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Project Titled: Biological Bases for Radiation Adaptive Responses in the Lung

Submitting Organization: Lovelace Respiratory Research Institute

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Background

Our main research objective was to determine the biological bases for low-dose, radiation-induced adaptive responses in the lung and use the knowledge gained to produce an improved risk model for radiation-induced lung cancer that accounts for activated natural protection, genetic influences, and the role of epigenetic regulation (epiregulation). Currently, low-dose radiation risk assessment is based on the linear-no-threshold hypothesis which now is known to be unsupported by a large volume of data.

Our intent was to develop a low-dose radiation biological effects knowledge base that would facilitate employment of a systems-biology-type framework to characterize low-dose radiation responses in the lung. However, our effort was cut short as a result of an unexpected loss of significant funds in the last year of the project related to the government sequester.

The research was carried out by a multidisciplinary team via four related subprojects:

Subproject 1 (headed by Yong Lin): Biological Bases for Radiation Adaptive Responses that Protect against Lung Epithelial Transformation and Cancer

This project mainly involved molecular (signaling pathways) and cellular level (survival, neoplastic transformation) experimental radiation-response studies with human bronchial epithelial and other cells (macrophages, fibroblasts) that participate in intercellular signaling in the lung.

Subproject 2 (headed by Julie Wilder): Biological Bases for Lung Cancer Suppression by Low-Dose-Radiation-Stimulated Immunity

This project mainly involved mouse studies where low doses of gamma rays were used in an attempt to boost immunity against benzo(a)pyrene (tobacco-constituent)-induced lung cancer.

Subproject 3 (headed by Steve Belinsky): Sequence Variation in Radiation Adaptive Response Genes and Gene Promoter Methylation in Radon-Associated Lung Cancer

This project involved molecular epidemiology studies of uranium miners related to determining if radiation adaptive-response genes (e.g., DNA repair and apoptosis genes) in key lung cell populations are silenced by high-level radon exposure facilitating lung cancer occurrence.

Subproject 4 (headed by Bobby Scott): Modeling Radiation Adaptive Responses in the Lung Using a Systems Biology Approach

This project involved using mathematical modeling to integrate key research findings from the other three projects as well as from external research groups participating in the DOE Low Dose Radiation Research Program and from others not participating in the program.

Key research findings are discussed below without going into details about study designs and methods employed. We refer those who have interest in such details to rely on our peer-reviewed publications which are listed in this report. We also list our numerous presentations at scientific meetings as they reflect the high level of research productivity by our research team.

Key Results from Subproject 1 on Cellular Studies

The effects of low-dose gamma rays on cell survival/death pathways were examined in vitro using state-of the-art methods. In human bronchial epithelial cells (HBEC-2) that received a dose of 60 mGy, c-Jun N-terminal kinase (JNK) was up-regulated, implicating JNK as a potential adaptive-response gene and also implicating epithelial cell participation in adapting to mild radiation stress.

Macrophages also participate in the adaptive response in the lung as was revealed after THP-1 (human macrophage) cells were exposed in vitro to single doses (30 or 60 mGy) of gamma rays.

In human lung fibroblasts (HFL-1 line), the tobacco carcinogen benzo[a]pyrene diol epoxide (BPDE) increased the secretion of CXCL5, CXCL1, IL-6, VEGF, FGF-4, and bFGF. These factors appear to promote lung cancer. While low-dose gamma irradiation (30, 60 and 90 mGy) had marginal effects on secretion of protein factors from human macrophages (THP-1 cell line) and human bronchial epithelial cells (HBEC-2), it significantly inhibited BPDE-induced CXCL5, CXCL1 and IL-6 secretion from HFL-1 cells. This implicates low-dose radiation such as received from multiple diagnostic imaging (e.g., multiple CT scans) as potentially preventing smoking-related lung cancer.

