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p53 Mutations: Gains or Losses?

Dan Michalovitz, Orna Halevy, and Moshe Oren

Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel

Abstract Although the case for p53 as a tumor suppressor gene appears very strong, one should still keep an open eye for the possibility that mutations in p53 do not necessarily imply a mere loss of "suppressor" activity. It is still possible that the presence of a p53 mutation in a tumor contributes, in a dominant positive manner, to tumorigenesis. In other words, certain p53 mutants may well be oncogenic in their own right, and carry distinct activities that promote growth deregulation and malignant progression. Elucidating this issue also has practical implications, since the nature of the resident mutations may greatly dictate the consequences of attempts to reintroduce wild-type (wt) p53 into particular types of tumor cells. There are two major obstacles along the road to meaningful answers: the limitations of the experimental systems used for evaluating the biological activities of wt and mutant p53 and a fundamental lack of knowledge about the relevant biochemistry of the p53 protein. These two aspects constitute primary experimental challenges for investigators in the field.

Key words: transformation, tumor suppressor genes, oncogenic mutations

The observations that p53 is overexpressed in a variety of transformed cells and that it forms specific complexes with a potent viral oncogene, the simian virus 40 (SV40) large T antigen, have prompted early interest in p53 as a potential modulator of cell proliferation [reviewed in 1–3]. Molecular cloning of p53 cDNA and genomic DNA paved the road to transfection experiments, in which this idea could be challenged directly. Consequently, p53 expression plasmids were found to exert measurable activities in a variety of systems. However, it is only very recently that we have gained enough knowledge to appreciate more correctly the biological significance of p53 and its relevance to growth control and to cancer. The intention of this overview is to discuss some of the more recent concepts as well as indicate some directions that future research in the field is likely to take.

HISTORICAL PERSPECTIVE: p53 THE ONCOGENE

Since 1984, a number of groups have described experimental systems in which p53 expression plasmids had distinct phenotypic effects. For the most part, this entailed the use of in vitro systems. Correspondingly, it was found that these plasmids could immortalize primary rat cells [4–6], transform such cells in concert with activated *ras* [7,8], and render nontransformed cells platelet-derived growth factor (PDGF)-independent [9,10]. In addition, p53 expression vectors also exerted in vivo effects: They enhanced tumor formation by weakly tumorigenic cell lines [11,12] and increased the metastatic capacity of tumor cells [13]. These features were, to a large extent, similar to those displayed by *myc*-overexpressing plasmids and suggested that p53 was, in fact, a *myc*-like oncogene. However, further work led to the realization that the plasmids employed in these studies actually encoded mutant versions of the protein [14,15]. To a large extent, this was due to the use of transformed cell lines as sources of RNA for cDNA cloning. As we now realize, such lines often express mutant rather than wild-type (wt) p53. An additional clone, of genomic origin, was expected to represent a normal mouse gene. However, it too was subsequently found to carry a point mutation, most probably arising as a laboratory artifact [15,16]. The amino acid sequences of several relatively early isolates are shown in Figure 1. Only two of those clones, pp53-17c and pCD53, possess a truly wt sequence; neither of these was used in the experiments described above.

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Address reprint requests to Moshe Oren, Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel.

