IMMUNOSUPPRESSION ASSOCIATED WITH COOPERATIVE INDUCTION OF LUNG ADENOCARCINOMA IN MICE BY MUTANT P53 AND ONCOGENIC K-RAS.


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Mutations in K-ras and p53 are among the most common genetic alterations in non-small cell lung cancer. To determine mechanisms of lung tumorigenesis, we obtained K-rasLA1 mice (developed in the laboratory of T. Jacks, MIT), which develop lung tumors with 100% frequency. To establish the molecular mechanisms of p53 function in the lung epithelium and its relation to neoplastic transformation, we disrupted wild-type p53 activities by transgenically expressing an oncogenic mutant form of human p53 (R175H mutation) specifically in the lung epithelium of mice using the human surfactant protein C (SPC) promoter, SPC-DNp53 mice. The SPC-DNp53 mice were interbred with the K-rasLA1 mice with the expectation of oncogenic cooperativity and lung tumorigenesis. Mice in the C57BL/6 inbred strain of the four possible genotypes (K-ras+/DNp53+, K-ras+, DNp53+, and wild-type) were monitored for the development of lung tumors. The K-ras+/DNp53+ mice displayed multifocal lung tumors with a median survival of 218 days. K-ras+ littermates developed large lung tumors at a lower multiplicity with a median survival of 388 days. DNp53+ and wild-type littermates had a median survival >500 days and did not develop lung tumors. Alveolar hyperplasias with distinct cytology were detected in the K-ras+/DNp53+ and K-ras+ mice by day 80. Recent studies have demonstrated that expression of mutant K-ras in lung epithelial cells elicits inflammation that promotes carcinogenesis in mice. Moreover, our previous results showed that SPC-DNp53 mice displayed exaggerated inflammation after lung injury. Whether or not inflammation is further enhanced during lung tumorigenesis induced by the combination of oncogenic K-ras and mutant p53 has not been determined. Inflammatory cytokine profiles were performed on whole lung extracts at early stages of tumor development (day 55-105) to correlate progression with altered inflammation in the lung. Relative to wild-type, overall inflammatory cytokine levels in lung extracts from mice at early times of tumor progression appeared similar in K-ras+, elevated in DNp53+, and reduced in K-ras+/DNp53+ mice. Assessment of individual cytokines in K-ras+/DNp53+ mice suggested selective reduction of cytokines correlating with a T helper-2 (Th2) phenotype. Linear regression analyses of cytokine levels versus age (a surrogate for tumor progression) revealed that the levels of only 5 cytokines [IL-12(p40), IL-17, KC, G-CSF and CCL2/MCP-1] increased in K-ras+/DNp53+ mice. Expression of these cytokines corresponds to induction of a Th17 response and macrophage activation during progression of K-ras+/DNp53+ lung tumors. Relative to their male counterparts, female K-ras+/DNp53+ mice displayed significantly higher levels of Th1 cytokines. In human lung adenocarcinoma, elevated serum levels of interferon-γ, a marker for the Th1 phenotype, correlates with a worse prognosis (Surgery 131(1 Suppl):S236-41, 2002). These observations suggest that oncogenic cooperation between K-ras and mutant p53 promotes lung tumorigenesis by modulating inflammation. (LEQSF (2005-08)-RD-A-36 to GM & NCI 1R01CA132603 to GM, BS, DS)