A mechanistic study we conducted using state-of-the-art methods demonstrated that low-dose gamma rays inhibit BPDE-induced IL-6 production from lung fibroblasts through

suppressing the NF-kappaB and ERK pathways. STAT3, which has been shown to be an important mediator of inflammation-associated lung cancer, is the major pathway that mediates the biological effect of IL-6. Pretreating HFL-1 cell with gamma-ray doses up to 90 mGy (which suppressed IL-6 secretion) markedly attenuated STAT3 activation by BPDE-conditioned medium from HFL-1 cells. These results strongly suggest that low doses of gamma rays suppress the tumor-prone microenvironment in the lung mediated by IL-6 secreted from fibroblasts that activates cellular pathways such as STAT3 in lung epithelial cells. In addition, we found IL-6 markedly potentiated BPDE-induced neoplastic transformation of bronchial epithelial cells.

It is now well-known that epithelial-to-mesenchymal transition (EMT) of human bronchial epithelial cells (HBECs) is involved in neoplastic transformation of HBECs and regulated by epigenetic mechanisms. Several research groups have demonstrated that gamma ray doses < 100 mGy can suppress spontaneous neoplastic transformation and it follows that tobacco-carcinogen-induced transformation may also be suppressed by low-dose gamma rays. In our in vitro neoplastic transformation study involving BPDE/MNU, treatment for 4 weeks induced EMT in HBEC-2 cells, increased the mesenchymal markers, and led to neoplastic transformation. Conditioned medium from BPDE/MNU-treated fibroblasts (HFL-1) potentiated the BPDE/MNU-induced change of EMT markers. Pretreatment of HFL-1 with low-dose gamma rays suppressed the BPDE/MNU-induced EMT potentiation activity from the fibroblasts; thus, revealing a novel adaptive-response mechanism which has important implications for lung cancer prevention among smokers. Interestingly, our research results also showed that IL-6 appears to negatively regulate interferon-alpha-inducible protein 27 (IFI27) expression, suggesting that IFI27 is one of the factors involved in low-dose radiation suppressing IL-6-mediated transformation.

We also performed methylation and cDNA microarray assays in tobacco-carcinogen-induced transformed cells derived from HBECs treated with and without low-dose radiation (5, once/2 weeks, 20-mGy gamma-ray doses) and with and without exposure to conditioned media from HFL-1 (tobacco-carcinogen exposed, with and without low-dose radiation, one 90-mGy dose). The number of methylated genes was increased (30 - 100%) in transformed HBEC cells as a result of exposure to conditioned media from HFL-1 cells exposed to tobacco carcinogen with and without low-dose radiation. Pathway analysis focusing on the transcriptome in which low-dose, radiation-reduced transformation of the HBECs (described above) revealed significant modulation of genes involved in both natural and innate immune response.

Our finding that low-dose radiation suppresses fibroblast-derived, IL-6-mediated transformation is supportive of the finding by others that the fibroblast-IL-6 axis is important for promoting non-small cell lung cancer.

Using a media-transfer approach and in vitro transformation model combined with expression arrays to search for genes that are involved in low-dose-radiation adaptive response, we identified a number of interesting genes that are impacted by low-dose radiation. One of these candidates is bone marrow stromal cell antigen 2 (BST2), a

protein involved in viral infection, cell apoptosis and migration. BST2 is an inducible gene of IFN-alpha, beta and gamma that has potential tumor suppressing properties. We confirmed that BST2 expression was effectively induced by IFN-gamma in HBECs. Interestingly, the IFN-gamma-induced BST2 expression was substantially suppressed by IL-6, which strongly suggests that low-dose radiation activation of BST2 expression in HBECs involves suppression of IL-6 secretion from fibroblasts. Further experiments showed that knockdown of BST2 in radiation-primed and BPDE/MNU-treated HBECs attenuated the transformation-suppression effect of low-dose radiation and facilitated colony formation in soft agar, indicating that low-dose-radiation-induced BST2 plays an important role in low-dose-radiation inhibition of tobacco-carcinogen-induced HBEC transformation.