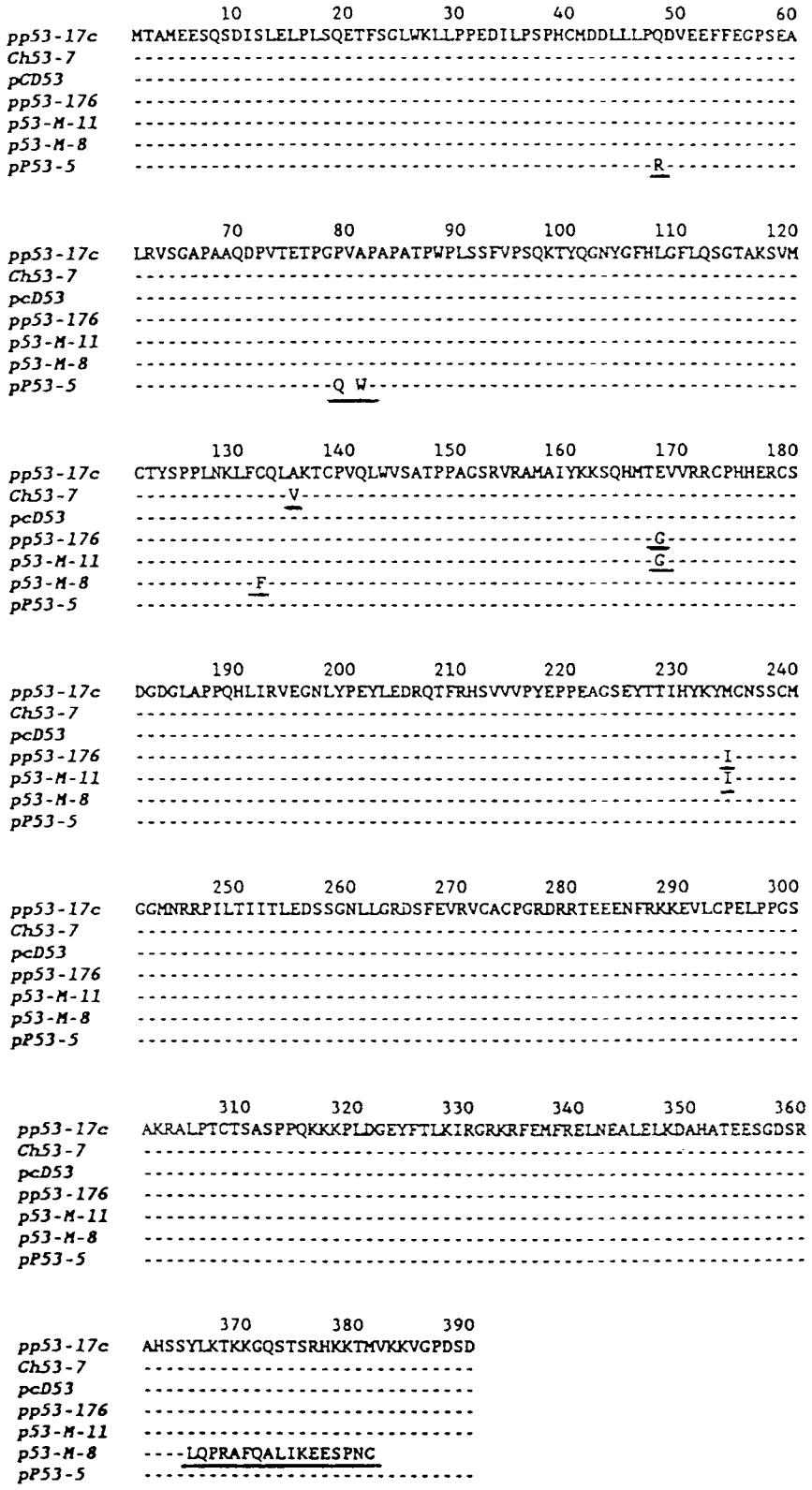

Fig. 1. Comparison of amino acid sequences of various mouse p53 DNA clones. Points of diversion from the wt consensus sequence are underlined. (Adapted from Finlay et al. [14] with permission of American Society for Microbiology, Washington D.C.)

The realization of the mutant nature of all the biologically active clones immediately brought up the issue of whether wt p53 was also oncogenic. Experiments performed to answer this question demonstrated that this was not the case, at least as measured by cotransformation with *ras,* and that wt p53 was devoid of any transforming activity [14–16]. Thus the oncogenic potential was only generated as a consequence of mutations, invoking a mechanism compatible with a model of protooncogene activation. These findings were consistent with earlier studies in which mutations were shown to endow a greatly enhanced immortalizing activity [5]. In the latter case, the starting plasmid already carried mutations (pP53-5; Fig. 1), but these mutations seem to have exerted only a mild effect on the protein, making it weakly active; further structural alterations resulted in a far more active protein [4,5].

