CSBC RESEARCH AND HIGHLIGHTS (2016-2020)

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The major goal of the NCI Cancer Systems Biology Consortium initiative is to advance the mechanistic understanding of cancer using systems biology approaches that build and test predictive models of disease initiation, progression, and response to treatment. While a translational research component is not required for CSBC-supported Centers and Projects the ultimate goal of CSBC research is to make a positive impact on the lives of cancer patients. Although not explicitly solicited, five major research themes (U54s) and questions (U01s) have emerged across the CSBC portfolio: (a) the role of tumor heterogeneity and evolution in cancer; (b) biological mechanisms of therapeutic sensitivity and resistance; (c) tumor-immune interactions in cancer progression and treatment; (d) cell-cell interactions and complexities of the tumor microenvironment; and (e) systems analysis of metastatic disease. This document provides CSBC research highlights related to the five broad areas above as compiled by NCI Program Staff. The overview is not meant to be an exhaustive literature review within these areas of cancer biology but reflect contributions from CSBC investigators. Therefore, all references are purposefully limited to CSBC-supported manuscripts to highlight the breadth of research and impact across the CSBC portfolio. In some cases, links to papers currently under review are provided. Only a subset of the over 430 consortium publications (as of May 15, 2020) are highlighted here, a more complete collection of publications and tools associated with CSBC research is available through the Cancer Complexity Knowledge Portal.

(a) The role of tumor heterogeneity and evolution in cancer progression

Tumors exhibit significant heterogeneity at the molecular, cellular, and structural levels making it difficult to predict disease progression and response to treatment. From an evolutionary biology standpoint, genetic heterogeneity can arise from either neutral or selective outgrowth of specific tumor cell populations [1]. Mapping tumor evolution using next generation sequencing can facilitate patient-specific predictive models but many challenges exist, including how to glean maximal insight from limited clinical samples. Mechanistic mathematical models, constructed by the Arizona Cancer and Evolution (ACE) Center, can guide effective multi-region and single-cell sampling protocols to capture true genomic heterogeneity from clinically realistic sampling [2, 3]. For example, modeling and subsequent experimental validation demonstrated that the degree of spatial mixing of tumor subclones within colon adenomas can be used as a proxy for tumor cell migration and therefore predict the future metastatic potential of premalignant lesions [4]. Furthermore, in contrast to the traditional view that tumor cells gain the ability to metastasize in a progressive manner upon accumulation of somatic mutations, model-guided sampling led to the discovery that multiple tumor subclones locally invade very early in colorectal carcinomas seeding lymph node and liver metastasis [5].

In many tumors genetic heterogeneity does not necessarily predict phenotypic heterogeneity. How a multitude of sometimes disparate somatic mutations across patients manifest in a rather limited number of disease processes or phenotypes remains an open question in cancer biology. The City of Hope U54 team addressed this question through an integrated analysis of longitudinal whole exome and single-cell RNA sequencing across multiple timepoints in breast cancer patients demonstrating that drug-resistant subclones converge on well-known tumor hallmark pathways that are amenable to further therapeutic targeting [6]. Similar studies with an expanded longitudinal patient cohort have suggested new drug combinations for triple-negative and ER+ breast cancers [7] and launched a recently approved clinical trial at the University of Utah that will test the combination of HDAC and CDK4/6 inhibitors.

Another way to examine the contribution of heterogeneous somatic mutations to phenotype on a per-patient basis is to quantify how tumor mutations disrupt the physical protein-protein interactions (PPIs) that control intracellular networks and, ultimately, cell processes [8]. The UCSF/UCSD Cancer Cell Map Initiative is building patient-specific disease networks to account for interpatient heterogeneity. The approach integrates large-scale PPI maps, high-throughput genetic interaction screens, and patient specific genomics using a novel “visible deep learning” framework that employs biological knowledge to interpret the resulting neural network [9, 10].

Incorporation of prior biological knowledge into deep learning algorithms makes them useful for understanding disease mechanisms. Current work within the UCSF/UCSD Center is partnering these interpretable Deep Learning networks with large-scale drug screening data to determine patient-specific treatments and to discover patient-specific drug mechanism of action.

