Editorial
The guardian of genome: p53

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Cancer is essentially a genetic disorder. So far, more than one hundred cancer related genes have been discovered, several of which are implicated in the natural history of cancer because they have constantly been found mutated.[1] The mutations could be inherited or acquired. Inherited mutations that predispose individuals to cancer formation are termed germline, while acquired mutations that contribute to tumor development are known as somatic. Mutations that occur in critical growth regulatory genes resulting in variations in cellular proliferation and survival, subsequently contribute to the selection of dominant tumor populations.

Oncogenes and tumor suppressor genes make two broad classes that become mutated contributing to cancer formation. Cancer-promoting genes or oncogenes were originally identified as viral genes that "transform" a normal cell into a malignant cell. Normal counterparts to these viral oncogenes in the human genome, well known as proto-oncogenes, have been detected, most of which function as growth-signaling molecules that become mutated and are perpetually "turned on". Tumor suppressor genes, on the other hand, negatively regulate cell growth or promote

cell death. Both copies of the tumor suppressor gene must be inactivated for complete loss of function unlike oncogenes. One group of tumor suppressor genes restricts cellular growth by inhibiting the cell cycle and cell division, down-regulating growth signals, or promoting cell death while the second group does not directly participate in growth regulation, but rather maintains the integrity of the human genome.

The p53 tumor-suppressor gene is the most striking example that is mutated in about half of almost all types of cancer arising from a wide spectrum of tissues.[1] The p53 gene is located on the long arm of chromosome 17 and contains 11 exons spanning some 20000 bp of genomic sequence. The gene encodes a 53 kd nuclear phosphoprotein of 393 amino acid residues which is well known as p53 protein. The p53, also termed as guardian of the genome (as it protects DNA integrity in response to cytotoxic stress, including radiation), was discovered in the late 1970s.[2,3] It has been implicated in the control of the cell cycle, DNA repair and synthesis, cell differentiation, genomic plasticity, and programmed cell death.[4,5] The activity of the p53 tumor-suppressor protein has a key role in controlling both cancer and aging. It would be pertinent to note here that underactivity of p53 encourages the growth of cancer, and overactivity can accelerate the aging process.

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The p53 protein which is synthesized after the infliction of DNA damage, functions to protect the cells from malignant transformation by causing cell-cycle arrest at the G1 phase until the DNA damage has been repaired. Once the damage is repaired, p53 is degraded. As mentioned earlier, a loss of this protective influence occurs in approximately 50% of human tumors in which p53 is inactivated by a mutation in its gene or by the binding of proteins encoded by viral or cellular oncogenes.[6] The mutations result in reduced binding of the p53 with the damaged DNA and subsequent accumulation of mutated p53 in the cell nuclei of the affected cells to the extent that it becomes detectable by routine immunocytochemistry.[7] This makes it the most frequently inactivated protein in human cancer and therefore an important pathway to target for cancer therapy. In addition to representing the most common genetic defects in human cancer, the spectrum of p53 mutations has characteristic fingerprints that can be correlated with the DNA damage specific to certain definitive causes of cancer (e.g. UV-B radiation, aflatoxin, and oxidative processes).[8]

The mutated forms of p53 may also interact with different sets of transcription sites, resulting in increased proliferation of cells because p53 is also a transcription factor.[9] Mutations in the p53 gene have been observed in many actinic keratoses, basal cell carcinomas, and squamous cell carcinomas, and in a small proportion of malignant melanomas. Specific types of pyrimidine transitions have pointed to a role for UV light in these mutations.[7]

The correlation between the incidence of squamous cell carcinoma and mutations in p53 tumor suppressor genes has been well characterized.[10] The chief risk factor for squamous-cell carcinoma, is exposure to ultraviolet light which is highly mutagenic, partly as a consequence of the characteristic pyrimidine dimer premutagenic lesions it generates in DNA.[11] Of all the experimentally examined mutagens, ultraviolet radiation leaves the most distinctive fingerprint in DNA: unrepaired cytosine dimers induce tandem mutations, in which two adjacent cytosine residues (cytosine-cytosine) are replaced by two thymine bases (thymine-thymine), an event that occurs very rarely unless there is exposure to ultraviolet radiation. Three of the first 15 mutations discovered in the p53 gene of squamous-cell carcinomas of the skin were just such tandem substitutions, directly incriminating both exposure to ultraviolet light as the cause of damage to the p53 gene and the loss of tumor-suppressor function in the development of the cancers.[10]

It would be interesting to note that p53 is not an oncogene and the mutated forms may not necessarily result in an oncogenic process. It was evident from the description of p53 mutations in at least two nonmalignant hyperproliferative processes including keloid and rheumatoid arthritis.[12,13]

It has also been hypothesized that p53 mutations predispose cells to hyperproliferation, resulting in keloid formation because p53 mutations have been noted in the keloid fibroblasts.[12]

The most challenging task is the development of drugs to mimic p53 tumor-suppressor function that is being aided by rapid advances in studies of p53 molecular mechanisms. The failure of chemotherapy and resistance to radiotherapy has been attributed to multidrug-resistance gene, MDR1, which confers cross-resistance to hydrophobic natural-product cytotoxic drugs making that treatment ineffective. It has been demonstrated that the expression of MDR1 is up-regulated by certain mutants of p53.[9,14] Then the role of normal functioning p53 in allowing time for the repair of radiation-induced DNA damage during the G1 phase of the cell cycle, suggests that the response to radiotherapy or chemotherapy may depend in part on the status of p53 in tumors before treatment. A full clinical analysis of various types of tumors still remains to be explored to learn whether treatment is more or less successful, depending on the type of p53 alteration in the primary tumor, and whether different treatments and treatment schedules should then be selected on the basis of the involvement of p53.

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