The 2019 FASEB Science Research Conference on the TGF-β Superfamily: Signaling in Development and Disease, July 28 to August 2, 2019, West Palm Beach, Florida, USA

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The nonprofit Federation of American Societies for Experimental Biology (FASEB) sponsors a series of Science Research Conferences (SRCs) each year. These conferences offer scientists a collegial and relaxing environment to discuss and explore new findings and approaches to specific research areas.

The TGF-β Superfamily Conference: Signaling in Development and Disease was held in West Palm Beach, Florida, from July 28 to August 2, 2019, at the West Palm Beach Marriot hotel (Fig. 1). The conference focused on the roles that members of the TGF-β superfamily, such as TGF-β, Nodal, activin, bone morphogenetic protein (BMP), and growth differentiation factor (GDF), exert in development and disease. Topics of discussion ranged from TGF-β signaling networks, crosstalk, and regulation to roles of TGF-β signaling on tissue growth, morphogenesis, and microenvironment dynamics, including inflammation, bone formation, vasculature development, and metabolism in development and diseases, as well as therapeutic frontiers of TGF-β signaling. The meeting was organized by Mary Mullins (University of Pennsylvania, Philadelphia, PA, USA) and Gareth Inman (University of Glasgow, Glasgow, United Kingdom). There were 29 invited and 1 keynote speaker, 22 speakers selected from the abstracts, and 48 poster presentations over the course of four and a half days. Newly added to this meeting were poster flash sessions, which were well received. Due to the format of this summary, we regret that only a few talks can be included here from this vibrant meeting.

The European Molecular Biology Organization (EMBO) keynote lecture on the opening evening was given by Dr. Angela Nieto, PhD (Institute of Neuroscience, Spanish National Research Council-Miguel Hernández University, Elche, Spain). Dr. Nieto first gave an overview on epithelial plasticity in health and disease and reflected about how the field of epithelial-to-mesenchymal transition (EMT) has developed over the last decades. EMT plays an important role in morphogenesis, stem cells, and tissue homeostasis, as well as in diseases like fibrosis and cancer, although universal markers to follow the EMT process have been difficult to identify. Dr. Nieto discussed this aspect and elaborated on the topic of partial vs. complete EMT. She also discussed the crucial role of the transcription factor Snail1 in renal fibrosis. Finally, she described novel and exciting data on the molecular mechanisms underlying left/right asymmetry pathways regulating the localization of the heart on the left side of the body in vertebrates. Nodal and BMP control a well-organized and asymmetric expression of a network of EMT transcription factors such as Snail1, paired-like home-domain transcription factor 1 also known as pituitary homeobox 1 (Pitx1), and Pitx2, as well as several microRNAs, which together drive heart morphogenesis and laterality in a contextual and species-dependent manner.

One of the major themes that emerged from the conference is the extensive crosstalk between TGF-β signaling and other signaling pathways and between different TGF-β family members. Following the keynote lecture, Dr. Rik Derynck from University of California San Francisco (UCSF; San Francisco, CA, USA) discussed the cooperation between Smad, a family of proteins similar to the gene products of the Drosophila gene “mothers against decapentaplegic” (Mad) and the Caenorhabditis elegans gene Sma, and protein kinase B (Akt)-mammalian target of rapamycin signaling in completing EMT, as prolonged TGF-β exposure completes or stabilizes EMT, conferring enhanced stem cell characteristics and cancer drug resistance. He went on to emphasize that cells also

ABBREVIATIONS: Akt, protein kinase B; ALK, anaplastic lymphoma kinase; BMP, bone morphogenetic protein; BMPR, BMP receptor; EMT, epithelial-to-mesenchymal transition; GDF, growth differentiation factor; HS, heparan sulphate; NGLY1, N-glycanase 1; TβRII, TGF-β type II receptor

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control the TGF-β receptor availability at the cell surface and hence the responsiveness to (autocrine) TGF-β. Intriguingly, Akt, when activated, induces transport of TGF-β receptors from intracellular stores to the cell surface, thus representing a novel mode of signaling amplification. Moreover, he also reported evidence that insulin, as a potent inducer of Akt signaling, promotes enhanced TGF-β responsiveness and that enhanced autocrine TGF-β signaling participates extensively in the cellular gene expression and angiogenic response to insulin. The knowledge of a synergistic crosstalk between TGF-β and insulin is expected to have future impact on our understanding of key events occurring in cancer cells.

