

Conference Report: Seventh Annual AACR International Conference on Frontiers in Cancer Prevention Research

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Abstract

In November, 2008 the AACR held the Seventh Annual Frontiers in Cancer Prevention Research meeting in Washington, DC. At this meeting, a wide range of cutting-edge cancer prevention research was presented. This summary highlights some of the most impactful presentations with a focus on the interaction between inflammation, infections, the immune system, and tumor microenvironment in promoting cancer. Several of these presentations described targeting host-tumor interactions as a means for cancer prevention. As discussed below, this meeting continues to represent all phases of cancer prevention research including epidemiologic studies, behavioral and lifestyle interventions, carcinogenesis research, preclinical studies testing novel preventive interventions, and the results of early- and late-phase cancer prevention trials. Major advances presented at the 2008 meeting included studies showing that immune cells can be either protumorigenic or antitumorigenic, efforts to develop more comprehensive human papillomavirus vaccines to more effectively prevent cervical cancer and other human papillomavirus-related cancers, controversial studies of vitamin D and cancer risk, and studies of single-nucleotide polymorphisms to better assess cancer risk. These and the other presentations at this meeting continue to provide strong support for the concept that cancer will be most effectively controlled by applying modern cancer prevention strategies

The role of inflammation in carcinogenesis was a common thread running through much of the research presented at the 2008 AACR Frontiers in Cancer Prevention Research Conference held in Washington, DC. Several key presentations on the immune system, infection, and aging focused on chronic inflammation. Other timely topics, including the role of vitamin D in carcinogenesis and personalized assessment of cancer risk, were also discussed. Highlights from several of these provocative sessions are summarized here.

Inflammation, Immune Responses, and Cancer

Dr. Tak Mak explored the role of the immune system in oncogenesis, focusing on the nuclear factor- κ B (NF κ B) family of transcription factors, which play a key role in coordinating

immune response. Inflammatory cells typically respond to bacteria, viruses, necrotic cell products, and various cytokines by activating NF κ B. Although a mediator of normal immune response, the aberrant consequences of NF κ B have been shown in many malignancies to influence growth, angiogenesis, apoptosis, and evolution to an invasive phenotype. Dr. Mak reviewed NF κ B activation in Hodgkin's and MALT lymphomas, citing paradoxical effects with regard to apoptosis, such as a recently reported therapeutic window related to the expected tumor necrosis factor- α activation of a prosurvival NF κ B pathway favoring tumor progression. In the absence of cellular inhibitor of apoptosis 1 and 2 proteins, tumor necrosis factor α defaults to the pro-death extrinsic apoptosis pathway. Other opportunities to modulate the chemopreventive potential of NF κ B are apparent, but require examination for any tissue-specific toxicities.

Attention to mediators of inflammation and immunity was next directed toward tumor-associated macrophages (TAM), which have the potential to mediate either protumor or antitumor activity. Dr. Michael Pollard focused on the appropriation of macrophage function by tumor cells through tumor-stromal interactions. The classic symbiotic interaction between tumor cells and TAMs has been described as one in which tumor cells recruit TAMs to the tumor mass. TAMs in turn adapt to the hypoxic tumor microenvironment by producing mutually beneficial mitogens and growth factors. Hence, a high density of tumor macrophages may portend a poor prognosis. This concept is experimentally supported by a mouse model that

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shows that tumor progression is delayed by the deletion of macrophage colony stimulating factor 1 (a primary TAM regulator), which deprives the system of TAM-mediated activation of the angiogenic switch.

Tumor-associated myeloid-derived suppressor cells (MDSC) are another group of immune effector cells that are attracted into the tumor microenvironment. MDSC are recruited and retained by tumors, where they block T-cell activation and the production of natural killer cells, and also promote T-cell tolerance of tumor. Dr. Suzanne Ostrand-Rosenberg explored the interplay between inflammation and tumor-induced immune suppression in her discussion of cross talk between murine MDSC and macrophages. In response to macrophages, MDSC increase their production of interleukin (IL)-10 and cause a decrease in IL-12 production in the macrophage population, leading to a relative expansion of the alternatively activated, protumor macrophage phenotype (M2) as compared with the classically activated, antitumor phenotype (M1). The S100 family of inflammatory mediators (including prostaglandin E2 and IL-1 β) sustains MDSC accumulation via NF κ B-related pathways, suggesting promising avenues for cancer immunoprevention.

