Review

TP53 mutations as biomarkers for cancer epidemiology in Latin America: Current knowledge and perspectives

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Abstract

Due to particular social and economical development, and to the impact of globalization of lifestyles, Latin America shows a superposition of cancers that are frequent in low resource countries (gastric, oesophageal squamous cell and cervical cancers) and high resource countries (cancers of breast, colon and rectum, lung and prostate). Latin America thus offers opportunities for investigating the impact on changing lifestyle patterns on the occurrence of cancer. At the molecular level, mutations in the tumor suppressor gene TP53 are common in many cancers and their distribution can be informative of the nature of the mutagenic mechanisms, thus giving clues to cancer etiology and molecular pathogenesis. However most of the data available are derived from studies in industrialized countries. In this review, we discuss current trends on cancer occurrence in Latin American countries, and we review the literature available on TP53 mutations and polymorphisms in patients from Latin America. Overall, a total of 285 mutations have been described in 1213 patients in 20 publications, representing 1.5% of the total number of mutations reported worldwide. Except for hematological cancers, TP53 mutation frequencies are similar to those reported in other regions of the world. The only tumor site presenting significant differences in mutation pattern as compared to other parts of the world is colon and rectum. However, this difference is based on a single study with 35 patients. Recently, a characteristic TP53 mutation at codon 337 (R337H) has been identified in the germline of children with adrenocortical carcinoma in Southern Brazil. Further and better focused analyses of TP53 mutation patterns in the context of epidemiological studies, should help to improve our understanding of cancer etiology in order to develop appropriate health policies and public health programs in Latin America.

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1. Introduction

Worldwide, cancer is considered as the second most common cause of mortality after cardiovascular diseases. It is estimated that more than six million people die of the disease every year, with marked regional differences [1]. It is commonly accepted that cancer is a major problem in high resource industrialized regions, however it is becoming also a burden in lower resource developing countries, especially in Latin America (Fig. 1) (definition of high and low resource countries according to the World Bank, http://www.mapsofworld.com).

Latin America is a part of the American continent formed by countries that were colonized by Spanish and Portuguese, spanning a large area from Mexico to Argentina. It represents a very interesting area to monitor and control trends in cancer incidence and mortality, as well as to study geographic variations in cancer patterns. Due to wide sociological and economical disparities, the global map of cancer in Latin America shows a superposition of cancers that are frequent in industrialized countries (breast, lung, prostate, colon), and of cancers that are more frequent in developing countries (cervix, oesophagus, oral, bladder, liver) [2,3]. While the former are likely to be associated with a number of lifestyle factors (in particular diet, tobacco and lack of physical exercise), many of the latter cancers may reflect the interactions between malnutrition, region-specific environmental exposures and, in several cases, viral infections [4]. This very complex situation makes it extremely difficult to develop global health policies for cancer prevention, detection and monitoring. Moreover, these trends are changing rapidly. Another element of complexity as far as genetic susceptibility of cancer is concerned, is the existence of multiple ethnic groups, some of them affected by strong founder effects that may explain the local or regional clustering of relatively rare cancers. Thus, the use of molecular biomarkers may be particularly helpful to identify the respective roles of environmental, biological, lifestyle and genetical risk factors in studies on cancer in Latin America.

Many constitutive or acquired genetic traits are potential biomarkers for molecular epidemiology studies. In this review, we will focus the interest on mutations in the TP53 tumor suppressor gene, as there is good evidence that these mutations may be informative on the nature of the mutagenic mechanisms at work in cancer causation. Moreover, these mutations may represent phenotypic changes in tumour cells, giving different pathological features
to the cancer cell, turning to be important clues to clinical decisions [5].

TP53 is the most commonly mutated gene in human cancers and its product, the p53 tumour suppressor protein, is a transcription factor activated in response to stress signals, in particular to genotoxic stress. Several observations lead investigators to consider the TP53 mutation pattern as a useful biomarker of mutagenesis: (1) mutations in TP53 are mostly missense and very diverse in their position and nature, allowing compilation and comparison of tumor-specific mutation spectra; (2) these point mutations are clustered in exons 4–9 (more than 80%) which facilitates analysis; (3) there is a large data set of mutation information on TP53, which is compiled in a dedicated, central database (http://www-p53.iarc.fr).

The purpose of this review is to discuss the usefulness of studies on TP53 mutation patterns as a tool to better understand the epidemiology of cancer in Latin America.

