Chapter

Introductory Chapter: Interactions between Environmental Chemicals and KRAS Oncogene in Different Cancers - Special Focus on Colorectal, Pancreatic, and Lung Cancers

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1. Introduction

v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) is an oncogene. The KRAS gene is located on the twelfth chromosome and belongs to the Ras family of oncogenes. These proteins play important roles in cell division, cell differentiation, and apoptotic cell death. Induction of KRAS with different environmental chemicals leads to high expression of K-Ras protein, which in turn causes high cellular proliferation. These cascade of events finally initiate certain types of cancers, particularly colorectal (CRC), pancreatic, and lung cancers. High calorie intake, diets rich in meat and fat, smoking, and alcohol consumption are the major risk factors of CRCs, and it was estimated that in CRC, mutated KRAS has an incidence of ~50%. Exposure to certain environmental chemicals [organochlorine insecticides such as DDT and its metabolite dichlorodiphenyltrichloroethylene (DDE); herbicides such as EPTC and pendimethalin; N-nitrosamines; polychlorinated biphenyls (PCBs); benzene] and drugs (anti-diabetics drugs) can also contribute to the increased incidence of PC throughout the world. It was stated that in adenocarcinomas of the pancreas, mutated KRAS has an incidence of ~70–90%. Lung cancer is the leading cause of deaths worldwide. KRAS gene mutations are much more common in long-term tobacco smokers with lung cancer when compared to nonsmokers. KRAS gene mutations are observed in 15–25% of all lung cancer cases, being more frequent in whites vs. Asian populations. Lung cancers with KRAS gene mutations typically indicate a poor prognosis and are associated with resistance to several cancer treatments. This chapter mainly focuses on KRAS, interactions between environmental chemicals, and KRAS oncogene in different cancers, particularly in colorectal, pancreatic, and lung cancers.

Most oncogenes are expressed as proto-oncogenes, involved in cell growth and proliferation or inhibition of apoptosis. If there are chemical, physical, or biological factors that cause mutations in such genes promoting cellular growth, these genes are mostly upregulated and cellular proliferation increases [1]. The cascade of events leading to proliferation usually predisposes the cell to cancer. In this case,

they are termed as "oncogenes" [1, 2]. These genes are mutated and/or overexpressed at high levels in tumor cells. Normally, cells repair themselves or undergo apoptosis if there is an interruption on the cell cycle. However, the high expression of multiple oncogenes, along with mutated apoptotic and/or tumor suppressor genes and exposure to environmental chemicals that trigger such mutations can all act in concert and finally cause tumorigenesis [1–3]. In the past 50 years, several oncogenes have been identified in different types of human cancers. There are many cancer drugs that target the proteins encoded by oncogenes [1–3].

Genetic and environmental interactions usually determine the profiles of cancers. v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) is a very important oncogene for the initiation of cancer [1]. It is usually found to be mutated in different types of cancer, particularly in colorectal cancers (CRCs), pancreatic cancer (PC), and lung cancer [4–6]. Concerning KRAS, different chemicals such as polychlorinated biphenyls (PCBs), certain antidiabetic drugs, and pesticides may be leading causes of KRAS mutations, and such mutations increase the expression of K-Ras protein in different tissues, leading to high cellular proliferation and finally carcinogenesis [7–9]. This chapter mainly focuses on CRCs, PC, and lung cancer and KRAS. Moreover, the interactions between KRAS mutations and environmental factors in these particular cancers will also be mentioned.

2. KRAS gene

The most important oncogene for several types of cancer is KRAS. Cytogenetic location of this gene is 12p12.1 [the short (p) arm of chromosome 12 at position 12.1] [10]. The KRAS gene belongs to the Ras family of oncogenes. RAS family oncogenes also include two other genes: H-RAS and N-RAS. These proteins play important roles in cell division, cell differentiation, and apoptotic cell death. KRAS causes the initiation of cancer through deregulation of the G1 cell cycle [10].