Somatic mutations can also directly or indirectly affect the repertoire of alternatively spliced protein isoforms adding more heterogeneity to network structure and feedback mechanisms. The U01 Research Project at Dana Farber Cancer Institute has developed a novel sequencing platform that increases isoform-specific detection and employed it to map dysregulation in gene regulatory networks due to alterations in alternative splicing of cancer-related transcription factors [11]. To combine the power of different approaches to map protein-protein interaction networks, the UCSF/UCSD U54, the DFCI U01, and the Center for Cancer Systems Therapeutics at Columbia University have launched a trans-CSBC initiative through the CSBC/PS-ON Protein-Protein Interaction Working Group to determine how variants of unknown significance rewire the BRCA1 interactome. The goal of the project is to accelerate the discovery of pathological variants and to predict their effect on breast cancer initiation or progression.

Phenotype plasticity, driven by epigenetic processes, can account for dynamic heterogeneities. For example, in triple negative breast cancer (TNBC) aberrant sequestration of the tumor suppressor GDF11 within the cytosol can led to heterogeneous cell phenotypes, despite homogenous gene expression across cells [12]. Restoration of nuclear shuttling can reverse these phenotypes and the UVA U01 Research Project (Janes) is developing "stochastic frequency matching", a method to reverse engineer how non-genetic heterogeneities, such as those driven by GDF11, arise within a cell population. Promiscuous binding of transcription factors, driven by changes in chromatin accessibility or differential localization of chromatin binding proteins, can also drive cell state changes. For example, dynamic phenotype plasticity in ER+ luminal breast cancer is promoted by differential, and context dependent, higher order assembly of transcription factor complexes associated with ERα binding to enhancer regions, as described by the UT Health Science Center San Antonio U54 [13]. Membership in these MegaTrans regulatory complexes promote epigenetic changes in gene expression that facilitate tumor progression, such as the heterogenous development of drug resistance [14].

Treatment with traditional or targeted therapies can uncover previously unappreciated cell plasticity and the OHSU Measuring, Modeling, and Controlling Heterogeneity Center found that genetically similar TNBCs exhibit significant transcriptional plasticity upon exposure to therapies targeting PI3K or MEK [15]. The plasticity is dynamic, steerable, reversible, and predictable via a mathematical model that describes cell state-switching [15-17]. Current work in the OHSU U54 Center is focused on understanding the epigenetic mechanisms underlying drug-induced plasticity across breast cancer sub-types. The computational methods developed within the OHSU Center, and supported by the CSBC, are being employed in the Serial Measurements of Molecular and Architectural Responses to Therapy (SMMART) program at OHSU to directly guide treatment of TNBC patients.

Finally, intratumor heterogeneity can also arise from interactions with neighboring tumor cells and other cell types within the microenvironment. To study these interactions, several CSBC investigators have utilized single-cell technologies to catalog cell types within the tumor ecosystem [18-29] and developed computational tools for processing of single-cell sequencing and imaging data [18, 30-36]. Importantly, investigators within the CSBC aim to derive biological insight from single-cell data that goes beyond cataloging cells, such as mapping cell-cell interaction networks [37, 38], inferring intracellular signaling network activity [39, 40], and discovering biologically meaningful spatial patterns that are predictive of disease progression [41-44]. Multiple CSBC awards are using single-cell transcriptome and protein-level data to represent tumor heterogeneity within predictive mathematical models. For example, the UCI Center for Complexity, Cooperation, and Community in Cancer has constructed cell-level mathematical models to understand how metabolic patterning in colon cancer arises [45] and more recently combined those models with single-cell RNA-seq to identify therapeutic targets. Relatedly, the U01 Research Projects at Moffitt Cancer Center and the University of Michigan will utilize single-cell level measurements to

parameterize agent-based models of lung cancer and bladder cancer, respectively, for subsequent *in silico* testing of immunotherapy drug combinations where the best performing combinations will graduate to *in vivo* validation. In both cases individual agents will reflect the true heterogeneity of the tumor due to the availability of single-cell transcriptomic and imaging data.