2. Cancer epidemiology in Latin America: the global burden of cancer and regional variations

The 20th century has witnessed two important socio-economic changes throughout the world: globalization and a historical shift in patterns of production and consumption [6]. The consequence of this global rearrangement is a different health profile of the developing world. These changes of health and disease patterns are known as epidemiological transition, characterized by a modification in the incidence and mortality profiles. Decreasing rates of infectious diseases and the increment of chronic-degenerative diseases, especially cancer and cardiovascular diseases are detected in countries where the income by person is very low [7,8].

In Latin America the epidemiological transition is not yet accomplished. In this region of the world the degenerative diseases are increasing, while the prevalence of infectious, respiratory and vector-borne diseases as malaria and dengue, and overall malnutri-
tion, remains high [7,8]. This dual aspect is related to the socio-economical class distribution in the region: on one side the poor rural and peri-urban population, including Indian people, and on the other side the wealthy urban elites. In the middle, we found the poor urbanbs living in urban slums known as “favelas,” “suburbios” and “pueblos jóvenes.” It is noteworthy that differences in ethnic distribution follow this social-economical class distribution. Currently, Latin America is the most urbanized of the less developed regions in the world, and this urban expansion has been accompanied by massive urban poverty [7,9].

The impact of this situation on the global burden of cancer is illustrated in Fig. 1. It is striking to observe that high global cancer incidence (Fig. 1A) coincides with economic prosperity (Fig. 1B), with the highest rates of cancer occurring in developed countries in the Western hemisphere as well as in Australia and the Southern part of Latin America. By contrast, the lowest rates are observed in equatorial and inter-tropical regions. This trend is noticeable both in men and, spectacularly, in women. As a result, there is, in Latin America, a North–South gradient in cancer incidence, with the lowest global burden observed in the relatively poor countries of Central America and of the North- and Eastern ridge of South America. The highest global incidences are observed in Chile, Argentina and, typically, Uruguay, which are the most “Westernized” of the Latin American countries.

Brazil represents an intermediate situation, reflecting the enormous local and socio-economical disparities that are prevalent throughout the country [10–12]. It should be emphasized that population coverage by cancer registries is, at best, only partial [2,3,6]. While data from Porto Alegre, an industrialized area, show a pattern of incidence compatible with “western” profile, the data from Belém, a rural area, are more similar to those of registries in the poorest countries of Latin America.

Fig. 2 compares the distribution of incidence and mortality for the six most common cancers in men and in women in Northern, Central and Southern Americas [11]. First, it appears that the global incidence of the main cancers is much higher in Northern than in Latin America. However, the two cancers that rank first in incidence among men, prostate and lung cancers are the same throughout the continent. Colorectal cancer is also common to the three Americas. In Latin America, however, a number of cancers that arise are uncommon in Northern America, in particular cancers of the stomach and oesophagus (squamous cell), as well as pancreas and leukemia in Central America. In women, the difference between Northern and Latin America is even more striking. Cervical cancer, which is rare in North America, appears in the first and second position in, respectively, Central and South America. Breast cancer, the dominant cancer in North America, is also the most common among women in South America. As observed in men, stomach cancer also features among the top five cancers in Latin America, but is much less frequent in Northern America. In contrast, lung cancers, that are now the second most frequent cancer in women in Northern America (and the first in mortality rate), are relatively rare in Latin America, with the exception of Brazil where recent figures indicate that it has also become the second main cause of cancer death among women [13]. Fig. 2 also illustrates important disparities between Northern and Latin Americas in mortality for manageable cancers such as prostate, breast and colorectal cancers. Thus, as a region of contrasts, Latin America has important regional differences in incidence and mortality patterns and trends. Among the cancers listed above, there are well-documented high incidence rates of stomach cancer in Latin America. Costa Rica, Ecuador and Colombia have three to four times higher rates than Paraguay and Cuba [14]. The analysis of mortality by gastric cancer in Brazil between 1979 and 2001, showed a decrease in incidence for both male and female [15,16]. In the State of Rio de Janeiro, this decrease is more marked in metropolitan than in rural areas. This type of cancer is linked to nutritional habits such as additives and high-salt foods that cause mucosal inflammation. Moreover, persistent infection with H. pylori, which is more common in lower social-economic population, is a decisive factor in the burden of this cancer in Latin America [17]. Verdecchia et al. [18] evaluated the gastric cancer survival in population-based registries in four continents, including Campinas, Brazil, and concluded that the large differences observed among the four areas were almost totally explained by differences in age, gender, period and stage, rather than by differences in patient management. The high incidence of squamous oesophageal cancers in Southern (but not Central) America has been
documented in several studies [19,20]. According to Parkin et al. [3], the highest incidences in Latin America are: Argentina-Concordia (ASR of 13.9/100,000 men and 3.1/100,000 women), Brazil-Goiana (ASR of 10.8/100,000 men and 3.0/100,000 women) and Uruguay (ASR of 10.7/100,000 men and 2.5/100,000 women). As in other areas of the world, the geographic distribution of oesophageal squamous cell cancers is extremely heterogenous, with high- and low-incidence areas throughout the continent. Main suspected risk factors include consumption of hot beverages (such as mate) as well as food habits such as charcoal grilled meat (‘‘churrasco’’). In addition to these specific factors, tobacco smoking together with alcohol drinking plays a major role, as observed in many western countries [21–24].