The KRAS gene expresses a protein called "K-Ras," which is part of a signaling pathway known as "the RAS/microtubule-associated protein (MAP) kinase signaling (MAPK) pathway." The protein carries the mitogenic signals from the "epidermal growth factor receptor (EGFR)" on the cell surface to the cell nucleus. These signals provide instructions for growth, proliferation, maturation, or differentiation to the cell. The K-Ras protein converts a molecule called guanosine-5′-triphosphate (GTP) into another molecule called guanosine-5′-diphosphate (GDP), and therefore, it is a "GTPase." By such conversion, K-Ras protein almost acts like a "switch," which is turned on and off by the GTP and GDP molecules. In order to transmit signals, K-Ras must bind to GTP, and this turns on the protein [10]. However, K-Ras protein is inactivated when it converts the GTP to GDP. This means that when this particular protein is bound to GDP, it does not send signals to the nucleus. In several pathological conditions [cardiofaciocutaneous syndrome, Noonan syndrome, Costello syndrome, autoimmune lymphoproliferative syndrome (ALPS), and epidermal nevus] and different cancers [colorectal (CRC), pancreatic (PC), and lung cancer; cholangiocarcinoma; and core binding factor acute myeloid leukemia (CBF-AML)], KRAS mutations are observed in patients [10].

3. Cancers associated with KRAS

3.1 Colorectal cancers

Colorectal cancers (adenomas or carcinomas) occur as a combination of unbalanced diet, environmental exposures, accumulation of genetic and epigenetic

instability, and oncogenic gene activations [11, 12]. It is certainly clear that unbalanced diet is a major risk factor for the development of CRCs. A constant, high, or prolonged exposure of colon to carcinogens is the primary cause for malignant transformation of colonocytes [11, 12]. If hereditary disposition (in terms of mutations in key genes controlling cell cycle and replication) is already present, genome instability will accelerate tumorigenesis process [13]. It was estimated that in CRC, mutated K-Ras has an incidence of ~50% [14].

The major genetic pathways of colorectal cancers (CRCs) are usually divided into two pathways [15, 16]:

1. "The Chromosome Instability Pathway" representing the pathway of sporadic CRC through the KRAS, adenomatous polyposis coli (APC), and tumor suppressor protein 53 (P53) mutations.

2. The "Microsatellite Instability Pathway" representing the pathway of hereditary non-2 primary KRAS mutation generally leads to a self-limiting hyperplastic or borderline lesion and may be implicated in the serrated pathway through which serrated adenomas and carcinomas may also develop.

The KRAS mutation alone is not sufficient or necessary to drive the malignant transformation. Therefore, additional "drivers" should be present in the development of CRC. These additional factors include but are not limited to high calorie intake, diets rich in meat and fat, smoking, and alcohol consumption [17]. KRAS mutations are frequently found in <95% of early dysplasia, including aberrant crypt foci (ACF), and also in hyperplastic polyps [18–20]. The sequence in which the KRAS mutation occurs in relation to the APC mutation is important. The dysplastic lesion often progresses to carcinogenesis if a mutation in KRAS gene occurs right after an APC mutation [21, 22]. Because of the key role in EGFR signaling, the presence of a KRAS mutation predicts a very poor response to specific antibody (monoclonal antibodies) treatment with EGFR inhibitors such as panitumumab and cetuximab [23, 24].

3.2 Pancreatic cancer

Pancreatic cancer is a multifactorial and extremely aggressive type of cancer. Pancreatic tumors are usually highly chemoresistant, and many types of PC have very bad prognoses. Little information regarding the possible association of different risk factors with the known genetic alterations (such as activation of KRAS oncogene and inactivation of the p53 gene) is present in the literature [8, 25]. However, it was stated that in adenocarcinomas of the pancreas, mutated KRAS has an incidence of ~70–90% [14].

Increasing data on the molecular pathogenesis of PC have shown that genetic alterations, such as mutations of KRAS and particularly epigenetic dysregulation (DNA methylation, histone acetylation, or microRNA expressions) of tumor-associated genes [i.e., silencing of the tumor suppressor p16 (ink4a)], are suggested to be hallmarks of PC. Serine/threonine-protein kinase (Raf), phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), and Ral guanine nucleotide dissociation stimulator (RaLGDS) are the major effectors of KRAS in adenomas of pancreas [26, 27].

