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Meeting Report

Summary of the 2015 American Association for Cancer Research (AACR) Annual Meeting

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The 2015 American Association for Cancer Research (AACR) Annual Meeting was held in Philadelphia, PA from April 18th to April 22nd, 2015. The theme of the meeting was "Bringing Discoveries to Patients". This year there were few gynecologic cancer-specific sessions, yet many talks on basic cancer biology have significance to cancers specific to women. True to its name, there were more sessions than prior years with updates on clinical trials, reports of programs seeking to globally profile patient samples, and efforts to understand cancer genomics as they relate to treatment and outcome. This conference report summarizes key abstracts and presentations relevant to the understanding and therapy of gynecologic malignancies.

1. Tumor genomics, heterogeneity, evolution, and resistance

Mike Stratton reported genomic insights gained from pan-cancer analysis of The Cancer Genome Atlas and International Cancer Genome Consortium and described several processes that could account for mutation patterns observed in various tumors. This was the result of analysis of 12,000 carcinoma samples from 40 different cancer types and about 8 million somatic substitutions from these samples. The intent is to identify patterns in types of mutations that can be used to categorize cause, prognosis, or basic biology of different cancers. They concluded that there were only thirty different mutational categories, a few of which were tumor type specific, but most were found across multiple tumor types. Certain environmental exposures produced signatures, such as a common mutational profile noted by exposure to UV radiation where C > T somatic substitutions predominate, or C > A mutations in lung cancer associated with smoking. In ovarian cancer, three major mutational signatures were noted. One of these was a signature of APOBEC's, a family of cytidine deaminases. A similar APOBEC mutational signature was also observed in cervical cancer associated with viral-induced carcinogenesis. Interestingly, viral DNA entry and retrotransposon remobilization may serve as mechanisms that switch on APOBEC enzymes. Mutational signatures associated with HR defects were also identified. Overall, he concluded that cancer genomes frequently contain "ketaegis" events, or clusters of hypermutated regions which are relatively random and not consistent from patient to patient. The underlying etiologies of these mutations patterns are not understood. A better understanding of underlying mutational processes associated with these signatures may lead to a better understanding of the initiating oncogenic switch, or treatment options specific to the signature, instead of tumor type.

Investigating the hierarchical organization of breast and ovarian cancer cells, John Stingl from the Cancer Research UK Cambridge Institute, discussed his findings in high grade serous ovarian carcinomas. He hypothesized that subpopulations of these tumors cell have stem-like qualities which render them resistant to chemotherapy. Analyzing 86 freshly isolated tissues, he found three distinct subpopulations of epithelial cells, one which expressed high levels of epithelial cell protein (EpCAM) and the other two which were both EpCAM negative, expressed podoplanin and varying levels of CD43, but had different types of daughter cells. A xenotransplantation model treated with cisplatin revealed that EpCAM negative cells were less sensitive to treatment, however, ultimately it was concluded that both EpCAM positive and negative cell populations have stem-like properties.

In a poster session, Paul Goodfellow presented a study that identified CTCF and ZFHX3 deletions and loss of function mutations in endometrial cancers. CTCF and ZFHX3 are tumor suppressor genes located near 16q21.2, and The Cancer Genome Atlas dataset on uterine corpus endometrioid carcinomas showed truncating nonsense and frameshift insertions and deletions in these genes. His group performed targeted sequencing of 541 endometrioid endometrial carcinomas and found single nucleotide variations and indels in 24% and 18% for CTCF and ZFHX3, respectively. His group found a significant co-occurrence of alterations in both genes, and these alterations are associated with high grade, lymphovascular space invasion, and shorter recurrence-free survival in endometrial cancers.