In women, the burden of cervical cancer is particularly high, as observed in countries such as Bolivia and Nicaragua, where incidences are among the highest registered anywhere (respectively, 58.1 and 61.1/100,000/year). These high incidence rates are the consequence of the huge public health impact of human papillomavirus (HPV) infections and other risk factors and of the limited coverage of the women population by cytology screening [25–29]. A recent study conducted in the city of São Paulo, Brazil showed a slight reduction in cervical cancer mortality rates that may point to an increase in the coverage of this cancer screening using the Pap smear [30].

In contrast, the patterns of incidence of breast cancer are indicative of an association with industrialization and adoption of a “Westernized” lifestyle. In Latin America, incidence rates for breast cancer have been consistently increasing for the past 40 years [31], and the highest incidences are detected in areas such as Uruguay, Argentina-Bahía Blanca and
Argentina-Concordia, with ASR of 114.9, 86.1 and 55.1 per 100,000 women, respectively [3]. In Brazil, the highest incidence rates are observed in Brasilia and Sao Paulo [13]. In USA, Hispanic women with breast cancer, especially first-generation, have tumor characteristics associated to delayed detection in the timeliness of their cancer diagnosis, such as a higher percentage of tumors larger than one centimeter [32].

In addition to the above-discussed situations, we should take into account that in some regions, as for example, the Northeastern of Brazil, cancer registration is nonexistent or incomplete due to many structural problems, thus introducing over- or underestimations of cancer rates in different regions. The differences in cancer registries may be important even within Latin American countries. However, these trends in cancer incidence and mortality show the relevance of the disease and the importance of increasing cancer epidemiological studies that are essential in development of health policies and public health programs.

3. **TP53 mutations as markers in molecular epidemiology**

Molecular epidemiology utilizes molecular biomarkers as intermediate end-points to solve epidemiological questions. The added value of this approach is that the results provide direct insights into mechanisms of disease development and can often be translated into therapeutic or public health decisions. It is clearly observed in cancer [33,34]. In this respect, accumulating evidence demonstrate that TP53 mutations can be biomarkers of carcinogen effect and cancer development, providing clues to both natural history and clinical evaluation of cancer.

3.1. **p53 Structure and functions**

The TP53 tumor suppressor gene is a key gene in carcinogenesis and impairment of the p53 protein functions seems to be central in the multistep development of cancer [5]. The human TP53 gene is located on chromosome 17p13.1, spanning 20 kb. It contains 11 exons, the first one being non-coding. This gene belongs to a family of highly conserved genes that contains at least two other members, P63 and TP73 [35–37].

The TP53 gene product is a protein of 393 residues with a structural organization typical of transcription factors: it presents (1) an acidic N-terminal domain containing a transcription activation domain (residues 1–44), and a proline-rich regulatory domain (residues 62–94), (2) a central sequence-specific well-conserved DNA-binding domain (residues 110–292), (3) an oligomerization domain (residues 325–363) (4) a C-terminal domain that contains multiple regulatory signals (residues 363–393) [38].

The recently described proteins p63 and p73 have similar structural organization, their DNA-binding domain presenting the highest similarity with p53 [38]. Although the three proteins regulate similar groups of genes, p53 has a unique role in tumor suppression, as illustrated by knock-out mice models which are developmentally normal but show multiple tumors at an early age [39]. In contrast, p63 or p73-deficient mice show developmental defects but no increase in tumor incidence.