Repeated acute pancreatic injury and inflammation are important contributing factors in the development of PC. Alcohol consumption, cigarette smoking, diet (high coffee consumption), environmental chemicals [organochlorine insecticides such as DDT and its metabolite dichlorodiphenyltrichloroethylene (DDE); herbicides such as s-ethyl dipropylthiocarbamate (EPTC) and pendimethalin; N-nitrosamines; polychlorinated biphenyls (PCBs); benzene], and drugs [diabetes

drugs like glucagon-like peptide-1 (GLP-1) agonists, such as exenatide; dipeptidyl-peptidase-4 inhibitors (DPP-4), such as sitagliptin; calcium channel blockers such as nifedipine, nicardipine, and diltiazem] can also contribute to the highly increasing incidence of PC throughout the world. On the other hand, gall stones, diabetes, and obesity are the major pathological factors associated with PC [27–29]. In a study by Slebos et al., mutations in KRAS codon 12 were found in 75% of the PC patients. However, there were no differences in blood PCB levels between the KRAS wild-type and mutant groups [8].

3.3 Lung cancer

Lung cancer is the primary cause of cancer-related deaths worldwide. Active and passive smoking are the two of primary causes of lung cancer. Lung cancers are classified as small cell (non-epithelial) or non-small cell carcinomas (epithelial-derived). Small cell carcinomas are highly malignant; has the ability to metastasize easily and chemotherapy is the choice of treatment. However, treatment of non-small cell cancer primarily involves surgical excision, supplemented by radiation or chemotherapy. Although this treatment method may provide partial or full recovery, it also increases the risk for concurrent diseases. Using anti-cancer drugs with "high efficacy and low-toxicity" is the priority goal in this field [30, 31].

KRAS gene mutations are observed in 15–25% of all lung cancer cases. These mutations are more frequent in white populations than in Asian populations. About 25–50% of whites with lung cancer have KRAS gene mutations, whereas 5–15% of Asians with lung cancer have KRAS gene mutations [14].

In lung adenocarcinomas, both KRAS-activating mutations and in and EGFR mutations can be observed. KRAS appear to be mutually exclusive. Three different mutations in the KRAS gene have been associated with lung cancer [32]. Nearly all of the KRAS gene mutations associated with lung cancer change the amino acid glycine at position 12 or 13 (Gly12 or Gly13) or change the amino acid glutamine at position 61 (Gln61) in the K-Ras protein. These mutations cause a constantly activated KRAS, which directs the cells to proliferate in an uncontrolled way, and the high cellular proliferation leads to tumor formation [33].

Even though KRAS mutations were identified in non-small cell lung tumors more than 20 years ago, the clinical value of determining KRAS tumor status is recently gaining importance. Recent studies indicate that patients with mutant KRAS tumors fail to benefit from adjuvant chemotherapy and do not respond to EGFR inhibitors. There is a clear need for therapies specifically developed for patients with KRAS-mutant non-small cell lung cancers [34, 35]. KRAS gene mutations are much more common in long-term tobacco smokers with lung cancer when compared to nonsmokers. Lung cancers with KRAS gene mutations typically indicate a poor prognosis and are associated with resistance to several cancer treatments [33–35].

4. Conclusion

KRAS is a very important oncogene. K-Ras protein is upregulated in different cancers and can cause bad prognosis of the disease. However, KRAS mutations are not sometimes enough to initiate cancer. Therefore, along with KRAS mutations, several environmental chemicals and drugs may contribute to the cascade of events leading to cancer.

It can be stated that in CRCs, PC, and lung cancer, KRAS mutations should be evaluated in clinics. On the other hand, the exposures of different environmental

chemicals and drugs (pesticides, PCBs, tobacco smoke, alcohol, N-nitrosamines, benzene, antidiabetics, calcium channel blockers, etc.) should be evaluated along with KRAS mutations, and the patients with preneoplastic lesions should be warned about such exposures. As KRAS gene mutations generally indicate a poor prognosis and are associated with resistance to several cancer treatments, new drugs targeting different molecules in KRAS triggering pathways should be developed in order to overcome this resistance, particularly in CRCs, PC, and lung cancer.

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