HISTORICAL PERSPECTIVE: p53 THE SUPPRESSOR GENE

The fact that wt p53 was devoid of any transforming activity made it clearly different from *myc.* Nevertheless, it still did not imply that wt p53 may have any negative effect on cell proliferation. The latter possibility, however, became increasingly viable with the work of Benchimol and coworkers [17–19]. Studying the induction of erythroleukemia by viral infection of mice, they discovered that an appreciable number of tumorigenic leukemic clones had totally lost the ability to produce p53; often, this involved gross rearrangements within the p53 genes. These findings, coupled with more sporadic reports about loss of p53 expression in human tumors [20,21], raised the possibility that wt p53 could actually act as a tumor suppressor or transformation-inhibitory gene, at least under certain circumstances. Direct support for this idea was provided by in vitro experiments utilizing the primary rat embryo fibroblast (REF) system. It was found that plasmids encoding wt p53 could effectively block oncogene-mediated transformation in this system [22,23]. Furthermore, this inhibitory activity was lost in mutants derived from rodent tumors as well as in a number of other transforming p53 mutants. Recent work utilizing a temperature-sensitive (ts) p53 mutant [24] and an inducible p53 gene [25] has demonstrated directly that overexpressed wt p53 can cause a reversible growth arrest. The arrested cells are found predominantly with a G1 DNA content, although a variable fraction appear to arrest also at other stages of the cell cycle, at least in some cell lines. These systems provide the first clues to mechanisms underlying at least some of the biological activities of wt p53 and could prove to be of seminal importance in the future. A summary of biological activities of mutant and wt p53 is presented in Table I.

TABLE I. Biological Effects of p53 Overexpression

p53 Introduced	Recipient cells	Effect	References
Mutant	Primary rat embryo fibroblasts	Immortalization	6
	Primary rat embryo fibroblasts	Transformation in concert with *ras*	7, 8
	Adult rat chondrocytes	Immortalization	4
	Mouse Swiss 3T3 line	Induction of cellular DNA synthesis	9, 10
	Abelson transformed mouse line L12	Conversion into more tumorigenic state	11
	Murine bladder carcinoma line	Increase in metastatic capacity	13
	Rat-1 line	Enhancement of tumorigenicity	12
Wild type	Primary rat embryo fibroblasts	Suppression of transformation	22, 23
	Rat-1 line	Reduction in cloning efficiency	22, 23
	Human glioblastoma line	Growth arrest	25
	Oncogene-transformed fibroblasts	Growth arrest	24

Independent support for the tumor-suppressor identity of wt p53 came from the study of human tumors. It was found that some solid tumors lacked any detectable p53 expression, whereas a great number of others carried mutant p53 alleles; very often, this was coupled with loss of heterozygosity (LOH) [26–30]. The latter property is a hallmark of canonical tumor-suppressor genes and is most simply interpreted as indicating a complete elimination of normal p53 function, involving the mutational inactivation of one allele together with the complete loss of the other allele. Recent studies, however, are revealing a growing number of tumors in which a mutant allele is coexpressed with a wt p53 allele [28] (also, O.H. and M.O., unpublished observations). This fact can still be accounted for by assuming that the product of the mutant allele is acting in a dominant negative fashion and is effectively blocking the function of its wt counterpart [31,32]. Such an interpretation is also consistent with the propensity of transforming p53 mutants to form oligomers with wt p53 [6,15,22,33] as well as with the basic ability of such mutants to cause transformation of primary cells, where they presumably encounter the "suppressor" activity of the resident wt p53. Nevertheless, tumors coexpressing wt and mutant p53 can also be consistent with a dominant positive role of such mutants. The following sections elaborate on the issue that these two modes of action of mutant p53 (i.e., negative dominant vs. positive dominant) need not be mutually exclusive and may both actually be supported by recent experimental evidence.

WHEN DOES AN ONCOGENE BECOME A TUMOR SUPPRESSOR GENE?