The expression of BST2 was not changed in HBECs after chronic BPDE/MNU treatment. However, when the cells were chronically exposed to BPDE/MNU together with conditioned medium from human lung fibroblasts also treated with BPDE/MNU, the expression of BST2 was increased by 4 fold when HBECs were primed with low-dose radiation prior to the treatment, suggesting that low-dose radiation activates BST2 expression in HBECs through influencing some factors from carcinogen-exposed fibroblasts.

We also found that BST2 expression is reduced in 4 of 6 lung cancer cell lines compared to that in HBEC-2 cells. Interestingly, BST2 expression in the BST2-suppressed cancer cell lines was effectively restored after treatment with the demethylation agent 5-Azacytidine, implicating an epigenetic mechanism for suppressing BST2 in lung cancer cells. To examine the role of BST2 in the lung cancer cell's oncogenic property, a YEFP-BST2 expression vector was constructed and stably transfected into H460 cancer cells to restore BST2 expression. The enforced expression of BST2 inhibited cell migration and sensitized cells to apoptosis induced by the anticancer agents adriamycin, etoposide and TRAIL. These results suggest that BST2 is a potential tumor suppressor related to preventing lung cancer.

Key Results from Subproject 2 on Animal Studies

This subproject focused on determining the role of low-dose-radiation-stimulated lung immunity in suppressing tobacco-carcinogen (benzo[a]pyrene (BaP)) induced lung cancer, to elucidate the mechanisms involved, and to assess the long-term implications for lung immunity.

We conducted a study on BaP-induced lung cancer in A/J mice. The study was designed to test whether low-dose radiation (repeated delivery of 10, 20 or 100 mGy doses of gamma rays) would affect the development or progression of lung cancer in the mice. A/J

mice received an intraperitoneal injection of 100 µg BaP on Day 0 of the study. Four weeks later, mice received gamma radiation via whole-body exposure at dose levels of 10, 20 or 100 mGy per exposure. Radiation treatments continued every two weeks until week 14 (six treatments in total). Histologic lesions were classified as hyperplastic foci, adenomas or carcinomas. In each BaP treated group, hyperplastic foci outnumbered adenomas which in turn outnumbered carcinomas representing the usual progression of lung cancer where transformation of lung epithelium by BaP treatment caused development of focal parenchymal lesions of hyperplastic bronchiolar and /or alveolar epithelium. With presumably more genetic and epigenetic changes, cells within hyperplastic foci were changed to allow growth into adenomas. More aggressive histologic features of malignant neoplasia were produced during the progression from adenoma to carcinoma. Repetitive exposure to 10 or 20 mGy (60 or 120 mGy in total) of gamma radiation after BaP treatment did not result in a reduction in either gross tumor counts or total number of histologic lesions. In contrast, exposure of BaP treated mice to repeated 100 mGy doses of gamma radiation (600 mGy in total) was associated with substantially less adenomas compared to mice receiving BaP alone. This suggested that the higher dose of radiation may have inhibited progression of cancer development from the hyperplastic phase to the adenoma stage. The data indicated that delivery of 100 mGy gamma radiation every two weeks over the course of 10 weeks (6 treatments in total) induced very few gross lung tumors or histological lesions in the absence of BaP treatment and no adenomas or carcinomas.

To understand what immune mechanisms might accompany the reduction in BaP-induced lung carcinogenesis by low-dose radiation, we undertook studies to examine the short term immunological effect of BaP injection, gamma radiation exposure or combinations of the two. A/J mice were treated with 10, 20, 100 or 1000 mGy on Day 0. On day 1, mice were injected with 100 µg BaP or vehicle. BaP injection proved to be both a cytotoxic and inflammatory stimulus. It induced a loss of spleen and lung lymphocytes within one week of injection while increasing lung neutrophilia. High dose (1000 mGy) radiation also significantly reduced splenocyte numbers, as well as total B cells and T cells.