The unique role of p53 in tumor suppression is explained by its key role in cellular response to various forms of stress. The p53 protein is expressed in almost all tissues as a constitutively repressed protein. The main mechanism of repression is protein-protein interaction with the product of the oncogene MDM2, which targets p53 protein to proteasome degradation. Several classes of signals can lead to the de-repression of p53 and to its accumulation by post-translational modifications. These signals include DNA-damaging agents (genotoxic stress), constitutive activation of growth signaling cascades (oncogenic stress), as well as other types of stress such as depletion in ribonucleotides or hypoxia [40]. Thus, p53 lies at the point of convergence of several, distinct stress–response pathways [41]. Fig. 3 shows an overall outline of the biological functions of p53. Activation of p53 is induced in response to signals generated by kinases such as ATM, ATR, Chk2 or JNK that recognize and transduce DNA-damage as well as other stress signals. Once activated, p53 regulates the expression of several classes of genes, either through sequence-specific DNA-binding or through protein-protein interactions. P53-regulated genes (activated or repressed) include genes involved in cell-cycle arrest (P21WAF1, GADD45), apoptosis (PUMA, BAX, FAS/CD95), DNA repair (Pol B, O6MGMT, MSH2) and angiogenesis (TSP1). Their coordinated regula-
tion by p53 results in anti-proliferative effects, allowing the preservation of genomic integrity [42].

3.2. Mutations in cancer: mutagenesis versus selection

TP53 alterations in human cancers include loss of alleles, gene mutations (mostly missense) and inactivation of the protein by sequestration by viral or cellular proteins. The most frequent alterations are mutations in the coding sequence which are found in almost every kind of human cancer. A database of mutations reported in human cancer is maintained at the International Agency for Research on Cancer (http://www-p53.iarc.fr). The overall mutation frequencies range from 5 to 50% depending on the tumor type and stage. Malignancies with high mutation frequencies (40–55%) include ovarian, esophageal, colorectal, head and neck and lung cancers. Tumors of the brain, breast, stomach and liver show an intermediate mutation frequency (20–35%). Malignancies with low mutation frequency include leukemia, sarcoma, testicular cancer, malignant melanoma and cervical cancer. In the latter cancers, p53 is thought to be inactivated by alternative mechanisms, such as HPV protein E6 that eliminates p53 by rapid degradation.

TP53 mutations cluster within the DNA-binding domain of the protein, between exons 5 and 8 [38]. Although most studies have screened only exons 5–8 after the observation that mutations clustered in this region, subsequent studies that have analyzed the entire coding sequence have shown that 80% of all mutations are located between exons 5 and 8. About 30% of these mutations fall at five “hotspot” codons (175, 245, 248, 273, 282) and have been found in almost every type of cancer. The other 70% of the mutations are distributed over more than 200 codons.

The nature, position, and relative prevalence of mutations vary among cancer types and population groups [38]. Two main factors contribute to the shaping of a tumor-specific “mutation pattern”. The first is mutagenesis: the type of damage caused by a mutagen can be specific in its nature and DNA sequence context, and the rate of mutation formation is limited by the cell’s capacity to repair DNA lesions. Specific mutation patterns have been observed in studies on populations exposed to high levels of
mutagens. Well-documented examples include hepatocellular carcinoma in individuals chronically infected by HBV and exposed to dietary aflatoxins, lung cancers in smokers and non-melanoma skin cancers in individuals exposed to solar UV. In several other cancers, such as bladder and oesophageal carcinomas, specific mutation profiles have been observed, but the mutagens have not been clearly identified. For the most frequent types of TP53 mutations, namely transitions (purine to purine or pyrimidine to pyrimidine) at CpG sites, it is considered that spontaneous deamination of methylated cytosine, leading to a substitution to thymine is the main mechanism involved. This process is greatly enhanced by oxyradicals, in particular nitric oxide (NO), which is generated endogenously during conditions such as inflammation or bacterial infection [43,44]. In colon cancer, NO production has been correlated with the presence of transition mutations at CpG sites in TP53 [45]. Overall, looking at specific TP53 mutation patterns may thus help to generate hypotheses on the mutagenic processes involved.

The second is biological selection: only mutants that have significant changes in their functional properties will induce a proliferative advantage and contribute to cancer. The fact that TP53 mutations cluster in the central DNA-binding domain indicates that transcriptional activation through specific response elements is the essential biological mechanism for tumor suppression [46–48]. However, TP53 mutations may result in the over-expression of the mutant protein, which is retained throughout cancer progression. Even in distant metastasis that mutant protein may exert some pro-oncogenic effects. These effects may vary from one tissue to another, resulting in the selection of different mutants.

A list of mutants with their biological activities, tested in human cells or yeast assays, and reported in the literature is available on the IARC TP53 website (TP53 function database at http://www-p53.iarc.fr).

