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The Eleventh ENBDC Workshop: Advances in Technology Help to Unveil Mechanisms of Mammary Gland Development and Cancerogenesis

Vida Vafaizadeh[1] · Emilia Peuhu[2,3] · Marja L. Mikkola[4] · Walid T. Khaled[5] · Mohamed Bentires-Alj[6] · Zuzana Koledova[7]

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Abstract

The eleventh annual workshop of the European Network for Breast Development and Cancer, *Methods in mammary gland biology and breast cancer*, took place on the 16th to 18th of May 2019 in Weggis, Switzerland. The main topics of the meeting were high resolution genomics and proteomics for the study of mammary gland development and cancer, breast cancer signaling, tumor microenvironment, preclinical models of breast cancer, and tissue morphogenesis. Exciting novel findings in, or highly relevant to, mammary gland biology and breast cancer field were presented, with insights into the methods used to obtain them. Among others, the discussed methods included single-cell RNA sequencing, genetic barcoding, lineage tracing, spatial transcriptomics, optogenetics, genetic mouse models and organoids.

Keywords Barcoding · Proteomics · Signaling · Tissue morphogenesis · Transcriptomics · Tumor microenvironment

Abbreviations

53BP1	p53-binding protein 1
BRCA1	BRCA1 DNA repair associated
cAMP	cyclic adenosine monophosphate
CAF	cancer-associated fibroblast
CDC42EP3	cell division cycle 42 effector protein 3
CREB1	cAMP responsive element binding protein 1
EGFR	epithelial growth factor receptor
ECM	extracellular matrix
EMBL	European Molecular Biology Laboratory
ENBDC	European Network of Breast Development and Cancer
ER	estrogen receptor
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
IDC	invasive ductal carcinoma
MSPC	mammary stem/progenitor cell
NOTCH4	notch receptor 4
PARP	poly (ADP-ribose) polymerase
PARPi	PARP inhibitor
PR	progesterone receptor
RSK2	p90 ribosomal S6 kinase 2
scRNAseq	single cell RNA sequencing
TNBC	triple negative breast cancer
UK	United Kingdom
VPS11	vacuolar protein sorting-associated protein 11 homolog
YAP	Yes-associated protein

Vida Vafaizadeh and Emilia Peuhu contributed equally to this work.

✉ Zuzana Koledova
koledova@med.muni.cz

[1] Department of Biomedicine, University of Basel, Basel, Switzerland

[2] Turku Bioscience Centre, University of Turku and Åbo Akademi University, Turku, Finland

[3] Cancer Research Laboratory FICAN West, University of Turku and Turku University Hospital, Turku, Finland

[4] Developmental Biology Program, Institute of Biotechnology, HiLIFE, University of Helsinki, Helsinki, Finland

[5] Department of Pharmacology, University of Cambridge, Cambridge, UK

[6] Department of Biomedicine, Department of Surgery, University Hospital Basel, University of Basel, Basel, Switzerland

[7] Department of Histology and Embryology, Faculty of Medicine, Masaryk University, Brno, Czech Republic

On the 16th to 18th of May 2019, the picturesque Swiss town Weggis became the buzzing hub of mammary gland biology and breast cancer research. It hosted, for the eleventh time, the