BaP also induced inflammatory cytokine expression as evidenced by increased IL-1beta, IL-6, IL-17 and TNF-alpha production by Con A-stimulated splenocytes. In contrast, 10 mGy of radiation induced increased levels of Con A-stimulated IL-2, IL-4 and IL-10, all T helper type 2 cytokines, none of which are considered inflammatory. These anti-inflammatory cytokines remained elevated after 10 mGy irradiation even when mice were treated with BaP one day after radiation. Interestingly, when mice were treated with both BaP and 10 mGy of radiation, the levels of BaP-induced pro-inflammatory cytokines produced by splenocytes were not reduced. However, in the lung, we observed

that BaP increased not only pro-inflammatory cytokines but also increased IL-4, IL-13 and IL-10 production by T lymphocytes. The source of BaP pro-inflammatory cytokines in both spleen and lung tissue was primarily CD8+ T cells, B cells and Gr-1+ cells (neutrophils and monocytes). Fibroblasts, likely a primary source of IL-6 as described below, were not evaluated in our experiment.

In an effort to determine alternative mechanisms by which low-dose radiation inhibited BaP-induced cancer progression, we tested whether increased oxidant response, apoptosis, DNA damage or KRAS mutations might be altered. Although we confirmed that BaP did induce increased lipid peroxidation in a short-term experiment, pre-conditioning the mice one day previously with low-dose radiation treatment did not reduce this response. Efforts to study apoptosis, DNA damage and changes in KRAS mutations were confounded by the lack of BaP to induce significant changes in these parameters at the time frame in which we measured them.

In another carcinogenesis experiment mice were pre-conditioned with 100 mGy of gamma irradiation one day prior to injection with either a high (25 mg/kg body weight) or low (12.5 mg/kg body weight) dose of BaP. Mice were treated accordingly every two weeks for a total of 6 treatments (600 mGy total radiation and 150 mg/kg or 75 mg/kg BaP total). Unfortunately, this study design change yielded less lesions than expected and upon statistical analysis no protective effects of low-dose radiation against BaP-induced lung lesions were seen regardless of histological classification at either carcinogen doses. These results may be due to insufficient tumor burden and effective clearance of the carcinogen when fractionated doses of BaP were administered at two week intervals in contrast to receiving the single bolus high dose (100 mg/kg) we delivered in our previous experimental design.

Key Results from Subproject 3 on Molecular epidemiological Studies

This subproject focused on molecular epidemiology for lung cancer (squamous cell carcinoma (SCC)) induction in radon-exposed uranium miners in Colorado. Both case-control and population studies were conducted. The case-control study was in collaboration with the NIH-funded grant "Genetic and Epigenetic Biomarkers for SCC of the Lung" (ES015262, Steven Belinsky, PI). SCC cases were identified from a cohort of 16,000 radon-exposed workers who participated in sputum cytology screening for lung cancer detection. Miners without lung cancer served as controls.

One of our studies focused on assessing the association between sequence variants in 16 genes involved in double strand DNA repair and related chromatin modifications to SCC in former uranium miners. We acquired DNA specimens from 692 subjects who mined

uranium in Colorado, 281 of which were diagnosed with SCC. Selection criteria were based on radon working level months and smoking status. A total of 384 SNPs (including some redundant SNPs) were selected to cover sequence variation of 16 genes and were genotyped. Quality assessment revealed 248 cases and 293 controls with sample call rate > 65%. Our analysis identified eight SNPs within HDAC2, XRCC5, PCAF, EP300-XRCC6, and SIRT1 with false discovery rate < 15% significantly ($p < 0.002 - 0.0002$) associated with risk for SCC. Six of these sequence variants were also significantly associated with survival. XRCC5 and XRCC6 are involved in non-homologous end joining with the remaining genes functioning in histone acetylation and deacetylation.