(b) Biological mechanisms of therapeutic sensitivity and resistance

The biological mechanisms underlying response to cancer therapy and the development of resistance to those therapies are complex and require a systems-level view to adequately address. For example, intratumor heterogeneity and tumor cell plasticity contribute significantly to therapy response and to the mechanisms underlying development of resistance to cancer therapies. Understanding which cells within a heterogeneous tumor population facilitate resistance is a focus of multiple CSBC grants. Coupling single-cell transcriptomics with an exquisitely sensitive dynamic cell mass measurement [46] allowed the MIT U54 Research Center to link transcriptional differences directly to drug response on a single-cell level in liquid and solid tumors [46, 47]. The approach facilitated identification of single drug resistant cells, and the potential molecular mechanisms of resistance. The coupled transcriptome-phenotype measurement is currently being tested in the clinic to identify cells that underlie minimal residual disease in leukemia patients [48] and has moved towards more widespread clinical use via Travera.

In solid tumors, such as melanoma, targeted therapies are initially very effective, with dramatic decreases in tumor burden that are often followed by disease recurrence. Although the emergence of resistance is often associated with expansion of a clone with an alternate and fitness-promoting mutation, non-genetic processes also contribute to drug resistance. For example, by coupling live-cell imaging of early cell response and mathematical modeling, the Harvard U54 Center for Cancer Systems Pharmacology found that $BRAF^{V600E}$ mutant tumors can become resistant to RAF or MEK inhibition through pulsatile reactivation of the MAPK pathway [49]. The sporadic activation of ERK, due to a balance between pathway redundancies with variable response to drug, can lead to tumor sustaining cell proliferation in the presence of inhibitor. Stochasticity can also be introduced into the system through transcriptional bursting and the University of Pennsylvania U01 Research Project has demonstrated through paired simulation and experimental validation that rare cells with high gene expression in specific pathways can also facilitate drug resistance in melanoma [50]. To identify these rare cells prior to treatment, the team has developed REWIND, a single-cell barcoding system, that facilitates characterization of cells before they give rise to resistant clones [51]. The teams at UPenn and Harvard are currently working together through a CSBC Collaborative Administrative Supplement to determine if the dynamic transcriptional- and protein-level mechanisms they independently discovered are coupled.

Currently, patients are matched with targeted therapies using sequencing panels to identify common mutations that confer sensitivity to drug. While this approach has resulted in great success for a small number of targets, it does not account for more complex regulatory structures such as feedback mechanisms and alternative signaling pathways that mediate resistance. Another approach is to infer and target small clusters of genes that regulate multiple orthogonal networks [52]. The Center for Cancer Systems Therapeutics at Columbia University refers to these clusters as “tumor checkpoints” [53] and has employed a suite of publicly available computational tools for identifying and targeting them across tumor types [15, 54-57]. The computational tools developed at the Columbia U54 Center have been licensed to Darwin Health to facilitate adoption by the pharmaceutical industry. The Vanderbilt U54 Research Center has utilized a similar approach to discover a new subtype of small cell lung cancer and describe the master regulators controlling tumor heterogeneity [58, 59]. In a complementary fashion that will allow comparison of gene regulatory network inference methods across the CSBC, two recently awarded CSBC U01 Research Projects from the University of Colorado and the Children’s Hospital of Philadelphia are extending network inference methods to include information derived from pathology images in prostate cancer [60] and gene fusions in pediatric B-cell acute lymphoblastic leukemia, respectively.

An alternative to expensive high throughput screening methods to identify cancer drugs is the construction of multiscale molecular models that connect signaling pathways to cell response and can be interrogated *in silico* to narrow the experimental search space. A range of modeling approaches are taken in the CSBC to construct such models, including those based upon classic mass action kinetics (Harvard U54 Center), network theory (MIT U01 Research Project), machine learning (University of North Carolina U01 Research Project), optimal control theory (UVA U01 Research Project), modular mechanistic modeling (PNNL U01 Research Project), and agent based models (Moffitt U01, University of Michigan U01, University of Southern California U01). A common thread to these projects is parameterization using protein-level data or through the integration of disparate data types.