Dr. Joan Massagué (Memorial Sloan Kettering Cancer Center, New York, NY, USA), discussed the potent role of rat sarcoma (RAS)/mitogen activated protein kinase (MAPK) signaling acting together with TGF-β signaling to strongly activate a very specific subset of target genes including Snail1 in order to trigger EMT plus fibrogenesis in adult epithelial progenitors and EMT plus differentiation in embryonic mesoderm progenitors. The MAPK input through a previously underappreciated RAS effector transcription factor leads to recruitment of TGF-β-activated Smads to specific gene loci driving the aforementioned responses in different contexts. The work promises to advance our knowledge of TGF-β-activated EMT programs in development, fibrosis, and cancer.

Dr. Carl-Henrik Heldin (Uppsala University, Uppsala, Sweden) then further discussed the crosstalk between TGF-β-Smad canonical signaling and JunB proto-oncogene, AP-1 transcription factor subunit in regulating gene expression and cell invasion, from work done in collaboration with Peter Ten Dijke’s laboratory. He also discussed the ways known today to interfere with TGF-β signaling that are causing cancer while leaving the growth inhibitory TGF-β signaling pathways intact.

Multiple talks discussed the roles of TGF-β signaling and its regulation in cancer and various diseases. Dr. Peter ten Dijke (Leiden University, Leiden, The Netherlands) described recent research from his laboratory on the identification of a deubiquitinating enzyme that promotes TGF-β-induced extravasation and metastasis of breast cancer cells. Significantly, higher levels of this enzyme were detected in the serum of patients with triple-negative breast cancer compared with normal control serum. Ten Dijke also discussed their findings regarding GREM1, DAN family BMP antagonist, an inhibitory regulator of BMP signaling whose elevated expression correlates with poorer breast cancer survival rates. GREM1 protein is produced by cancer-associated fibroblasts and promotes their fibrogenic activation and also the invasion of adjacent breast cancer cells. These novel data might become useful in the future to identify risk factors for women with breast cancer.
Dr. Xia Lin (Baylor College of Medicine, Houston, TX, USA) presented their novel findings on how the anaplastic lymphoma kinase (ALK) tumor-promoting protein counteracts the tumor-suppressing effects of the TGF-β-canonical Smad signaling pathway by binding to Smad4 and phosphorylating Smad4 on Tyr95 in its Mad homology 1 (MH1) at the N-terminus, thereby counteracting the DNA-binding capability of Smad4. Similarly, they found that other tyrosine kinases can also phosphorylate Smad4 and inhibit the antiproliferative activity of TGF-β signaling. These findings provide insight into the interplay between oncoproteins and tumor suppressors in tumorigenesis.

Further insights in the crosstalk between different TGF-β family members were provided by Dr. Caroline Hill (The Francis Crick Institute, London, United Kingdom). She presented interesting data from genetic studies in zebrafish in which CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9) was used to knock out Smad4, the major Smad4 in early embryos. Zebrafish deficient of both maternal and zygotic Smad4 showed a severe phenotype, and a high number of genes were found to be deregulated, demonstrating the crucial role for Smad4 in normal embryogenesis. Surprisingly though, not all transcription downstream of TGF-β signaling, the latter facilitating retrieval of active TGF-β from its latent deposits following a mechanical input. Fibrillin1 itself showed up-regulation of fibrillin1 and the TGF-β-competent binding protein. Dr. Petra Knaus (Freie Universität, Berlin, Germany) discussed the powerful physiologic effects of various kinds of mechanical forces that cells are exposed to, which impact on gene regulation. Loss of BMP receptor (BMPR) expression is absolutely required to preserve aortic homeostasis, as 40% of smooth muscle from TGF-βRII ablated GDF11 signaling but with limited effect on TGF-β signaling. These findings highlight the importance of TGF-β signaling in this crosstalk. These data may have great impact on our understanding of mechanisms of aneurysm formation and may affect future therapeutic interventions aimed at treating aneurysmal disease.