Il-6 was identified by Yong Lin's group as being important in promoting transformation of HBEC. One of our studies characterized the functional potential for an IL-6 promoter SNP (rs1800797) that was identified to be associated with increased risk for lung SCC (OR=1.34, 95%CI=1.05-1.70, p=0.019) in miners. The risk allele (A) of rs1800797 was associated with increased gene expression of IL-6 in primary human bronchial epithelial cell cultures (n=88) in a dose-dependent manner ($p = 0.002$). Similar genotype/gene expression correlation was also identified in lung tumors with unmethylated IL-6 in The Cancer Genome Atlas (TCGA) project and primary skin fibroblast cells cultures. Resequencing of the IL-6 promoter (690 bps, chr7:22,766,182-22,766,871, genome build 37) in 35 samples identified two major haplotype alleles (rs1800797-rs1800796-rs36215814-rs1800795, G-G-10A11T-G, A-G-8A12T-C). Luciferase assay suggested that haplotype allele A-G-8A12T-C that carries the risk allele of rs1800797 had 30-60% increased promoter activity compared with G-G-10A11T-G in HFL-1 and 293 cell lines. Thus, the results from both in vivo and in vitro experiments support that IL-6 is pro-carcinogenic.

To extend the findings by Yong Lin's group that low-dose gamma radiation repressed IL-6 induction in lung fibroblast cells by tobacco carcinogens, we conducted experiments to test whether radon exposure can induce IL-6 secretion and whether low-dose gamma radiation can repress this induction. This experiment was conducted in six skin fibroblast cell lines with three wildtype homozygotes (G/G) and three heterozygotes (A/G) for rs1800797. H_2O_2 was used to mimic reactive DNA damages resulting from radon. A dose-dependent induction of IL-6 secretion was identified in skin fibroblast cell lines treated with H_2O_2 for an hour. In addition, an approximate 50-90% increased secretion of IL-6 was consistently seen in heterozygotes compared to wildtype homozygotes in cultures with and without H_2O_2 treatment. Most importantly, low-dose gamma radiation (90 mGy) inhibited the H_2O_2-induced IL-6 secretion by 50%. Thus, these results combined with the previous findings from Yong Lin's group suggest that IL-6 induction due to high level radon exposure and/or tobacco carcinogens may contribute to the lung carcinogenesis in uranium miners. In contrast, low-dose gamma radiation (or low-dose X

rays, e.g. from several CT scans) has the potential to reduce the risk for lung cancer in this occupational population.

The IL-6 promoter was methylated in 10% lung adenocarcinomas and 30% lung squamous cell carcinomas in the TCGA project ($p = 3.1 \times 10(-9)$). The methylation of the IL-6 promoter in lung tumors (n=181) was significantly correlated with reduced gene expression ($p = 0.018$), suggesting that the IL-6 promoter methylation was functionally silencing the gene. The silencing of IL-6 gene expression by promoter methylation was also validated in 12 lung tumor cell lines. Association analyses between IL-6 methylation and tumor characteristics (tumor stage and prognosis) in lung tumor patients found that IL-6 methylation was associated with advanced stage and worse prognosis in lung adenocarcinomas. Because both paracrine and autocrine signaling were involved in IL-6 regulation in lung cancer cells, we hypothesized that lung adenocarcinoma cell lines with different IL-6 methylation status may respond to environmental IL-6 levels differently. Scratch assays were conducted in two lung adenocarcinoma cell lines (H1299 and H1975) to assess whether environmental IL-6 added to the medium containing 0.5% FBS would change the cell migration rate. Four doses of external IL-6 (0, 0.01, 0.1, and 1 ng/μl) were selected to cover the physiological range of IL-6 levels in human blood. IL-6 dose-dependent increase in migration rate was identified at each time point (24, 48, and 72 hr after scratching, $p = 0.01$) in H1299 with fully methylated IL-6 promoter and undetectable IL-6 gene expression. In contrast, the addition of IL-6 to H1975 (unmethylated IL-6 promoter) had no effect on the rate of migration ($p = 0.14$). These results demonstrate a critical role for IL-6 in affecting cancer susceptibility and tumor phenotype that could be influenced by low-dose radiation.