3.3. TP53 germline mutations and polymorphisms

Inherited TP53 mutations are associated with a rare autosomal dominant disorder, the Li–Fraumeni syndrome (LFS). LFS is clinically defined by a familial clustering of tumors diagnosed before 45 years of age, mostly sarcomas, breast, brain and adrenocortical cancers [49]. About 70% of LFS families have been shown to carry a mutant TP53 allele [50,51]. LFS patients are heterozygous for TP53 mutation, but cancer cells developing in these patients loose the wild-type allele. The penetrance of the mutant allele is close to 100%, suggesting a causal link between the constitutive mutation and the subsequent somatic inactivation of the wild-type allele. This hypothesis is consistent with the fact that normal cells from individuals with germline TP53 mutations show altered genomic stability [52]. In TP53 mutation carriers, 80% of the tumors are sarcomas, breast cancer, brain tumors and adrenocortical carcinomas, breast cancers and sarcomas representing 50% of all tumors [53].

Several TP53 polymorphisms have been identified in human populations, most of them being localised in introns, outside consensus splicing sites (list available at http://www-p53.iarc.fr/Polymorphism.html). Only two polymorphisms, serine to proline at residue 47 and arginine to proline at residue 72, alter the amino acid sequence of p53. The Pro47 variant is a rare polymorphism affecting a codon well conserved in evolution [54]. For residue 72, sharp ethnic differences of allele frequencies have been observed [55]. Numerous studies have investigated the associations of codon 72 polymorphism with increased risk for different cancers related or not to HPV, but the associations that have been found in some studies have always been challenged by subsequent studies [56,57]. Recently, Langerod et al. [58] observed that in breast tumors the presence of TP53 mutation was significantly more often found on the Arg72 allele than the Pro72 allele, suggesting a role of the Arg72 allele in the mechanism of breast cancer development. So far, evidence that TP53 polymorphisms may have a role in cancer susceptibility remains to be established.

4. TP53 mutation analysis in Latin America

4.1. Somatic mutations

The list of all studies that have been published so far on TP53 somatic mutations in Latin America is presented in Table 1. This list shows that only 20 studies have been published and they come mainly from Brazil (12/20 studies) (Table 1). Moreover, most
studies are small, with only 6 studies having analyzed more than 50 samples. The largest studies are on breast (total of 414 samples), oesophagus (total of 156 samples), bladder (total of 126 samples), cervix (total of 122 samples), head and neck (total of 90 samples) and colorectum (total of 74 samples). Only one study has been reported for stomach cancer, which is the fourth most frequent cancer in Latin America, and no study has been found on lung and prostate cancers, which are among the most frequent cancers. In Uruguay, where the overall incidence of cancer is the highest in Latin America, there is only one small study on cancer of the oesophagus. It is also of note that most studies performed in Latin America are recent (after 1998), compared to studies from the US or Europe, which started in the early 1990s. Although the number of studies seems to increase, 55% were done since 2000, the overall coverage of TP53 mutation in Latin America is thus very sparse.

In these studies, TP53 mutations have been screened by SSCP or direct sequencing and have mainly analyzed exons 5–8. Mutation frequencies are similar to frequencies reported worldwide (see IARC TP53 database at http://www-p53.iarc.fr), except for hematological cancers which show a higher frequency of mutation (22–40% versus 10% in IARC TP53 database).

The detailed mutation data of studies listed in Table 1 are available through the IARC TP53 database (http://www-p53.iarc.fr). Below, we analyze the mutation patterns of cancers for which the largest data sets are available. Almost all samples from Latin America have been screened from exons 5–8 and because the type of mutations in these exons differ significantly from the type of mutation outside these exons, we only analyzed mutations located in exons 5–8. TP53 mutations in cancer from Japan, Europe, and Northern America were used as comparison groups.

4.2. Breast cancer

Two studies are available on breast cancer, both from Brazil: Rio de Janeiro [59] and São Paulo [60]. The overall pattern of mutations reported in the studies from Brazil showed a higher proportion of insertions/deletions and G:C > T:A transversions than any other area (Fig. 4). In contrast, the proportion of G:C > A:T transitions at non-CpG was lower than in other areas. In Japan and Northern America, insertions and deletions have been reported to be more common in elderly women. In contrast, G:C > T:A transversions were more common among younger women in Europe. While the significance of these trends remains to be determined, it is possible that they may