To a large extent, the apparent inconsistency between the "old" concept of p53 as an oncogene (in its mutated form) and the "new" concept of its being a tumor suppressor gene (in its wt form) merely reflects variations in semantics and in operational definitions. This is perhaps best illustrated by the case of *ras*. To many, *ras* is the standard bearer of dominantly acting oncogenes. However, there are cases in which the progression of a tumor harboring one mutant *ras* allele is coupled to the loss of the normal counterpart [34]. Such an observation could be consistent with normal *ras* acting as a tumor suppressor gene in this context, an idea discussed by Balmain and coworkers [34]. Moreover, in certain cell types, overexpressed *ras* has been found to induce differentiation, a process usually considered antithetical to neoplastic transformation [35]. By bringing forth these facts, we by no means intend to imply that p53 and *ras* are equally eligible to the title of "suppressor genes." In fact, the difference between the two is perhaps best epitomized by the fact that dominant-negative p53 mutations promote transformation [22,23,32], whereas dominant-negative *ras* mutations interfere with transformation [36]. Nevertheless, the above *ras*-related findings can serve to illustrate two important points, which are highly relevant for p53. First, the fact that in many tumors the presence of one mutant p53 allele is coupled with the loss of the other allele does not necessarily prove that the mutation inactivates a suppressor gene. Second, the ability of a normal gene to exhibit attributes of a tumor suppressor is not inconsistent with the possibility that mutant versions of this gene could be overtly oncogenic. Hence, it will not be surprising if certain p53 mutants turn out to operate via a truly dominant positive mechanism and not only by abrogating the "suppressor" activity of wt p53.

NEGATIVE MUTATIONS AND POSITIVE MUTATIONS

In light of the considerations raised above, one may anticipate that the p53 mutations present in tumors could fall into three classes. 1) The first class is true null mutations, where the protein does not engage in any interaction and whose presence is tantamount to the actual loss of the gene. Such mutations should not score in any assay. 2) The second class is dominant negative mutations, which couple the loss of a growth-inhibitory activity with the ability to interfere with the function of coexpressed wt p53. This can occur either via direct binding of the latter, as has been reported for a number of p53 mutants [6,15,22,33], or via competition for limiting molecular targets [37]. Mutants of this group will be recognized as oncogenic only in cells that still coexpress a wt or wt-like p53. Furthermore, such mutants will not provide a direct oncogenic stimulus but rather eliminate an inhibitory factor. Therefore, one could expect them to perform efficiently only in transformation assays in which initiating events are provided by other, positively dominant oncogenes, and in which loss of suppression becomes a rate-limiting event. 3) The third class is dominant positive mutants, which have gained an overt transforming func-

tion. Such mutants should, in principle, contribute to growth deregulation and malignancy also in cells that do not express any endogenous wt p53. Additionally, they may provide a positive initiating event and relieve the need for "standard" oncogenes. It is conceivable that many mutants may combine the properties of the last two categories, namely, possess a dominant positive oncogenic activity along with the ability to extinguish the inhibitory effects of coexpressed wt p53.

An example of such a double action mutant is perhaps provided by p53val135 [14–16]. In lines derived from foci induced by cotransfecting REF with a combination of p53val135 and *ras,* the levels of mutant p53 are usually very high and in great excess over the endogenous p53 [2,14–16]. The latter pattern is more consistent with a negative-dominant mechanism [31,32]. Such an observation could, nevertheless, be reconciled with the notion of positively acting mutants, if one considers the salient features of the REF cotransformation assay. The targets for transformation in this assay are primary cells that are almost certainly expressing wt p53. For a given p53 mutant to score as highly transforming (with *ras*), it may have both to possess the ability to overcome the antisuppressor effect of the endogenous wt p53 and to exhibit some additional, novel or enhanced, biochemical property. Whereas the latter may determine the extent to which such a mutant is oncogenic, the former may be a prerequisite for any detectable transforming activity in this assay and allow only cells in which the mutant p53 is vastly overexpressed to develop into visible foci.

Ideally, one would wish to assess the net dominant positive potential of p53 mutants in a system devoid of endogenous p53, such that there is no need to inactivate the wt protein. A system conforming to these requirements is the one described by Wolf et al. [11], in which mutant p53 can increase the tumorigenicity of a p53-negative, virally transformed lymphoid line. It would be of interest to find out whether plasmids encoding mutant p53 in more or less physiological levels could still be effective in this system. An apparent drawback of this in vivo assay is its being time consuming and relatively expensive. As is discussed below, in vivo tumor progression assays may be inevitable when seeking to gain a full understanding of the role of p53 mutations in tumorigenesis. Nevertheless, developing in vitro assays in which one could monitor the induction of a more transformed phenotype in p53-nonproducing cells, transfected by various p53 mutants, could be of great value.