(c) Tumor-immune interactions in cancer progression and treatment

The immune system is the first line of defense against tumor progression. Tumors escape immune elimination through a variety of mechanisms, including somatic mutations in HLA or B2M genes that dysregulate antigen presentation [61], immunoediting that selects for non-antigenic growth-favoring mutations [62], and through co-opting of cell function [63]. Predicting how and when tumors will successfully evade the immune system requires a systems-level view of tumor-immune interactions within the primary tumor microenvironment and at sites of metastasis. Rich datasets, such as single-cell RNA-seq, highly multiplexed immunofluorescence, and single-cell proteomics provide a snapshot of the diversity of immune cells within the tumor microenvironment [18, 19, 28, 29, 33, 64] and can be modeled to derive testable hypotheses regarding cell-cell interactions that drive tumor progression and metastasis [19, 37, 65]. For example, motivated by findings that cancer therapy can give rise to distinct tumor-associated macrophage populations that facilitate dysregulated cell-cell interaction [66], the Yale U01 Research Project will combine single-cell transcriptomics, proteomics and imaging approaches to build computational models that predict how rewiring of intercellular networks drive tumor responses to immunotherapy in melanoma.

Individual immune cell *states* are also impacted by cell-cell interactions within the tumor microenvironment. The MSKCC Center for Cancer Systems Immunology found that exposure to pre-malignant lesions resulted in T-cell dysfunction that was characterized by changes in chromatin accessibility and gene transcription. The dysfunction was initially plastic and could be reversed through inhibition of checkpoint receptors. However, tumor progression quickly resulted in a locked dysfunctional T-cell state that was not reversible [67]. This seminal 2017 finding has been replicated across multiple tumor types. Follow-up studies within the MSKCC U54, and published in tandem with two independent manuscripts, demonstrated that upregulation of the transcription factor TOX and activation of NFAT drives the resulting T-cell dysfunction but that inactivation of TOX alone was not sufficient to rescue cytotoxic T-cell activity or responses to immunotherapy [68]. These studies demonstrated that reversal of T-cell state in the presence of immune checkpoint blockade does not guarantee a return to normal cytotoxic function providing an important potential basic biological mechanism for failure of immunotherapies.

Tumors and tumor therapies can act systemically to alter the immune system. In collaborative work with Harvard Medical School, the MIT U54 Research Center found that the efficacy of BRAF- and MAPK-targeted therapies on melanoma and ovarian cancer cells is significantly decreased due to drug-specific activation of tumor-associated macrophages which provide survival signals to the tumor [69]. In forthcoming work, the Harvard U54 Research Center reports that PARP inhibitors directly impact the differentiation and metabolism of tumor-associated macrophages in TNBC increasing the effectiveness of treatment (imaging data can be found here). Collectively these studies demonstrate that considering the impact of traditionally tumor-targeted therapy on cells within the immune system (and the stroma as a whole) will be key to designing optimal therapies, especially those that overcome presumed cell-intrinsic resistance mechanisms. Experimental systems that facilitate high throughput, immune cell-specific perturbation *in vivo* will accelerate our understanding of the effect of therapies on this important cell compartment and may identify new immunotherapies [70, 71].