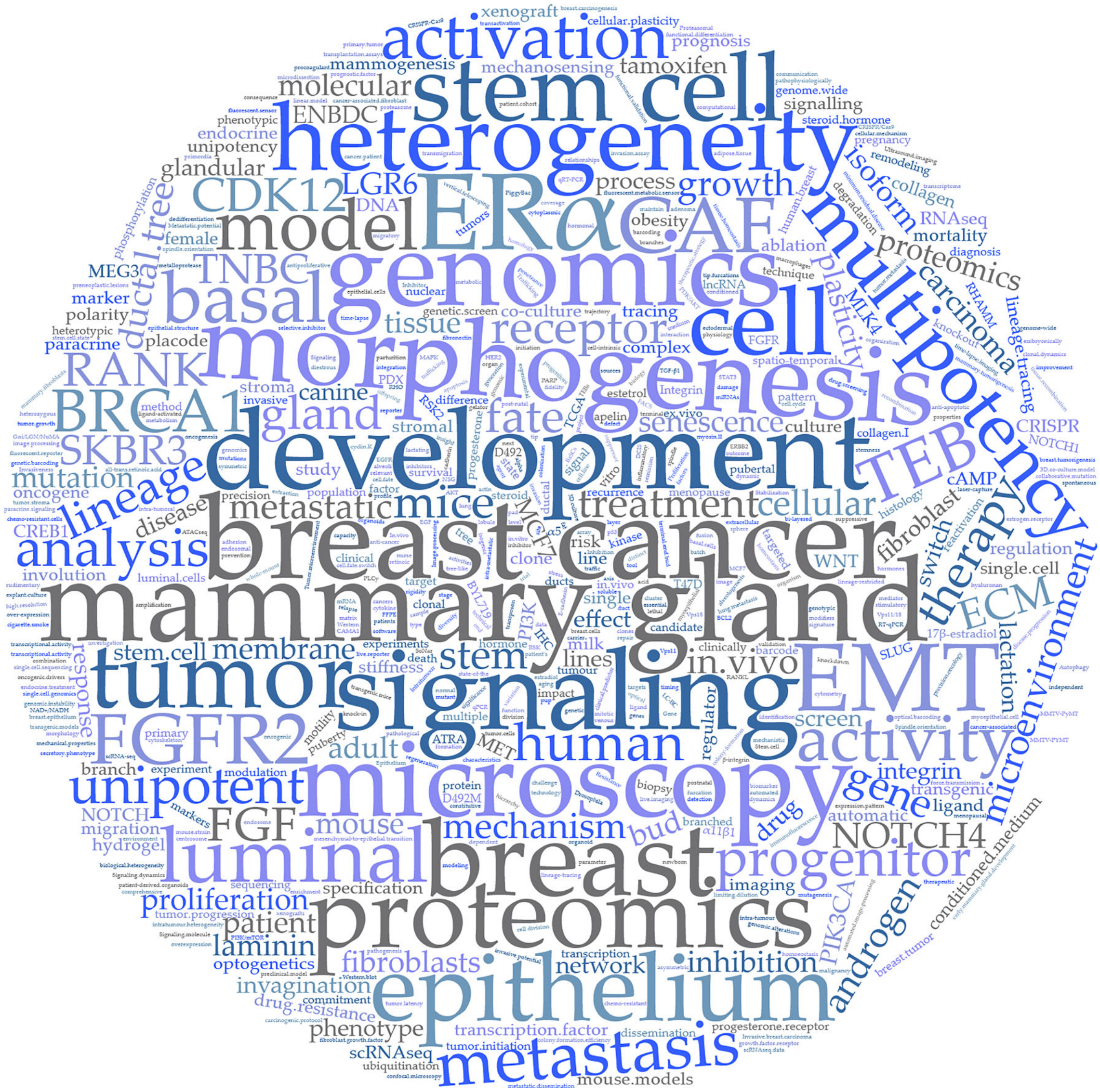

Fig. 1 Graphical presentation of the content of the 11th ENBDC workshop. The word cloud was generated from the terms used in the invited talks and submitted abstracts. The size of the words depicts their frequency. This is an artistic presentation only; due to space constraints, some words were omitted

annual workshop of the European Network for Breast Development and Cancer (ENBDC; www.enbdc.org), *Methods in mammary gland biology and breast cancer*. 65 scientists from 14 different countries gathered in the inspiring surroundings near lake Lucerne at the foot of the Rigi mountain for three days of exciting scientific talks, poster presentations, discussions and networking. The wide spectrum of topics that were discussed is depicted in Fig. 1.

The first session of the meeting focused on the use of high-resolution genomics and proteomics to interrogate various aspects of mammary gland development and breast cancer. Bhupinder Pal from Olivia Newton John's Cancer Research Institute (Australia) started the session by describing the use of single cell RNA sequencing (scRNAseq) technology to identify the different mammary epithelial cell types at various postnatal developmental stages as reported in their previous study [1]. Dr. Pal has now expanded the use of scRNAseq to interrogate primary triple negative breast cancer (TNBC) tumors revealing the dynamics of immune cells in this process. The second speaker Delphine Merino also from Olivia Newton John's Cancer Research Institute described the use of genetic barcodes to track clonal dynamics of tumor cells in primary and metastatic sites and in response to therapeutic interventions as described in their recent study [2]. Her work suggested that only a fraction of cancer cells is able to grow as 'seeders' of metastases. She is currently characterizing the molecular properties of these clones in multiple metastatic sites. Michaela Asp from KTH Royal Institute of Technology (Sweden) gave the final talk in this session where she described the use of spatial transcriptomics to study the cellular interactions in time and space. Dr. Asp described the technology developed in their lab [3] and provided examples

of how the same technology which was used to study the human heart is currently being used by other members of her team to study breast cancer samples [4].