WHAT DO WE LEARN FROM TUMOR-DERIVED MUTANTS?

The rapidly growing arsenal of p53 mutants cloned from tumors now creates the opportunity to embark on a comprehensive biological characterization of such mutants. Conceivably, these would be the mutants of choice for further studies, since they represent the products of actual in vivo selection during tumorigenesis. As such, they should reflect properties that are of true relevance, rather than features encountered only in in vitro-generated mutants and having biological manifestations only when the proteins are expressed at nonphysiological levels in arbitrary experimental systems.

The limited information gathered so far in our laboratory from the analysis of tumor-derived mouse p53 variants has led to some provocative results. Thus, a previously well characterized mutant, p53val135, is very effective both in transformation and in binding the endogenous wt p53 [14–16,22,23]. On the other hand, two tumor-derived mutants exhibit a surprising uncoupling of these properties: One binds efficiently the endogenous p53 but is only weakly transforming; the other binds more weakly but is a potent transformer [38]. These data demonstrate that different classes of p53 mutants do exist in tumors. Moreover, they seem to support the notion that certain mutants possess a distinctly dominant positive activity, which is largely independent of their ability to oligomerize with wt p53. Clearly, additional mutants need to be analyzed to be able to compile a comprehensive picture. In addition, one may wish to set up new experimental systems, in which the biological properties of such mutants can be assessed. A major shortcoming, at present, is that the bulk of the contemporary in vitro work utilizes fibroblasts, whereas the vast majority of tumors reported so far to harbor p53 mutations are of epithelial origin. One may therefore want to consider the establishment of reliable in vitro systems for p53 analysis that employ epithelial cells. In addition, features selected for during in vitro transformation may be quite remote from those selected for in the course

of in vivo tumor progression. More specifically, the "suppressor" effect of wt p53 is manifest in tissue culture systems as an antiproliferative activity, which leads to growth arrest [24,25]. On the other hand, the putative inactivation of wt p53 may often constitute a late step in the progression of the tumor. In such cases, p53-related alterations are not expected to provide the primary trigger for deregulated cell proliferation. Rather, they may have to do more with tumor-host interactions. The true relevance of such alterations may therefore be missed in assays that are restricted to tissue culture. One could draw encouragement from the fact that, so far, all tumor-derived p53 mutants appear to be completely devoid of "suppressor" activity in the REF system [22,23,38]. This would support the interpretation that the same basic activity of the protein that is selected against in vivo is also the one responsible for the antiproliferative capacity in vitro. Nevertheless, the number of tumor-derived mutants that have been subjected to such analysis is very small and may still be insufficient to generate confidence in in vitro assays. Hence, despite the extra complications imposed by in vivo studies, one would envisage that in the long run much more work should be done on animal models. Investigating the effect of different p53 mutations on tumor formation in transgenic mice would seem most appropriate. In fact, a first study along these lines has already revealed that the constitutive overexpression of mutant p53 results in the induction of tumors in such animals and that these tumors exhibit a nonrandom pattern of tissue distribution [39]. Nevertheless, the levels of mutant protein produced in such mice were well above those seen in naturally occurring tumors, a fact that calls for caution in interpreting the data. Ideally, one would want to compare the tumorigenic potential of various p53 mutants when expressed at more physiological levels. This could perhaps be better approached by using methods such as gene replacement in transgenic mice.

SOME PRACTICAL CONCERNS

Although investigators often avoid discussing the idea openly, perhaps the major long-term goal of studying tumor-suppressor genes is to be able to reintroduce them into tumors and reverse tumor progression. In the case of p53, the most reasonable first step should be an attempt to cause the phenotypic reversion of transformed cells by stable transfection with wt p53 expression plasmids. The choice of target cells may not be trivial. For one thing, even if the abrogation of wt p53 function played a role in the neoplastic conversion of a given cell population, such cells may become nonresponsive to wt p53 upon further progression of their malignant phenotype. For instance, mutation of the p53 genes may be followed by elimination of a molecular target of wt p53, provided that the latter event confers an additional selective advantage. In this case, it is possible that the reintroduction of wt p53 will be of no consequence.