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>Country</th>
<th>Reference</th>
<th>Year</th>
<th>Method</th>
<th>Region analysed</th>
<th>Mutation frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>Argentina/Chile</td>
<td>[67]</td>
<td>2003</td>
<td>Dir.Seq.</td>
<td>Exons 5–8</td>
<td>35.7% (45/126)</td>
</tr>
<tr>
<td>Bone</td>
<td>Brazil</td>
<td>[84]</td>
<td>2001</td>
<td>SSCP</td>
<td>Exons 5–8</td>
<td>na (1/1)</td>
</tr>
<tr>
<td>Brain</td>
<td>Brazil</td>
<td>[85]</td>
<td>1997</td>
<td>Dir. Seq.</td>
<td>Exons 5–8</td>
<td>na (1/1)</td>
</tr>
<tr>
<td>Breast</td>
<td>Brazil</td>
<td>[59]</td>
<td>2002</td>
<td>SSCP</td>
<td>Exons 5–8</td>
<td>20% (24/120)</td>
</tr>
<tr>
<td>Breast</td>
<td>Brazil</td>
<td>[60]</td>
<td>2003</td>
<td>SSCP</td>
<td>Exons 4–9</td>
<td>17% (50/294)</td>
</tr>
<tr>
<td>Cervix Uteri</td>
<td>Brazil</td>
<td>[86]</td>
<td>2001</td>
<td>SSCP</td>
<td>Exons 5–8</td>
<td>3.2% (4/122)</td>
</tr>
<tr>
<td>Colorectum</td>
<td>Brazil</td>
<td>[87]</td>
<td>1996</td>
<td>SSCP</td>
<td>Exons 5–8</td>
<td>38.5% (15/39)</td>
</tr>
<tr>
<td>Colorectum</td>
<td>Chile</td>
<td>[88]</td>
<td>2000</td>
<td>Dir. Seq.</td>
<td>Exons 5–9</td>
<td>60% (21/35)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Brazil</td>
<td>[89]</td>
<td>2000</td>
<td>Dir. Seq.</td>
<td>Exons 5–8</td>
<td>na (2/2)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Brazil</td>
<td>[90]</td>
<td>2002</td>
<td>SSCP</td>
<td>Exons 5–9</td>
<td>34.8% (47/135)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Uruguay</td>
<td>[91]</td>
<td>1991</td>
<td>Dir. Seq.</td>
<td>Exons 5–8</td>
<td>44.1% (6/19)</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>Chile</td>
<td>[92]</td>
<td>1998</td>
<td>Dir. Seq.</td>
<td>Exons 5–8</td>
<td>52.4% (22/42)</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>Chile</td>
<td>[93]</td>
<td>2000</td>
<td>Dir. Seq.</td>
<td>Exons 5–8</td>
<td>52% (13/25)</td>
</tr>
<tr>
<td>Head&amp; Neck</td>
<td>Brazil</td>
<td>[94]</td>
<td>1998</td>
<td>SSCP</td>
<td>Exons 5–8</td>
<td>53.3% (48/90)</td>
</tr>
<tr>
<td>Hematol</td>
<td>Argentina/ Brazil</td>
<td>[95]</td>
<td>1992</td>
<td>SSCP</td>
<td>Exons 5–8</td>
<td>40.7% (11/27)</td>
</tr>
<tr>
<td>Hematol</td>
<td>Brazil</td>
<td>[96]</td>
<td>2003</td>
<td>SSCP</td>
<td>Exons 5–9</td>
<td>22.5% (11/49)</td>
</tr>
<tr>
<td>Liver</td>
<td>Mexico</td>
<td>[97]</td>
<td>1996</td>
<td>Dir. Seq.</td>
<td>Exon 7</td>
<td>18.7% (3/16)</td>
</tr>
<tr>
<td>Naso-pharynx</td>
<td>Mexico</td>
<td>[98]</td>
<td>2001</td>
<td>DHPLC</td>
<td>Exons 5–8</td>
<td>23.8% (5/21)</td>
</tr>
<tr>
<td>Penis</td>
<td>Brazil</td>
<td>[99]</td>
<td>1998</td>
<td>SSCP</td>
<td>Exons 5–8</td>
<td>28.6% (6/21)</td>
</tr>
<tr>
<td>Stomach</td>
<td>Brazil</td>
<td>[100]</td>
<td>1996</td>
<td>Dir. Seq.</td>
<td>Exons 5–8</td>
<td>32.1% (9/28)</td>
</tr>
</tbody>
</table>
correspond to differences in mutagenic processes that remain to be identified.