Charles Swanton described clonal evolution of tumors over time using the "tree" model, whereby the trunk represents initial (and persistent) mutations, and branches represent subsequent mutations that may be disparate in different metastatic lesions. The difficulty lies in knowing whether subsequent "branch" mutations are drivers or passengers, in which case they would be irrelevant to patient-directed therapeutics. His analysis indicated that chemotherapy may be "trimming" the multiple branches, but leaving cells with the more crucial trunk mutations that can persist. Additionally, he provided evidence that patients with heterogeneous tumors consisting of multiple subclonal drivers showed poor overall survival. This would be the case for ovarian cancer, since the TP53 "trunk" mutation would repeatedly give rise to multiple branches. However, his dataset was not specific to ovarian cancer, being concentrated on colon cancers, and additional research is required to know if these findings are generalizable.

Dr. Levi Garraway then expanded on the theme of evolving cancer resistance by describing molecular mechanisms associated with resistance to targeted therapy. Using functional screens, his group addressed whether candidate genes mediating resistance are necessary and sufficient for resistance to targeted therapies, whether these candidate genes reactivate signaling pathways downstream of the drug targets, and the relevance of such candidate genes in clinical resistance. He described that pathway reactivation is a common mechanism of resistance

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to pathway-targeted cancer therapies. For example, C-RAF overexpression can overcome B-RAF inhibition, and so is downstream activation of Mek1/2. Other growth factor singling pathways that crosstalk with a targeted pathway may also result in resistance to pathway-targeted therapies. For example, resistance to RAS/Raf pathway inhibitors can be mediated by downstream transcription factors, upstream G-protein coupled receptor, or activators of Protein Kinase A. Pathway reactivation, pathway bypass, pathway indifference (alternative oncogenic transcriptional outcome) are generalized concepts involved in pathway-targeted cancer therapy resistance. Pathway inhibition will select for pathway-independent resistant mechanisms, and these mechanisms may converge on transcription factors that are actual effectors of the pathway. Dr. Garraway also described known challenges to clinical drug resistance studies, such as the multi-factorial nature of drug resistance, under-sampling, and intratumor heterogeneity. Therefore, it would be important to target points of convergence to reverse resistance.

2. Epigenetics

Dr. Steve Baylin described epigenetic alterations in cancer, including focal regions of hypermethylation and wide regions of hypomethylation in cancer genomes. He also described IDH1 mutations and their association with CpG island methylator phenotype (CIMP). He then discussed the extent to which abnormal epigenetics programming can contribute to tumorigenesis and how abnormal epigenetics programming in established tumor cells may be targeted for therapeutic benefits. One exciting area that Dr. Baylin highlighted is the use of low dose 5-azacidine (DNA methyltransferase inhibitor) for the purpose of immunostimulation and enhancing immunotherapy. He then described a potential role of endogenous retroviral remobilization in stimulating IFNγ and the therapeutic potential of epigenetics reprogramming by 5 azaC in immunoreactive molecular subtype of ovarian cancer.

3. Mouse models

Dr. Tyler Jacks from MIT reviewed traditional and novel approaches to generate genetically engineered mouse models of cancer to characterize the role of candidate genes in tumor immunology and tumor biology. He described development of a transgenic mouse line with FoxP3-driven diphtheria toxin receptor for immunotherapy. Upon administration of diphtheria toxin, FoxP3-expressing Treg cells were depleted, and T cell infiltration of tumor was observed in these mice, demonstrating the potent role of Tregs in the suppression of tumor immunity. Also described was the exciting development of the CRIPSR/Cas9 system, whereby genetic editing can be performed to specifically knock in or out genes, or even change one nucleotide to induce a mutation. Dr. Jacks and his colleagues generated lentiviral expression constructs that expressed both guide RNA (gRNA) and Cas9, and disrupted p53 and PTEN. These mice showed the onset of tumor development within 6 months of injection of lentiviral particles. Unlike conventional knockout models, where construction of targeting vectors, screening of ES cells, and generation of knockout mouse lines are quite laborious and time consuming, lentiviral delivered CRISPR/Cas9 system is rapid, reproducible, and relatively simple.