In the second session, breast cancer signaling was discussed. Chiara Francavilla from The University of Manchester (United Kingdom, UK) spoke on *Proteomics analysis of proximal signaling in breast cancer cells*. Dr. Francavilla focuses on the molecular determinants of cell signaling specificity using functional phospho-proteomics. Using this approach, she elucidated the mechanism how stimulation of fibroblast growth factor receptor 2b (FGFR2b) by distinct FGF ligands generates specific cellular responses. She found that stimulation by FGF7 or FGF10 leads to differential phosphorylation of FGFR2b on a specific tyrosine residue (Y734), resulting in different receptor fate and cellular outputs. Upon FGF7 stimulation, Y734 is not phosphorylated and FGFR2b is degraded, leading to cell proliferation. In contrast FGF10 induces phosphorylation on Y734, which leads to recruitment of PI3K and SH3BP4, receptor recycling and cell migration [5]. In follow-up studies in breast cancer cell lines, Dr. Francavilla revealed cell-specific clusters of up-regulated phosphorylated sites on FGFR2b and identified several recycling adapters that were phosphorylated upon stimulation with FGF10 and resulted in a crosstalk with the epithelial growth factor receptor (EGFR). The nature and mechanisms of this crosstalk are being investigated.

In the following short talk, Rafal Sadej from University of Gdansk (Poland) focused on the interaction of FGFR signaling with estrogen receptor (ER) and progesterone receptor (PR) signaling in invasive ductal carcinoma (IDC). His group recently found that FGF7-FGFR2 signaling leads to PR phosphorylation, ubiquitination and degradation, and they identified the p90 ribosomal S6 kinase 2 (RSK2) as the mediator of the FGFR2 action towards the PR [6]. They are currently investigating, how FGFR2 signaling modulates ER signaling and ER-dependent gene expression. Through his work, Dr. Sadej aims to elucidate mechanisms that are implicated in IDC progression towards a more aggressive steroid-hormone independent phenotype and that might contribute to failure of endocrine therapy [7].

Didier Picard from Université de Genève (Switzerland) talked about unexpected regulators of ERα transcriptional activity. His group discovered that cyclic adenosine monophosphate (cAMP)-responsive element binding protein 1 (CREB1) stimulates and is necessary for ERα activity in response to estrogen and to ligand-independent activation by cAMP [8]. Moreover, they found that ERα signaling is fine-tuned by proteins involved in membrane trafficking, vacuolar protein sorting-associated protein 11 homolog (VPS11) and VPS18 [9]. Importantly, CREB1 and VPS11/VPS18 levels correlate with disease outcome in breast cancer patients, indicating that these novel ER regulators are clinically relevant.

The critical role of tumor microenvironment in regulation of cancer behavior, including spreading through the body, survival at distant sites and resistance to therapy, was highlighted in the superb keynote talk by Erik Sahai from The Francis Crick Institute (UK). His laboratory has contributed several major discoveries on how cancer-associated fibroblasts (CAFs) promote invasion of cancer cells. They found that CAFs enable collective migration of carcinoma cells by creating tracks in extracellular matrix (ECM), in which cancer cells move [10]. To generate these tracks, CAFs use both protease- and force-mediated ECM remodeling mechanisms [10]. Moreover, Dr. Sahai's team discovered that CAFs exhibit a characteristic activation of transcription factor Yes-associated protein (YAP) [11]. Analysis of YAP function in CAFs revealed that YAP activity is required for CAFs to promote ECM remodeling. Importantly, YAP regulates expression of several cytoskeletal regulators, such as anillin actin binding protein and diaphanous related formin 3, and protein levels of myosin chains, thereby regulating CAF mechanotransduction. CAF sensing of stiff matrices further activates YAP, thereby maintaining the CAF phenotype [11]. But how do CAFs emerge? Often, they arise from resident normal fibroblasts in response to cancer-cell derived soluble factors. Using a functional siRNA screen of genes differentially expressed in normal fibroblasts and CAFs, Dr. Sahai's team discovered that upregulation of cell division cycle 42 effector protein 3 (CDC42EP3) is required for fibroblast activation to CAFs [12]. CDC42EP3 coordinates actin and septin cytoskeleton and enables CAF responses to changes in matrix stiffness [12]. The work of Dr. Sahai leads to new ways of prediction how the cancer will spread, and to identifying potential targets for new treatments to stop it. And because the tumor microenvironment complexity goes beyond the CAFs and ECM, so does the research focus of Dr. Sahai, who in the second part of his talk provided a peek into their unpublished data on new microenvironmental cell players in breast cancer metastasis.