4.3. Colon cancer

Two studies have reported TP53 mutations in cancer of the colon and rectum, one from Brazil and one from Chile (Table 1). The pattern of mutations reported for these two studies differ significantly from the pattern in other areas (not shown, \( p < 0.001 \)). However, the difference is exclusively due to the Chilian study which reports a very unusual spectrum of mutation, while the data on the Brazilain patients are similar to those of the comparison groups. Most studies on cancer of colon and rectum report a high frequency of G:C > A:T transitions at CpG sites (45–50%) and low levels of deletions or mutations on A:T bases. This is the case for the Brazilian cohort, but in the Chilian series, there are only 20% G:C > A:T transitions at CpG sites, whereas deletions and mutations on A:T bases are over-represented (16% versus 8% and 26% versus 14%, respectively). The reasons for this unusual pattern of mutation are thus unknown and would need further investigation. In particular, there is no evidence that patients had a history of past exposure to well-defined risk factors.

4.4. Oesophageal cancer

The three studies on oesophageal cancer in LA have analysed squamous cell carcinoma (SCC) cases from high incidence areas in Southern Brazil and Uruguay (Table 1). Striking geographic variations in incidence rates, TP53 mutation prevalence and proportion of certain TP53 mutation types have been reported for SCC [61–64]. In Europe, high prevalence of mutations on A:T bases have been linked to exposure to metabolites of alcohol, and in high incidence areas of China, a high prevalence of transition mutations at G:C has been tentatively correlated with various dietary habits including exposure to nitrosamines and consumption of scalding hot tea. In most cancers of the upper-aerodigestive tract, transversions at G:C base pairs have been interpreted as possible “signatures” of tobacco carcinogens. Fig. 5 compares the proportion of these various types of mutations in the three studies from LA with those observed in high incidence areas of
Western Europe and central China. The pattern of mutations in SCC from LA tends to be more similar to the one observed in China than in Europe. This similarity may underline the role of comparable risk factors between the two areas, including in particular thermal injury inflicted by hot beverages. Interestingly, the proportion of A:T mutations in LA is intermediate between China and Europe, suggesting a possible contribution of alcohol to TP53 mutagenesis in SCC from LA. Further analysis on cohorts of patients with very well defined data on individual exposure should help to better identify the causes of these mutations.

4.5. Head and neck cancer

One study has been performed on head and neck squamous cell carcinoma (HNSCC) from Brazil (Table 1). The pattern of mutation described is characterized by a high frequency of insertions/deletions and G:C > A:T transitions (not shown), which is similar to the pattern observed in other countries. It has been previously reported that deletions and insertions leading to frameshift mutations were more frequent in a sub-group of patients exposed to both alcohol and tobacco, the two major risk factors for HNSCC [65,66]. It is thus possible that the combined effect of tobacco and alcohol favor the formation of frameshift mutations. However, no experimental evidence supports these observations.

4.6. Bladder cancer

The LA study on bladder cancer has been conducted on individuals exposed to tobacco and arsenic [67]. Tobacco smoking, occupational exposure to chemical dyes and inflammatory reactions to parasitic or other infections account for the majority of the bladder cancer cases in the world and specific TP53 mutation patterns have been linked to these exposures. G:C > A:T transitions at non-CpG sites are over-represented in patients exposed to tobacco and/or aromatic amines. These mutations cluster between codons 271 and 285 and in particular at codons 280 and 285 (4.3 and 4.9% of all mutations, respectively) which are in the same DNA sequence context (AGAG for codon 280 and AGAG for codon 285). It has been suggested that this sequence may represent a preferential target for specific carcinogens, such as aromatic amines [68]. In contrast, bladder tumors from regions of endemic parasitic infections show a high prevalence of G:C > A:T transitions at CpG sites [69], which is suspected to be an effect of nitric oxide (a common mediator of inflammation) on the rate of deamination of 5-methylcytosine. For arsenic exposure, no study is available in the IARC TP53 database on arsenic-exposed bladder cancer patients, but a case-control study of bladder cancer and drinking water arsenic performed in Western United States has found an increased risk of bladder cancer for smokers who ingest arsenic [70].

Authors from the Latin American study did not find any association between arsenic exposure and specific types of mutations, but found an increase in G:C > A:T transitions at CpG sites in smokers with >20 pack year of exposure and a significant association between a hotspot codon at position 273 and tobacco consumption. Five mutations were found at codons 280/285. Because of the epidemiological evidence linking arsenic and tobacco in the risk of developing bladder cancer, it would be interesting to further investigate if this unusual spectrum of mutation could be due to the combined effect of arsenic and tobacco.