Key Results in Subproject 4 on Dose-Response Modeling Studies

Work in this subproject focused on developing dose-response models that will facilitate implementation of a systems-biology approach for characterizing radiation adaptive responses in the lung and their impact on lung cancer suppression.

We introduced a novel multicellular signaling model (MULTISIG1) to simulate the kinetics of repair of DNA double-strand breaks (DSBs) that were induced in confluent cultured cells by a very low radiation dose, where at most a single induced DSB would be expected in a given cell nucleus. The repair kinetics was modeled as representing what is now called an epigenetically-regulated (epiregulated) cell-community-wide (epicellcom) response to radiation stress. DSB repair initiation was assumed to require a threshold number of cells with DSBs participating in intercellular stress-response signaling. The MULTISIG1 model was extended to apply to moderate doses where several DSBs can occur on the same DNA molecule. The repair of multiple breaks on the same molecule

was treated as sequential stochastic events. For cells of differing genetic characteristics and epigenetic statuses, relationships were provided for evaluating the relative susceptibility (RS) for DSB induction, relative repair capacity (RRC) for DSB repair, and relative epiapoptosis capacity (REC), for epigenetically regulated apoptosis. The modified MULTISIG1 model was used to characterize the expected repair kinetics for confluent, human lung fibroblasts (MRC-5 line) briefly exposed in vitro to 90-kV x-rays.

A first generation stochastic gene episilencing (Step 1) model was developed and applied to in vitro carcinogen exposure. In addition to developing mathematical functions for evaluating the single-target-gene episilencing probability, functions were also developed for the multi-target-gene episilencing probability for simultaneously silencing of multiple tumor-suppressor micro RNA genes.

We have shown that our systems-biology-related, hormetic relative risk (HRR) model is consistent with lung cancer data for residential radon exposure. Based on the model, low-level radon exposure in the home is credited for activated natural protection (ANP) against lung cancer, especially smoking-related. High-level radon is predicted to epigenetically silence (episilence) adaptive response genes and may epigenetically activate (epiactivate) cancer promoting genes (e.g., IL-6) as suggested by findings in Subproject 1 for tobacco carcinogen exposure. The low-dose ANP involves a hierarchy of adaptive mechanisms that include DNA damage repair, selective apoptosis of pre-cancer cells, and anticancer immunity. Research in Subproject 1 identified an additional adaptive mechanism in the lung, namely the suppression of cigarette-smoke-carcinogen-induced secretion of cancer promoting cytokines (e.g., IL-6) from fibroblasts. A key feature of our HRR model is a hypothesized epicellcom response to low-dose radiation which has now been validated by other researchers in the Low Dose Radiation Research Program. The current version of the HRR model includes a benefit function B(x) representing the proportion of the population deriving a protective benefit (ANP) from radiation dose or exposure level x. Interestingly, at the EPA's action level of x = 4 pCi/L for residential radon, everyone seems to benefit from ANP against lung cancer. The radon ANP in turn appears to prevent greater than 50% of lung tumors caused by other agents. More importantly, our findings indicate that eliminating radon from the home could in many cases increase the risk of lung cancer.

Demonstrated Benefits of Low-Dose Radiation

We reviewed the current literature for published benefits of low-dose radiation. Known benefits derived from cellular, animal and human studies are as follows:

1. Low-dose radiation can stimulate antioxidant production, protecting from oxidative damage.

2. Low-dose radiation can activate DNA damage repair and protective apoptosis.

3. Low-dose radiation can stimulate selective removal of precancerous and other aberrant cells via intercellular signaling.

4. Low-dose radiation can suppress inflammation and thereby protects from inflammatory diseases.

5. Low-dose radiation can stimulate anticancer and other immunity.

6. Low-dose-radiation exposure during gestation can cause lasting protective epigenetic changes in male offspring.

7. Low-dose radiation can slow aging and prolong life.

Project Publications

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Project Presentations

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