Opportunities to suppress tumor growth by targeting MDSC were discussed by Dr. Augusto Ochoa. Many human solid tumors (e.g., renal, colon, head and neck, and lung cancers) escape antitumor surveillance and induce tumor tolerance via immunomodulation. This is achieved by “hijacking” the normal tissue remodeling response, as shown by MDSC activity in the tumor microenvironment. Arginine depletion is a key mechanism influencing T-cell function, a classic characteristic of immune anergy that ultimately enhances tumor growth. In human renal cell carcinoma, a tumor-expanded population of MDSC releases arginase I into the circulation, depletes T cells of L-arginine, and thereby contributes to a profound derangement of T-cell function. In preclinical systems, arginase inhibition with nor-NOHA (*N*^ω-hydroxynor-L-arginine), sildenafil, and a cyclooxygenase-2 (COX-2) inhibitor (sc-58125) have been shown to reverse MDSC-mediated arginase I immune suppression, suggesting the clinical utility of immunotherapies that reduce MDSC and decrease plasma levels of arginase I.

Oncogene-induced cellular senescence (OIS) is an antiproliferative response that limits the proliferation of early neoplastic cells. OIS occurs in advance of replicative senescence that is related to telomere shortening. Dr. Daniel Peeper discussed IL-6, which acts as a central regulator of an inflammatory network that induces OIS and can stimulate the proliferation of cells that have lost the ability to senesce. As a result, OIS is gaining attention as a possible explanation for growth arrest in proliferative lesions that do not undergo malignant transformation, such as melanocytic nevi. There is of great interest in understanding mechanisms underlying this process, which might be exploited to reduce cancer risk.

Dr. Andrew Chan presented data supporting a role for chronic inflammation in the pathogenesis of sporadic colorectal cancer. He explored whether routine aspirin use preferentially reduced the risk of COX-2-positive tumors and showed that certain subsets of the population may derive different levels of benefit from anti-inflammatory drugs. Aspirin has been shown to decrease cellular proliferation and increase apoptosis by a variety of mechanisms, including inhibition of COX-2,

inhibition of nuclear factor- κ B, induction of p38 kinase, and polyamine catabolism. Dr. Chan's pooled analysis of the Nurses Health Study ($N = 121,700$) and the Health Professionals Follow-up Study ($N = 51,539$) found a statistically significant 36% reduced risk of COX-2-positive colorectal cancer among regular aspirin users (at least 2 tablets weekly), as compared with nonaspirin users. This analysis also detected a significant trend toward further decreases in COX-2-positive colorectal cancer risk with increased aspirin dose and duration of use. Data showing associations between higher prediagnostic levels of soluble tumor necrosis factor receptor 2, an inflammatory marker, and the likelihood of benefit from anti-inflammatory drugs to reduce the risk of colorectal cancer were also shown.

Infections and Cancer

Infectious and noninfectious responses converge in inflammatory models of carcinogenesis when infection triggers immune responses that promote cancer. In these instances, cancer prevention options include interventions that prevent or curb infection.

Infectious and parasitic diseases exact a huge toll on human health. Certain microorganisms—in particular, viruses and helicobacter bacteria—have been causally linked to cancers and suggest compelling preventive strategies. Indeed, Prof. Dr. Harald zur Hausen was awarded a 2008 Nobel Prize in medicine for key findings linking oncogenic human papillomavirus (HPV) to cervical carcinogenesis, work that paved the way for the development of prophylactic vaccines against the third most prevalent cancer afflicting women worldwide.

Dr. Maura Gillison addressed this topic from a global perspective, citing that nearly 18% of human cancers are attributable to infectious agents, including an estimated 8% of cancers in industrialized countries and more than 25% of cancers in developing countries. By Dr. Gillison's estimate, half of these cancers are preventable through the use of existing and emerging vaccines.

In a session on controversies in viral-tumor associations, Dr. Eric Engels discussed viruses as established causes of certain cancers and suspected causes in the etiology of others. Although highly sensitive molecular techniques, such as PCR, have been useful in identifying causal links, Engels cautioned that over-reliance on these methods has generated controversial and, in some cases, irreproducible results. For example, although SV40 has been linked by PCR studies to several cancers, infection was not detected by other methods. Moreover, the epidemiologic data did not support the hypothesis that SV40 infection preceded cancer and increased cancer risk. As a result, Dr. Engels advocates validation of proposed causal relationships via replication of the initial findings by independent research groups and evaluation of proposed viral associations using complementary laboratory and epidemiologic approaches.