Novel preclinical models for accurately capturing both intrinsic and extrinsic factors affecting tumor cell metabolism, motility, drug responses and therapy resistance were the central theme of the session chaired by post-docs Vida Vafaizadeh (University of Basel, Switzerland) and Emilia Peuhu (University of Turku, Finland). Sven Rottenberg from University of Bern (Switzerland) opened the session by showing unique genetically engineered mouse models for BRCA1 DNA repair associated (BRCA1)-/BRCA2-deficient cancers and tumor-derived organoid cultures for studying mechanisms of drug sensitivity and resistance [13, 14]. These models of hereditary breast cancer closely mimic the human disease and are hypersensitive to DNA-damaging agents including poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi). However, like in patients, the tumors eventually acquire drug resistance. In order to identify the underlying mechanisms of PARPi resistance, the Rottenberg group performs functional genetic screens using shRNA, CRISPR and insertional

mutagenesis. They identified several distinct mechanisms, including restoration of PARP1 signaling due to poly(ADP-ribose) glycohydrolase depletion [14], as well as obtained exciting insights into basic mechanisms of the DNA damage response, such as the role of shieldin as the ultimate mediator of p53-binding protein 1(53BP1)-dependent DNA repair [15]. Their work helps to reveal new cancer vulnerabilities that can be exploited therapeutically, such as hypersensitivity to ionizing radiation in 53BP1;BRCA1-deficient cells [16].

The crucial role of ECM in regulation of tumor cell behavior was discussed by Chris Madsen (Lund University, Sweden). During tumor progression, ECM acquires tumor-promoting characteristics. This process is linked to increased ECM deposition, stiffness and mechanotransduction [17, 18]. The Madsen group uses α-smooth muscle actin-red fluorescent protein reporter mice to study CAFs, the key mediators of tissue stiffening, and they investigate how the expression of ECM proteins changes during tumor progression. Using two-photon microscopy, the Madsen group investigates the structural composition of the ECM in decellularized tissue from animal models of cancer [19]. Through their work, differential expression patterns of ECM proteins between healthy and cancerous tissue have been identified, including changes in basement membrane organization in different types of blood vessels [19]. These expression patterns could potentially be utilized in the design of diagnostic and theranostic tools for breast cancer. ECM stiffening contributes also to the increased interstitial fluid pressure and poor vascular penetration in tumors, which in turn counteract drug delivery [20]. The Madsen group is developing novel methods for monitoring pharmacokinetics and drug delivery into tumors using multispectral optoacoustic tomography in conjunction with ultrasound imaging.

In the following short talk, Megan Thompson from the Robert Clarke's laboratory (Manchester Cancer Research Centre, The University of Manchester, UK) described an intrinsic mechanism of tamoxifen resistance in ER positive breast cancer. The Clarke group discovered that Notch receptor 4 (NOTCH4) drives breast cancer stem cells and endocrine therapy resistance [21]. In this project, she compared parental to therapy-resistant breast cancer cells and found that *NOTCH4* CRISPR knockout was able to reduce tamoxifen resistance. She is currently investigating NOTCH4 signaling pathways in breast cancer stem cells; early results indicate signaling via the ligand-independent pathway that occurs upon NOTCH4 endocytosis. Further studies will investigate the signaling in detail and its relevance in breast cancer stem cells.

Metabolic heterogeneity of breast cancer cells and its role in minimal residual disease was the topic of the short talk by Matthew Boucher from the research group of Martin Jechlinger (European Molecular Biology Laboratory (EMBL) Heidelberg, Germany). He introduced their approach that utilizes metabolic sensor SoNar [22] to investigate the cytoplasmic NAD^+/NADH ratio for spatial and temporal assessment of how cancer cells adapt to targeted therapy. They observe metabolism at single cell level using selective plane illumination microscopy, or overall cell response using high throughput approaches. Their goal is to identify and characterize new modulators of cancer cell metabolism.

The fourth session focused on tissue morphogenesis. Epithelial invagination and bending are fundamental processes that regulate the formation of nearly all organs [23, 24]. During development of multicellular organisms, cells undergo complex shape changes yet their causal relationship to different morphogenetic processes is often poorly understood. Jeremy Green from King's College London (UK) described a novel mechanism for epithelial invagination that seems to operate in salivary glands [25]. They showed that salivary gland placodes show no signs of apical constriction or "basal wedging", but rather the initial steps of invagination occur through coordinated vertical cell movement termed vertical telescoping. This was described to include vertical upward movement at the periphery of the placode while the more central cells move downwards to generate the invagination. This was associated with a unique cell shape of the peripheral cells with apical protrusions planar polarized centripetally.