(d) Cell-cell interactions and complexities of the tumor microenvironment

In addition to cells of the immune system, most solid tumors are infiltrated or surrounded by stromal components that can direct tumor cell behaviors. Work completed by or in collaboration with CSBC investigators has led to insights regarding the heterogeneity of normal and cancer associated fibroblasts [23, 72, 73], lymphatic endothelial cells [74], adipose stromal cells [75] and pericytes [76]. Multiple methods have been developed with CSBC funding to map tumor-stroma interactions using single-cell [37, 38] and bulk [72] transcriptional data. Such inference techniques produce multiple candidate interactions which can be difficult to prioritize for validation. Further, current algorithms lack the ability to infer additive or synergistic effects of multiple significant interactions. In currently ongoing work within the consortium, complementary *in vitro* experiments that are guided by computational analysis facilitate systematic evaluation of pairs or small sets of relevant ligands and extracellular matrix components (ECM) on tumor cell behaviors. For example, the OHSU Measuring, Modeling, and Controlling Heterogeneity Center is using the Microenvironment Microarray (MEMA) platform [77] to study how signals from the ECM or local stromal cells impacts drug response [15]. By utilizing deep learning approaches the Center is also able to interrogate cellular phenotypes beyond cell death and survival [36] and results from MEMA analysis are informing advanced 3D bioprinted *in vitro* models capable of recapitulating *in vivo* tumor behaviors and tumor-stromal interactions [17]. Such highly controllable *in vitro* systems that closely mimic tumor response *in vivo* can be utilized to parameterize agent-based models of the tumor microenvironment, which in turn, can rapidly generate further testable hypotheses *in silico*. One such example is the open source PhysiCell environment [78], an agent-based modeling platform which is being parameterized using data collected from colorectal cancer organoid models by the USC U01 Research Project to study metabolic dependencies between tumor cells and cancer associated fibroblasts.

While it is clear that tumor-stromal interactions are important in cancer biology, the prognostic value of specific cell-cell interactions has not been well defined. The Stanford U54 Research Center created a public tool for exploring the prognostic value of cell-cell crosstalk in non-small cell lung cancer, the Lung-Tumor Microenvironment Interactome. Mining of the resource identified cancer associated fibroblast expression of GREM1 as being prognostically unfavorable due to increased tumor proliferation via activation of VEGFR2 on neighboring tumor cells [72]. Examples of fibroblast-driven tumor progression have been reported in other cancers and the Arizona Cancer and Evolution (ACE) Center postulated that components of the tumor stroma could be viewed as ecological 'resources' (fibroblasts/endothelial cells) or 'hazards' (immune cells) that promote or inhibit tumor growth, respectively. Local habitats defined by the balance of cell types were quantified using automated image analysis and an EcoScore was calculated to represent the ratio of resources to hazards. A low EcoScore (more hazards than resources) is predictive of better outcome in patients with high grade serous ovarian cancer [79], demonstrating that the spatial context of the tumor microenvironment is independently prognostic of outcome.

These studies suggest that organization of the tumor microenvironment may not be random and could be optimized for tumor growth. Using an *in vitro* microphysiological system mimicking mammary tumor geometries and flow patterns, the MSKCC Center for Cancer Systems Immunology found that metabolites secreted by hypoxic tumor cells reprogrammed tumor-associated macrophages towards pro-angiogenic signaling by increasing VEGFA secretion and sprouting of new vasculature [80]. In this system, tumor-secreted metabolite gradients patterned tumor-associated macrophages into zones of differential gene expression that relayed cell state information to the surrounding endothelial cells. Such pattern formation is reminiscent of developmental processes and suggests that tumor formation and progression may proceed, at least in some cases, through organized principles versus chaotic growth.

(e) Systems analysis of metastatic disease

Most cancer deaths can be attributed to the effects of metastatic disease. Evidence from human and experimental models support multiple concurrent and partially overlapping routes to distant metastasis that require the

acquisition of both cell autonomous and environment-mediated metastasis-promoting phenotypes [81]. The dogma that metastasis only occurs late in disease and through a linear cascade of events is no longer a widely held view. Many genomic studies point to the potential for cell invasion and subsequent metastasis early in disease, including in colorectal cancer [5] and breast cancer [82]. The most common clinical predictor of metastasis is the presence of cancer cells in tumor draining lymph nodes. Through multi-region sequencing of lymph nodes from a small number of breast cancer patients without evidence for distant metastasis, the Arizona Cancer and Evolution (ACE) Center found two distinct mutational patterns; one that was similar to the primary tumor (no divergence) or one that was indicative of early divergence within the lymph node [82]. Longitudinal monitoring of ctDNA found evidence of both primary tumor and lymph node somatic mutations in the plasma and was able to capture the private mutations associated with lymph node lesions after primary tumor resection. Further technical and computational developments coupling genomic sequencing and methylation state of ctDNA allowed for detection of specific metastatic sites through plasma measurements and supported the notion of early dissemination in breast cancer [83].