Another parameter affecting the outcome of such reconstitution experiments is the nature of the p53-related lesions present in the target cells. This is where understanding the differences between various classes of p53 mutants comes into play. In cells expressing only a null mutant, it may suffice to restore physiological expression levels of wt p53. Such an option is distinctly advantageous, since extensive overexpression of wt p53 may be deleterious also to nontransformed cells [16,22,23]. On the other hand, cells expressing a dominant negative p53 mutant may be able to neutralize exogenous wt p53; such cells will require relatively high levels of reintroduced wt p53 in order to be affected. Finally, when an overtly dominant positive p53 mutation is present, the restoration of wt p53 expression may inhibit the proliferation of the cells no better than that of nontransformed cells. These concerns should be taken into account when setting up in vitro assays to monitor the efficacy of the reconstitution of wt p53 expression.

Reconstitution experiments of this kind will undoubtedly draw much effort and attention in the near future. Although the experience gained thus far along these lines is limited, it already underscores a potential problem. Cells transformed by various oncogene combinations in the presence of a wt p53 plasmid occasionally express conspicuous levels of the transfected p53. In such cases, the p53 encoded by the transgene often displays properties indicative of mutational alterations [22] (also D.M., unpublished data). Thus, under strong selective pressure, cells transfected with a wt p53 gene may end up acquiring a new mutant p53. In such cases, the end product may be a more malignant cell rather than a revertant. Future work will reveal

whether this should be regarded as a major risk factor.

MISSING LINKS

The major area in which our present knowledge about p53 is the least satisfactory is the biochemical characterization of the protein. This is important not only for academic reasons. In fact, such knowledge could be instrumental in resolving the difficulties brought up in the previous sections. For instance, let us assume that p53 is found to be a transcriptional transactivator. In this case, even if the target genes involved in its antiproliferative effects are distinct from those responsible for in vivo tumor suppression, the expression of all these genes will be similarly affected by mutations that abolish the ability of p53 to serve as a transactivator. In such a case, the in vitro suppression assay will indeed become relevant.

Unfortunately, the study of p53 biochemistry is still in its infancy. The fact that it is a nuclear [40] DNA binding protein [41,42] naturally raises the possibility that it regulates processes related to gene expression or DNA replication. Most nuclear oncoproteins are turning out to be transcriptional regulators. Therefore, it seems reasonable that p53 also plays a role in modulating gene expression, especially since it possesses structural features reminiscent of transcriptional activators. As yet, however, there is no direct evidence to support this contention. As far as the replication option is concerned, there has been a report that p53 can bind to putative cellular origins of replication and promote their ability to act as origins in a cell-free replication system [43]. It is not yet known whether the p53 used in these studies was wt or mutant. A more serious concern has to do with the fact that there is at present no acceptable definition for an authentic mammalian replication origin, so the significance of the above findings is hard to assess.

A simpler picture is emerging from the study of large T antigen-dependent SV40 DNA replication. Whereas wt p53 can efficiently inhibit this process both in vivo [44] and in vitro [45,46], many mutants fail to do so. Importantly, all tumor-derived p53 mutants tested so far, as well as a number of in vitro-generated mutants of similar biological properties, share the feature of having a greatly reduced affinity for SV40 large T antigen [38,47,48]. All we have to do now is assume that there is a cellular "T-like" protein, which is similarly involved in controlling cell DNA replication and which is a target for the "suppressor" activity of wt p53. This, however, is still purely speculative, and the true picture may be much more complicated or altogether unrelated to the role of large T in viral DNA replication. In any event, the SV40 DNA replication studies set the trend for what should be a major direction in future research, namely, the identification of biochemical activities present in wt p53 and absent in nonsuppressing mutants. The surge of interest in p53 will undoubtedly also prompt more ambitious investigations into the biochemistry of the protein. Once p53 is convincingly assigned a proper biochemical identity, the study of the different types of mutations will be approachable in a much more profound and meaningful manner.

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