Stefano De Renzis from EMBL in Heidelberg (Germany) gave a fantastic overview on optogenetics and how his group has used this technique to synthetically reconstruct epithelial morphogenesis. He presented recent work from his lab aimed at studying the relationship between apical constriction and epithelial folding. As an experimental system, they used the *Drosophila* embryo at a stage when it is composed of a monolayer of epithelial cells that display no morphological differences along the antero-posterior or dorso-ventral axes. Remarkably, they found that localized activation of Rho signaling at the apical surface of the cells is sufficient to trigger apical constriction and tissue folding. The shape of the photo-activated tissue affected invagination such that a square box leads to isotropic apical constrictions while a rectangular shape results in preferential constriction along the minor axis of the rectangle [26]. However, apical constriction was not sufficient to drive closure of the invagination furrow into a tube-like structure. This last step depends on myosin II de-activation at the basal surface which causes basal relaxation and cell shortening [27]. These experiments provide a clear demonstration how optogenetic techniques can be adapted to control tissue morphogenesis with high spatio-temporal precision and open new avenues for studying cancer processes *in vivo*.

The bilayered mammary epithelium consists of basal and luminal cells that are maintained by unipotent mammary stem/progenitor cells (MSPCs) [28, 29]. Mechanisms that regulate MSPC proliferation, differentiation and potency were discussed in short talks by Maria Fankhaenel and Alessia Centonze. Maria Fankhaenel from Salah Elias' group (University of Southhampton, UK)

addressed the question whether MSPCs balance proliferation and differentiation through symmetric versus asymmetric cell division. In many developmental contests, asymmetric cell divisions are controlled by the alignment of the mitotic spindle along a polarity axis via the conserved Gαi/LGN/NuMA complex [30]. The Elias lab tackles this question using a proteomics approach on a mammary cell line expressing LGN-green fluorescent protein and their LGN interactome has revealed novel, previously unidentified proteins that directly interact with LGN. More detailed analyses are on the way.

Basal progenitors can reactivate multipotency upon transplantation or oncogene expression, suggesting that an active mechanism may limit multipotency. Alessia Centonze from Cedric Blanpain's lab (Université Libre de Bruxelles, Belgium) used *in vivo* ablation of luminal progenitors in combination with basal cell lineage tracing to assess whether basal and luminal cell-cell communication restricts multipotency in glandular tissues. Bulk and single cell RNA sequencing revealed activation of the NOTCH, WNT and EGFR pathways in basal cells upon luminal cell ablation. Suppression of these pathways inhibited basal cell multipotency, indicating that heterotypic cell-cell communication is essential to maintain lineage fidelity in epithelial progenitors during homoeostasis.

Exciting research, new methodological approaches and though-provoking ideas were presented also during poster sessions. The topics included, among others, cellular and signaling mechanism of early mammary gland development and mammary branching morphogenesis [31], mechanisms of mammary fate specification in development [32] and cell plasticity in breast cancer, the role of mammary fibroblasts in normal development [33, 34] and cancer, genetic and drug screening strategies to identify mechanisms of breast cancer resistance. The poster prizes, generously provided by European Association for Cancer Research, were awarded to Florian Gourgue (Université Catholique de Louvain, Belgium) for his work on link between obesity and breast cancer, to Anna Marusiak (University of Warsaw, Poland) for deciphering the role of mixed-lineage kinase 4 in TNBC [35], and to Fabiana Lüönd (University of Basel, Switzerland) for her study on epithelial-to-mesenchymal transition in breast cancer.

Conclusions

After the jubilee tenth ENBDC workshop in 2018 [36], the eleventh ENBDC workshop has successfully started off another decade of collaboration and data and know-how sharing in mammary gland biology and breast cancer research in Europe and beyond. The 2019 workshop brought shining examples of how advances in technology combined with creativity and problem-solving skills of scientists help to significantly advance our understanding of fundamental developmental processes and breast cancer intricacies. Thanks to high resolution genomics and proteomics tools, advanced microscopy techniques and genetic engineering, we are not only witnesses, but also future contributors to unprecedented novel findings on epithelial tissue morphogenesis, cell-cell interactions and relationships, signaling nuances in normal and cancer cells, and intricacies of tumor microenvironment. The 12th ENBDC meeting will take place on 26th to 28th of March 2020 it and will be chaired by Alexandra Van Keymeulen (Université Libre de Bruxelles, Belgium), with the support of post-doc and PhD student chairs Gunnhildur Traustadottir (University of Iceland, Iceland) and Elsa Charifou (Institut Pasteur, France).

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Compliance with Ethical Standards

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication The manuscript has been read and approved by all authors, has not been published previously in print or electronic format, and is not under consideration by another publication or electronic medium. Consent for publication has been obtained from all the speakers.

Conflict of Interest The authors declare that they have no conflict of interest.

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