Dr. Huichen Feng discussed the potential of emerging technologies to facilitate the discovery of new pathogens and thereby advance the discovery of novel chemopreventives. Feng's group developed digital transcript subtraction, which enables *in silico* subtraction of known human sequences from expression library databases. This simple screening method provides quantitative evidence for viral etiology when viral

transcripts are otherwise undetectable by conventional means. Feng illustrated this point with a new method that revealed the low-level presence of a previously unidentified Merkel cell polyomavirus in 80% of Merkel cell carcinomas.

In a related session, Dr. Temitope Keku discussed the role of gut microbiota in colorectal cancer. The human body houses up to 100 trillion commensal bacteria, most of which reside in the gut. New molecular techniques have facilitated the characterization of these bacterial communities. Keku described the use of terminal RFLP analysis to characterize microbiota via sequencing and fluorescence *in situ* hybridization analysis in a case-control study of patients undergoing screening colonoscopy. Comparing cases to controls, he found a higher proportion of bacteria from the Proteobacteria phylum and a lower proportion from the Bacteroidetes phylum. Keku suggested there was a critical balance between "beneficial" and "detrimental" bacteria in the gut, and that diet-induced disruptions of this balance can induce local inflammation, which in turn can contribute to the development of colorectal carcinogenesis.

Dr. Douglas Lowy provided an overview of available prophylactic HPV vaccines and investigational ones currently under development. He shared data showing how Gardasil (Merck) and Cervarix (GlaxoSmithKline) reduce the incidence of benign and malignant genital HPV infections. He also presented data supporting vaccination of girls before sexual debut, along with new data showing the protective value of Gardasil in males. Despite the public health promise of this approach, he cautioned that serious HPV infection will still occur owing to the type-restricted protection of current vaccines. As a result, screening with PAP smears remains an important strategy to reduce cervical cancer incidence. Expectations for upcoming HPV prophylactic vaccines include (1) broader coverage against more HPV types, (2) formulations with therapeutic as well as prophylactic components, and (3) simplified vaccine production and/or administration. Dr. Lowy described the status of the next developmental generation of HPV vaccines, specifically efforts to target HPV L2, a minor capsid protein that plays a role in HPV entry into cells, localization of viral components to the nucleus, DNA binding, and capsid formation/stability. This approach is expected to confer broader protection by eliciting antibodies that are more cross-reactive between HPV types than the major capsid protein L1, leading to HPV release from the membrane and inhibiting its binding to other cells. Dr. Lowy concluded that maximal reduction in HPV-associated cancers will require new vaccines, widespread vaccination, and combined vaccination and screening efforts.

Vitamin D

Vitamin D deficiency is caused by insufficient sunlight exposure and certain absorption disorders. Although typically associated with rickets and osteomalacia, associations with cancer have also been observed. Dr. Michael Holick reviewed data on the prevalence of low levels of the active form of vitamin D, dihydroxyvitamin D [1,25(OH)₂D], in the U.S. population. He concluded that vitamin D deficiency is an unrecognized epidemic among individuals older than age 20 years owing to increasing use of sunscreen products and decreased sun exposure. Dr. Cedric Garland reviewed data from

retrospective cohort studies evaluating the association between serum levels of 1,25(OH)₂D and breast cancer risk. A dose response was observed, and higher serum levels of 1,25(OH)₂D were associated with a 30% to 50% decrease in the risk of premenopausal and postmenopausal breast cancer. It is postulated that the protective effect of vitamin D against carcinogenesis and metastasis may result from its role in regulating cell differentiation, apoptosis, and the preservation of tight junctions between epithelial cells. Dr. William Grant examined the epidemiologic evidence for the possible role of vitamin D in cancer prevention, acknowledging the inherent limitations of ecological studies, some of which have found inverse associations between sunlight exposure and cancer risk or mortality. The panelists concluded that population-based guidelines for sensible sun exposure and vitamin D supplementation are needed with the goal of maintaining vitamin D levels >30 ng/mL.

Aging and Cancer

Aging, the major cancer risk factor, is gaining prominence in prevention research. Dr. Jerry Shay examined how cellular aging promotes tumorigenesis, focusing attention on telomeres, which are repeating nucleotide sequences that cap the ends of chromosomes and are gradually lost with each new cell generation. After several generations, telomere loss is believed to contribute to the eventual cell death. Premalignant tissues have short telomeres, and in order to grow, cancer cells engage a mechanism that stabilizes telomere length. The hypothesis that this is achieved by telomerase, an enzyme that adds new DNA to telomere ends, is supported by studies showing increased survival in patients with malignant tumors that lack telomerase. Consequently, telomerase has emerged as a potential target for drug development, with the hope that chemotherapy combined with telomerase inhibition might result in more durable responses than chemotherapy alone.