4.7. Germline TP53 mutations

The only report of germline TP53 mutation in Latin America represents a very special situation where one specific mutation has been described in several unrelated children from Southern Brazil who were affected by childhood adrenocortical carcinoma. Interestingly, the mutation was described in 35 of the 36 analyzed cases and the patients were not related, as shown by intragenic polymorphic markers, ruling out a possible founder effect [71]. This situation is the only example of a TP53 mutation that would lead exclusively to one type of cancer. This mutation is a missense mutation at codon 337 (R337H) located in the oligomerisation domain of the protein. Functional analysis has shown that this mutant protein is pH-sensitive, i.e. inactive (mutant-like) at pH >7.7 and active (wild-type-like) at pH <7.7 [72]. The protein may thus adopt a mutant phenotype only under particular physiological conditions leading to a rise in intracellular pH. Although this effect does provide a
clear explanation for the tissue-specificity of the R337H mutant, this example illustrates the fact that mutant p53 protein function may depend on the cellular context. The reason why such a particular, familial mutation has not been found in other parts of the world deserves further attention.

4.8. TP53 polymorphisms

Over 14 different polymorphisms have been described in TP53 (http://www-p53.iarc.fr/Polymorphism.html). The most studied is the Arg/Pro polymorphism in codon 72, which impact on the coding sequence and may be associated with cancer risk. Eight studies have addressed this issue in Latin America: one in Argentina [73], one in Peru [74], one in Mexico [75] and five in Brazil [76–80]. All studies were done using PCR-based techniques and the Arg72 allele was described to be the most common in all populations except in the study from Peru, where the Pro72 allele was more frequent. Six studies analysed the association between codon 72 genotypes and papillomavirus-induced cervical cancer [73,75] and none of them supported the existence of an association with a risk of HPV-induced cancer. Three studies, all from Brazil, address the possible association between codon 72 polymorphism and risk of skin-cancer [78], oral squamous cell carcinoma [79] and thyroid cancer [80]. Studies have also been conducted to compare the frequency of three distinct polymorphisms (BstUI and MspI RFLPs in exon 4 and intron 6, respectively, and a 16 bp duplication in intron 3) in 114 Amerindians from different Brazilian Indian Tribes, 95 Euro-Brazilians and 70 Afro-Brazilians [81]. This analysis helped to identify populations of the same ethnic group. In one tribe, the Wai–Wai people, a rare haplotype was found which was only described in a Chinese study. TP53 polymorphisms are, therefore, interesting markers to understand population distribution in Latin America.

5. Perspectives: design of studies on TP53 mutations in LA

Studying cancer aetiology and implementing prevention measures are complex challenges in Latin American countries due to the inherent genetic complexity of the populations, the wide socio-economic discrepancies and, the rapidly changing trends in lifestyles throughout the continent, illustrated by the development of huge urbanized areas. Within this complex pattern, genetics can provide a useful tool to compare populations and assess gene-environment interactions that underlie cancer development. Analysis of TP53 mutations in normal and cancer tissues represents an affordable, easy to manage approach to gather important information on cancer aetiology. Formation of mutations in TP53 is the consequence of a succession of processes involving DNA damage, DNA repair and biological selection of mutants that confer a selective growth advantage. All these processes are, to some extent, dependent upon genetic susceptibility, nature of DNA damaging agents, local DNA sequence context and impact of the mutation upon protein structure and function. Thus, the pattern of TP53 mutation may show wide differences, not only among pathologies, but also among groups of subjects, depending upon their genetic background, environmental exposures, or socio-economic status. Therefore, it would be of great interest to develop systematic collections of tumor specimens (surgical specimens or biopsies) in studies comparing the position and type of TP53 mutations in patients positive- or negative for a specific risk factor. This case–case design would be more appropriate than most current studies that are based on the evaluation of mutation patterns in consecutive, unselected groups of patients. An example of the power of this approach is given in the recent study by Dai et al. [82], who have shown significant differences in the prevalence and pattern of TP53 mutations in matched, human papilloma virus 16 positive and negative patients with oral squamous cancer. We would like to advocate that close interactions between epidemiologists, pathologists and molecular biologists in the development of such studies might result in rapid and important advances in understanding the aetiology of common cancers in Latin America. The information from TP53 mutation pattern can be of particular interest in the context of studies addressing the statistical significance of polymorphisms in cancer susceptibility genes. Recent studies have shown that such polymorphism may influence not only the prevalence but also the type of mutations, in relation with susceptibility to specific DNA-damaging agents.
For example, a polymorphism at codon 399 in the DNA excision-repair enzyme XRCC1 is associated with higher frequency of adenine to guanine TP53 mutations in lung cancers of smokers, suggesting a role of this gene in the repair of cigarette smoking-induced DNA damage [83]. By means of a carefully matched study design, it may be possible to rule out the role of a number of confounding factors and to obtain significant results rapidly that would impact on the development of focused and appropriate prevention strategies.

References


