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Review Paper

Cancer Gene Therapy to Restore P53 Function: A New Way for an Old Aim

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ABSTRACT

Millions of people are living with cancer having specific mutation in p53 gene while every single person is truly unique in genetic basis or clinical manifestation. The gene encodes transcription factor p53, which plays a central role in regulating cell cycle progression, senescence, differentiation, DNA repair and apoptosis in response to DNA damage or other stress signals. P53 activity is up regulated to initiate a cascade of biological events that ultimately results in prevention of tumor development. Mutations in p53 abrogate normal tumor suppressor functions, contributing to the survival and proliferation of abnormal cells. Cancer cells containing mutant p53 are associated with more aggressive disease, increased resistance to chemotherapy and radiation therapy, and poor prognosis. However the majority of p53 mutations are missense and great number of these mutants represent GOF (Gain of Function) effect resulting increased invasion and metastasis in tumors. These mutations confer a dominant-negative activity over the remaining wild-type allele by functionally inactive hetero-oligomers interactions of the mutants with the wild-type protein. Increasing evidence indicates that many p53 mutants also gain new oncogenic properties that are independent from wild-type p53. Several factors including type of p53 mutations in cancers may limit the efficacy and application of p53 gene therapy. As a result, there is a great interest in therapeutic strategies aimed at restoring the function of p53 for the treatment of cancer. Increasing evidence demonstrate that silencing GOF mutations (targeted antisense therapy) reduce the transactivation activity of mutant p53 and induce apoptosis in cells bearing these mutations then provide a potential strategy to inhibit the oncogenic functions of mutant p53 and improve mutant p53-targeted cancer therapies.

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The first description of p53 protein is related to 1979 and since that time there have been more than 35 000 papers published on this topic (1, 2). However Even after 30 years after its discovery, it is still somewhat of a mystery (3). The gene encodes transcription factor p53 is TP53, noted that it is one of the most commonly altered genes in human cancers (4).

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The P53 protein is a nuclear phosphoprotein, having 393-aminoacids (5), possesses an acidic N-terminal transactivation domain and proline-rich domain, with a located sequence-specific DNA-binding domain in the center, following by an oligomerization domainand and a basic C-terminal regulatory domain (Figure1) ;this is all about the structure; Wild-type p53 functions as a homotetramer in cells (6), which play a central role to regulate cell cycle progression, differentiation, senescence, DNA repair, and apoptosis in response of DNA damage or other stress signals, p53 activity up regulate then initiate a series of biological event cascade that eventually results in prevention of tumor development and expansion (7). Recent studies showed, about 50% of human cancers have p53 mutation (8) but the frequency of it vary considerably between cancer types, ranging from ~10% in hematopoietic malignancies to 50–70% in ovarian, colorectal and head and neck cancers (9). The major part of P53 mutations, observed in human cancers dissolve the sequence specific DNA binding activity about wild type p53 responsive elements (10). Recent studies shows greater than 80% of the these cancer-associated p53 mutations are run across in the core domain, where it has six hot spots including Arg-175, Gly-245, Arg-248, Arg -249, Arg-273 and Arg-282 and they perform about 40% of all p53 mutations (11). Mutations in p53 abrogate its normal tumor suppressor functions finally contributing to the survival and/or amplification of aberrant cells with poorly differentiated phenotypes, Cancer cells consist mutant p53 are associated more aggressive disease, increased resistance to radiation therapy and chemotherapy, with poor prognosis of the disease (12). Other impact Contains lack of sensitivity to drugs, resistance to apoptosis, increased cell proliferation and/or migration, enhanced chromosomal instability and non homologous recombination are characteristics of all hot spot mutp53 proteins, such as mutp53GOFs (11).

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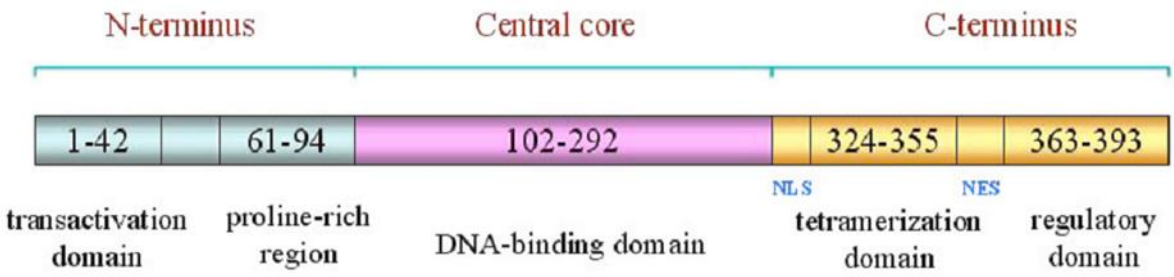

Figure1: Domain structure of p53. p53 contains a natively unfolded amino-terminal transactivation domain (TAD), followed by a proline-rich region (PRR) with a located sequence-specific core DNA-binding domain, an oligomerization domain and C-terminal regulatory domain (13)

Dominant negative or Gain of Function mutations of TP53 gene

The presence of p53 mutation does not necessarily mean the loss of p53 activity when a cell possess a wild-type allele together with the mutant allele. In this heterozygous stage, a cell containing a trans dominant mutant has reduced p53 activity and thus has a growth advantage. Moreover, p53 mutant cancer cells confer a dominant-negative activity better to say Gain of Function (GOF) activity. This effect arises from the fact that p53 binds DNA in the act of tetramer, consisting a dimer of dimers. The mutant and wild-type p53 proteins form hetero-oligomers and disable to interact correct DNA target, on the other hand Mutant p53 inhibit wild-type p53 inducing target gene transcription and tumour suppressor function (14). Increasing evidence showed that many p53 mutant cells also gain new oncogenic properties that are independent from wild-type p53. p53 mutants that promote tumor progression or/and resistance to therapies become the most common prognostic marker for both tumor recurrence and death caused by cancer (9). These mutations reduce the ability of the wild type p53 to bind to its target gene responsive element. For example, in one study, mutant TP53 was found in 24 of 92 (26.1%) endometrial cancers, in which 14 cases showed dominant-negative activity that was associated with progressed stages, non endometrioid type tumors. It showed, the presence of a dominant negative mutant p53 was related to poor outcomes, suggesting that dominant negative mutant TP53 should play a pivotal role in the progression of endometrial cancer (15).

TP53 cancer gene therapeutic way

On the result of many researches that p53 inactivation is common in human cancers, it may be assumed that reactivation of p53 and functional restoration of the p53 tumor suppressor pathway is a potential and detrimental therapeutic way against cancer. Gene therapy using wild-type p53, delivered

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By adenovirus vectors, is now widespread and other bio-logic approaches like the development of oncolytic viruses designed to replicate and kill only p53 defective cells. The other way is the development of siRNA and antisense RNA's that activate p53 by inhibiting the function of the negative regulators Mdm2, MdmX, and HPV E6 is effective too. In conclusion Adenovirus-based p53 gene therapy as well as using small molecules include PRIMA that can restore the transcriptional function to mutant p53 cell, or NUT-LIN and RITAwhich interfere with MDM2-directed p53 degradation, have been tested in a preclinical stage and some of these approaches are currently in clinical development.

Conclusion

There is one question more needed to be answer: Cancer gene therapy on restoring p53 function: augmentation the wild-type p53 or silencing the mutant allele With respect to the result of all researches about p53, this 30 years old protein, which one is better to act or which one could have better result in the way of cancer gene therapy.