Dr. Nir Barzilai discussed the genetics of human longevity. He shared data showing that children of centenarians are significantly less likely to have age-related diseases than their matched controls, and described one study showing them to have significantly longer telomeres. In addition, short stature and higher levels of insulin-like growth factor I (IGF-I) have been found among female offspring of centenarians versus controls. This observation correlates with a mouse model, in which slightly smaller size and increased IGF-I levels are associated with a longer life span in female, but not male, mice. Such findings may be the result of reduced IGF-IR signaling with consequent feedback increases in IGF-I levels.

Dr. Judith Campisi described how cellular senescence, a well-described mechanism for cancer prevention, also contributes to aging, age-related disease, and carcinogenesis. She shared recent work on the senescence-associated secretory phenotype, which secretes inflammatory proteins that have been shown to stimulate tumorigenesis and drive transformation in neighboring premalignant cells/tissues. This provocative finding suggests that cellular senescence benefits the young while potentially setting the stage for cancer development later in life.

Dr. Jeanne Mandelblatt focused on the topic of aging and breast cancer, exploring ways to translate this research into clinical healthcare and policy settings. She applied stochastic

simulation models to estimate the effect of screening and treatment diffusion on U.S. breast cancer mortality, acknowledging the potential harms of screening (e.g., overdiagnosis, over-treatment, and patient anxiety). Her conclusion was that the healthiest older women benefit most from screening, and that biennial screening up to age 79 might be considered most “efficient,” considering that overdiagnosis increases with age. These simulation models are limited by our understanding of tumor biology in older women, the effectiveness of prescription drugs beyond age 74, and the natural history of ductal carcinoma *in situ*. As a result, more data on tumor growth, biomarkers of prognosis, and the effectiveness of new treatments are needed to determine appropriate cancer screening and treatment strategies for older individuals.

Risk

Personalized cancer risk assessment models could significantly reduce cancer incidence and mortality by identifying high-risk individuals who would benefit from lifestyle changes, chemoprevention, and screening. Dr. Margaret Spitz presented the results of a lung cancer risk prediction model consisting of clinical and epidemiologic risk factors, as well as molecular markers of bleomycin sensitivity and DNA repair capacity. This risk prediction model was applied to 725 Caucasian lung cancer patients and 625 matched controls, yielding a discriminatory accuracy measured by the area under the curve of 0.70 for predicting the likelihood of developing lung cancer for current and former smokers, respectively. Dr. Xifeng Wu presented results of a bladder cancer risk prediction model that incorporated epidemiologic risk factors and mutagen sensitivity, discussing how cancer risk prediction models might be improved through the addition of genetic factors. Dr. Mitchell Gail discussed the results of a study evaluating the utility of single-nucleotide polymorphisms (SNP) to assess breast cancer risk. Using a hypothetical model, he showed how seven SNPs that are positively associated with breast cancer could

boost the discriminatory accuracy of the Gail 2 risk prediction model by 4.1%. The panelists concluded that validation should be done in independent sample sets and that the identification of new gene-gene and gene-environment interactions is expected to improve personalized cancer risk prediction models.

Dr. Stephen Chanock discussed the promises and pitfalls of genome-wide association studies conducted in prostate, colorectal, and breast cancers. Although genome-wide association studies have identified low penetrance genetic variants in germ-line DNA associated with cancer, the clinical utilization of these markers for risk prediction remains challenging. Dr. Brian Reid discussed the role of SNP array technology in the assessment of genomic and epigenomic abnormalities in Barrett's esophagus, a premalignant condition for esophageal carcinoma. He presented the intriguing results of a study showing the use of Illumina Infinium arrays to assess genome-wide SNP-based quantification of aneuploidy and DNA methylation on the same tissue samples of patients, representing different stages of progression from early Barrett's esophagus to advanced esophageal carcinoma.

Overall Impact of the Meeting

This year's Frontiers meeting focused on cutting-edge science at the intersection of inflammation, infection, and carcinogenesis research. As discussed, advances in these areas are already leading to novel cancer preventive interventions that will hopefully reduce the global burden of cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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