The role of tumor draining lymph nodes as active or passive participants in promoting distant metastasis remains an unanswered question. In work that is currently under review (and available soon as a Cell Sneak Peek), the Stanford U54 Research Center has discovered that early dissemination of tumor cells to the lymph node can lead to systemic tolerance for widespread metastasis in multiple tumor types, including melanoma, head and neck cancer, and breast cancer. Tumor cell dissemination to the lymph node occurs through evasion of Natural Killer cells through downregulation of MHC-1 genes. After arrival in the lymph node, tumor cells facilitate systemic immune tolerance through induction of T-regulatory cells.

Once they colonize distant organs the Center for Cancer Systems Immunology found that early disseminated lung adenocarcinoma (LUAD) cells remain undetectable due to consistent NK cell pruning of micrometastases [65]. Single-cell analysis of primary and metastatic tumors demonstrated that LUAD cells occupy a range of developmental states defined by a balance of Sox2 and Sox9 expression. Cells that formed overt metastases tended to be defined by high Sox2 expression and decreased expression of MHC-1 genes. Conversely, early disseminated tumor cells, which may represent the population traditionally thought of as dormant, are kept in check through a program that includes expression of Sox 9. Interestingly, macrometatases that formed upon NK-cell depletion in a Kras-driven LUAD mouse model appeared to arise from initial monoclonal seeding, suggesting that metastatic cells are plastic with regards to developmental lineages and entirely different strategies are needed if targeting the Sox9 (dormant) versus Sox2 (growth) states [65].

In addition to contributing to immune cell evasion, single-cell heterogeneity drives local invasion of primary tumors and is prognostic for disease outcome. Employing a cell state model [84] and a novel 3D *in vitro* culture system that allows for purification and analysis of specific LUAD cell subsets the Yale U54 Research Center found that “leader” cells, those that pioneer collective invasion into the ECM, are more metabolically active than “follower” cells [85], do not require an epithelial-to-mesenchymal transition (EMT) for efficient invasion [86], and can be identified in LUAD patients using a mutational signature derived from genes on chromosome 16 [87, 88]. In complementary studies in glioblastoma, a micropatterned device (RACE assay) was utilized to quantify the proportion of migratory to proliferative cells upon tumor resection. Patients whose tumors had high proportions of RACE assay-identified migratory cells exhibited a short time to disease recurrence [89].

As demonstrated by the Marcus lab [86] and others, the ability of carcinoma cells to metastasize does not always require a complete epithelial-to-mesenchymal transition (EMT). However, the Hallmark EMT gene expression signature has provided prognostic value in some contexts [6], suggesting that knowledge of the EMT state of individual cells may provide for more informed tumor staging and guide choice of therapy. To address this need, the Stanford U54 Research Center constructed a lung-cancer focused EMT-mesenchymal-to-epithelial (MET) Phenotypic State Map (EMT-MET PHENOSTAMP) utilizing high resolution time course single-cell protein mass cytometry (CyTOF) data collected from non-small cell lung cancer cell lines treated with TNFβ [90]. The EMT-MET

PHENOSTAMP, which can be thought of as an atlas of lung EMT states, was utilized to classify patient tumors along an EMT-MET trajectory and interpret clinical specimen data, including differences in mutational status. This type of systematic approach could be extended to a range of cellular phenotypes that involve cell state transitions.

Conclusion

The investigators of the NCI Cancer Systems Biology Consortium employ a range of computational and experimental systems to understand the biological mechanisms underlying cancer initiation, progression, metastasis, and treatment. Less than one-third of the total CSBC publications (as of May 15, 2020) are represented by this mini-review and highlight document. Advances were chosen to not only provide specific examples but to also reflect the breadth and depth of the research being conducted by the CSBC investigators. A major thread that ties these studies together is the consideration of cancer as a systems-level problem, as only a small number of publications from the CSBC focus on the role of an individual molecule. Rather, the insights gained by CSBC investigators consider the context in which molecules, cells, and tumors reside, true to the systems biology goals of the program.

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