Dr. Maurizio Pacifici (The Children’s Hospital of Philadelphia, Philadelphia, PA, USA) discussed the roles of heparan sulfate (HS) in regulating bioavailability and signaling of TGF-β superfamily members through its interactions with their Cardin-Weintraub HS-binding domain. He talked about the presence of distinct Cardin-Weintraub domains in different TGF-β family members and the antagonistic effects of HS on BMP signaling. The latter is particularly relevant to the pediatric congenital disorder multiple osteochondroma, in which loss-of-function mutations in the Golgi HS polymerases exostosin glucosyltransferase 1 or 2 (EXT1/2) cause HS deficiency, higher BMP signaling, and osteochondroma formation. These findings provide insights for possible therapeutic interventions on multiple osteochondroma and other diseases caused by deregulated TGF-β signaling.

Several talks at the conference focused on studies that provide insight into the mechanistic understanding of the signal transduction mechanism at the ligand-receptor level. Dr. Thomas Thompson (University of Cincinnati, Cincinnati, OH, USA) discussed the structural basis of ligand-receptor interactions. In particular, he talked about the crystal structure of the ternary complex of an activin class member. The structure, which consists of Activin A receptor, type IIB (ActRIIB)/activin receptor-like kinase 5 (ALK5)/GDF11, revealed insight into how the activin class utilizes a third binding paradigm for receptor specificity, which includes novel interactions with the ligand fingertips and the type I receptor. These structural studies also revealed how TGF-β and activin class ligands differently engage the common type I receptor Alk5. Whereas TGF-β relies on cooperative interactions with TßRII, GDF11 utilizes a “knob-in-hole” mechanism. These structural insights allowed them to create mutations in Alk5 that ablated GDF11 signaling but with limited effect on TGF-β.

In a short talk selected from the abstracts, Benjamin Tajer from Dr. Mary Mullins’ laboratory at the University of Pennsylvania presented elegant studies on the roles of type I and type II receptors in a BMP heterodimer-receptor complex. The Mullins group has previously shown that BMP2/7 heterodimers function in dorsoventral patterning in zebrafish embryos and that these heterodimers act through 2 different type I receptors, Bmpr1 and Activin A receptor type 1 (Acvr1). Intriguingly, these type I receptors exhibit differential kinase activity requirements. These studies raised important questions regarding the specific roles of each of the 2 type I and 2 type II receptor molecules in the tetrameric receptor complex in BMP signaling.

Dr. Hamed Jafar-Nejad from Baylor College of Medicine discussed the roles of deglycosylation in the regulation of BMP signaling. Their work is focused on N-glycanase 1 (NGLY1), an evolutionarily conserved cytoplasmic enzyme that removes N-glycans from glycoproteins. Using Drosophila and mammalian cells as models, Dr. Jafar-Nejad’s group has found that NGLY1 is required in BMP signal-sending cells to promote BMP signaling. These findings highlight the importance of...
glycosylation in regulating BMP signaling and provide a framework for understanding the basis for the human disease caused by NGLY1 deficiency.

The Anita Roberts travel award, which was established to celebrate the pioneering work of Dr. Anita Roberts (1942–2006) in the TGF-β field and her contribution in mentoring the next generation of scientists, was given to Dr. Iacovos Michael, postdoc at Ecole polytechnique fédérale de Lausanne (EPFL)-Lausanne (Lausanne, Switzerland), with a talk titled MicroRNA-Mediated Suppression of the ALK7 Homeostatic Tissue Barrier Enables Tumorigenesis and Metastasis; to Giulia Boezio, graduate student at Max Planck Institute for Heart and Lung Research-Bad Nauheim (Bad Nauheim, Germany), with a talk titled Endothelium-Smooth Muscle Cross-talk in the Developing Cardiac Outflow Tract is Orchestrated by ALK5 Signaling; to Dr. Luisina Ongaro Gambino, postdoc at McGill University (Montreal, Quebec, Canada), with a talk titled Mice Lacking ALK4 and ALK5 in Gonadotropes are FSH Deficient and Hypogonadal; and to Erich Goebel, graduate student at the University of Cincinnati, with a talk titled Structural Characterization of an Activin Class Ternary Receptor Complex Reveals a Third Paradigm for Receptor Specificity.

Results from the feedback evaluation showed that attendees appreciated the overall good organization of the meeting, the broad range of scientific topics covered, and the high quality of the talks presented. Most respondents also had favorable comments on the ample opportunities that the meeting provided for discussions with other colleagues in the field. More than 80% of the respondents indicated that they plan to attend this conference again and that they would recommend this meeting to other researchers.

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AUTHOR CONTRIBUTIONS

M. Landström and J. Liu attended the conference and contributed equally to the writing and editing of the summary.