc Majora, also from the Institute for Environmental Medical Research in Düsseldorf, focused on the effect of UV radiation on skin fibroblasts and presented data that point to a role for mitochondrial DNA damage in skin fibroblast aging. Georg Reiser (Otto-von-Guericke University, Magdeburg) continued on the topic of mitochondria in aging; he provided evidence that the uptake of cytosolic calcium by mitochondria, which induces opening of the permeability transition pore, is an important part of the initiation of programmed cell death (*15*).

Signaling in Immune Cells

This workshop on signaling in immune cells, funded by the German Research Foundation, was the special focus of the 2008 meeting and included four keynote addresses, two of which concerned signaling in T cells. Keynote speaker Mark Philips (New York University School of Medicine) discussed the role of compartmentalization in RAS signaling in T cells. Stimulation of T cells with CD3 alone leads to activation of RAS at the Golgi, but stimulation with CD3 in combination with the β_2 integrin LFA-1 (lymphocyte function–associated antigen–1), results in RAS activation at both the plasma membrane and the Golgi (*16*). Keynote speaker Stefan Feske (New York University School of Medicine) presented data from patients with severe combined immunodeficiency (SCID). Lymphocytes from these patients show a defective biphasic calcium response—the intracellular calcium flux is normal, but they lack the extracellular calcium influx through calcium release–activated calcium (CRAC) channels. Mutations in subunits of these channels—for example, the ORAI1 protein—are associated with the SCID syndrome (*17*). Claudia Brandt (German Rheumatism Research Centre, Berlin) also discussed T cell signaling in disease, focusing on her study showing that low-dose cyclosporin A treatment benefited patients with atopic dermatitis, an autoinflammatory skin disease. The benefit was based on reduced T cell–receptor signaling and an increased number of T_{regs}.

The special focus workshop also included two keynote seminars and two talks selected from submitted abstracts on signaling in B cells. Ed Clark (University of Washington) presented a keynote lecture on the regulation of the B cell cycle, showing that the adaptor protein BAM32 promotes entry into the cell cycle, whereas superoxides have an inhibitory effect. BAM32 and the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex compete for binding of phosphatidylinositol bisphosphate (PIP_2) and RAC1, which may fine-tune the B cell cycle (*18*). Keynote speaker Facundo Batista (Cancer Research UK, London Research Institute) described the morphological changes that B cells undergo when they bind to antigen on the surface of antigen-presenting cells and how these changes are related to activation (*19*). Jürgen Wienands (University of Göttingen) presented work showing the differences between naïve and antigen-experienced B cell signaling in DT40 cells. His group identified a phosphorylation site in the immunoglobulin G (IgG) heavy chain that, on antigen binding, is phosphorylated by the tyrosine kinase SYK, which leads to recruitment of GRB2, enhanced phospholipase C activation, and calcium flux (*20*). Edgar Serfling (University of Würzburg), who also uses the DT40 B cell model, showed that high amounts of the αA isoform of NFATc1 protected B cells from activation-induced cell death (AICD) by promoting the transcription of antiapoptotic proteins such as BCL-6. He found that this isoform is present in a subset of germinal center B cell nuclei, which suggests that NFATc1αA contributes to the survival of mature germinal center B cells.

The seminars in this workshop that did not focus on T or B cells covered a wide range of other immunology topics, including the regulation of natural killer (NK) cell activity and macrophages. Doris Urlaub (University of Heidelberg) used a bioinformatics approach to address the mechanism of NK cell decision-making, presenting a model of how an NK cell chooses whether or not to kill a target cell that included the SRC kinase and its substrate VAV1, as well as the antagonistic phosphatase SHP-1. Simone Keck (University of Freiburg) presented data on the role of the SRC kinase LYN in negatively regulating TLR signaling in bone marrow–derived macrophages. She showed that macrophages from LYN-deficient mice secreted higher levels of proinflammatory cytokines in response to TLR ligands than their wild-type counterparts.

René Eulenfeld (Technical University of Aachen) addressed the role of subcellular localization in immune-cell signaling, presenting a mechanism for the regulation of recruitment of the adaptor protein GAB1 to the plasma membrane. In resting immune cells, GAB1 is cytosolic, but translocates to the plasma membrane on stimulation by IL-6, for example. René Eulenfeld and Fred Schaper have found that phosphorylation of GAB1 is crucial for its plekstrin homology domain–dependent recruitment to the plasma membrane (*21*).

Adhesion, Motility, Morphology

The final workshop of the meeting included a diverse set of talks on the topic of cell dynamics and adhesion. The keynote lecture was given by Harvey McMahon (Medical Research Council, Cambridge, UK), who described the varied mechanisms of endocytosis. McMahon distinguished between endocytotic pathways that involve the coat protein clathrin from those that are clathrin-independent, such as those defined by pleiomorphic clathrin-independent carriers or glycosylphosphatidylinositol (GPI)–anchored protein–enriched early endosomal compartments, or GEECs (*22*). Cornelia Dietrich (University of Mainz), who shared the 2008 STS Science Award with Norbert Reiling, studies toxins such as the halogenated aromatic hydrocarbon 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which do not require endocytosis to enter cells because they diffuse across the membrane. Her group investigated regulation of the aryl hydrocarbon receptor, which is a transcription factor involved in the cellular response to TCDD. She discussed an aryl hydrocarbon receptor–dependent signaling pathway involving JunD and cyclin A that was induced by TCDD and leads to a loss of contact inhibition and increased proliferation in rat liver oval cells (*23*).

Other talks in this session focused on cellular migration. Lars Müller (University of Kiel) discussed the inflammatory response of cancer-associated fibroblasts induced by TNFα, which leads to the production of inflammatory cytokines and chemokines, such as IL-6 and the monocyte-chemotactic protein–1, which promote chemotaxis of colon carcinoma cells. The fibroblasts used in this study were isolated from colorectal cancer metastases in the liver; this may provide insight their formation in the liver (*24*). Sven Kröning (University of Erlangen) introduced a cell migration assay in which, instead of scratching to create a wound in a cell monolayer as in a traditional scratch assay, a barrier is placed on the matrix-coated plate before seeding and is removed after the cells reach confluence. This updated version of the scratch assay prevents destruction of the matrix so that the cells migrate over a more natural substrate than uncoated plastic or glass.

Concluding Remarks

The 12th annual meeting of the Signal Transduction Society left us with the impression that the STS not only managed to successfully unite the signaling-oriented study groups of various scientific societies, but also established a communication platform for both basic researchers and clinicians. We witnessed an increasing number of contributions that translated our present knowledge and understanding from in vitro studies and model organisms to clinical benefits for patients—from bench to bedside. We are very much looking forward to continuing to develop these connections between basic research and clinical practice, and we cordially invite you to the next meeting and the Signal Transduction Society in Weimar.

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