4. Immunology

There were numerous sessions on advances in preclinical immunologic approaches to cancer, one of which was specific to ovarian cancer. George Coukos from the University Hospital of Lausanne presented "Opportunities for Immunotherapy in Ovarian Cancer", which emphasized the importance of evaluating the presence or absence of tumor-infiltrating lymphocytes (TILs) in ovarian cancer. Of their cohort of patients with TILs present in tumors, greater than 60% had improved survival rates and 50% never relapsed. In comparing tumors with and without TILs, their group found that high levels of FASL, mediated by VEGF and PGE2, encouraged T-cell death in the tumors. Blocking VEGF and PGE2 reduced FASL levels, allowing T-cell accumulation and restoration of an immunogenic tumor. In another important approach, they demonstrated that the absence of TILs predicted failure to anti-PD-1 therapy. However, this could be partially overcome by addition of a vaccine generated specifically to tumor antigens, increasing therapeutic response.

Jeong Kim (Genentech) presented "Unleashing anti-tumor immunity through anti-OX40 monotherapy and in combination with anti-PD-L1". OX40 (aka Tumor necrosis factor receptor superfamily member 4 (TNFRSF4) or CD134) is a receptor expressed only on activated CD4 and CD8 lymphocytes. It is typically upregulated 48–72 h after T-cell activation, and promotes proliferation and clonal expansion of effector and memory populations. Anti-OX40 is an agonistic monoclonal antibody that is effective via a dual mechanism of 1) co-stimulating effector T-cells increasing their proliferation and the production of cytokines and 2) inhibiting regulatory T-cells. Mouse studies demonstrated that anti-OX40 treatment reduced tumor burden and established immune memory, making the mice resistant to tumor rechallenge. Additionally, combining anti-OX40 agonistic MAb with anti-PD-L1 treatment increased the therapeutic response compared to either treatment alone.

Dr. Robert Schreiber from Washington University at St. Louis described the application of genomics to personalize cancer immunotherapy. He first described the concept of immunoediting involving the "3E's": elimination, equilibrium, and escape that may account for the mechanisms of tumor cell evolution to immune evasion. For example, recombination-activating gene 2 (RAG2) is one of the 2 genes responsible for rearrangement and recombination of genes during V(D)J recombination as immunoglobulin and T-cell receptors undergo maturation. RAG2(−/−) mice develop tumors quicker than wild type, and tumors taken from Rag2(−/−) mice are rejected in Rag+/+. Tumors that developed in Rag2(+/+) mice showed reduced immunogenicity providing evidence that immunogenicity is "edited". He went on to describe how genomics might be used to personalize cancer immunotherapy. NetMHC is a server at the Center for Biological Sequence Analysis at the Technical University of Denmark that can be used to predict which tumor-specific mutations form tumor-specific mutant rejection antigens. These could be used for rapid generation of immunotherapy approaches by tumor profiling. Finally, he presented evidence that checkpoint blocking therapy (such as anti-PD-1-based therapies) targets specific mutant neoantigens. Here, mutated proteins can serve as neoantigens that are recognized by immune cells, even if the mutant proteins were not necessarily drivers of disease progression. These neoantigens can be used to develop personalized vaccines, with data presented that such vaccines are effective in blocking immune checkpoints. Furthermore, combining neoantigen personalized vaccine and checkpoint blocking therapy was more effective than either alone. Specifically, while immune checkpoint blocking therapies are less effective when started late in the disease course, adding a personalized vaccine increased checkpoint therapy efficacy even in late stages of tumor progression.

5. Tumor dormancy and senescence

Several talks were presented examining the mechanisms underlying tumor dormancy. Lewis Chodosh used an inducible HER2-overexpression breast cancer model to demonstrate that the initial oncogenic pathways responsible for primary tumor cell development were not identical to those mediating recurrent disease. For example, when HER2-positive tumors were treated to no evidence of disease, recurrent tumors could be induced by re-expression of HER2, but recurrent tumors then overexpressed other genes or pathways that were minimally expressed in primary tumors, including single-stranded binding protein Ssb1, mediators of Notch signaling, c-Met, and autophagy. Recurrence could be prevented in some