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IS THERE A BIOLOGICAL PLAUSABILITY FOR P53 CODON 72 POLYMORPHISM INFLUENCE On Cervical Cancer Development?

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SUMMARY

The interaction between HPV E6 and p53 protein is known as the most important event in HPV-associated carcinogenesis. Some *in vitro* studies suggested that p53 genetic variants are targeted for ubiquitin-proteasome degradation induced by E6 with different abilities. A common p53 variant at position 72 (R72P) has leaded to the development of several studies regarding its role on cervical cancer development. However, only few reports have shown an association between the Arginine (R) variant at position 52 of p53 and increased susceptibility to HPV E6 mediated degradation and thus to increased cancer susceptibility.

We revised the literature in order to obtain plausible data to discuss about these evidences for cervical cancer susceptibility. The more recent studies, including meta-analysis reviews, point out that there is no association of this p53 variant and cervical cancer development. This variant seems to be differently segregated in different ethnic/geographical locations; therefore, there might be a possible role of this genetic variant associated with a certain genetic background, which can explain why some studies reveal increased risk of cervical cancer development associated with Arginine p53 variant.

RESUMO

EXISTEM EVIDÊNCIAS BIOLÓGICAS DO PAPEL DO POLIFORFISMO NO CODÃO 72 DA P53 NA SUSCEPSTIBILIDADE

Para cancro do Colo do Útero

A interacção entre a proteína E6 do Vírus do Papiloma Humano (HPV) e a proteína p53 é considerado o principal evento no processo de carcinogénese no desenvolvimento de tumores associados à presença do Vírus do Papiloma Humano (HPV). Vários estudos sugerem que diferentes variantes da proteína p53 são induzidas degradação pela via proteolítica da ubiquitina com sensibilidades diferentes. Uma variante na posição 73 proteína p53 (R72P) tem sido exaustivamente estudada no cancro do colo do útero. Contudo, apenas alguns estudos demontraram uma associação entre a variante Arginina (R) e um aumento da sua degradação mediada pela E6 dos HPVs e que consequentemente estava associada a uma susceptibilidade aumentada para desenvolvimento de cancro.

Neste estudo foi revista a literatura existente em busca das evidências biológicas para o papel desta variante no desenvolvimento de cancro do colo do útero. Alguns estudos, incluindo meta-análises, demonstram que não existe associação entre a variante Arginina e o desenvolvimento do cancro do colo do útero. No entanto, estudos demonstram que esta variante parece estar distribuída de forma diferente de acordo com a localização geográfica/étnica, o que pode ajudar a explicar um possível papel desta variante de acordo com o *background* genético de determinadas populações, e que explica o porquê de alguns estudos encontrarem associação para o desenvolvimento de cancro do colo do útero.

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CERVICAL CANCER: A CRITICAL HEALTH PROBLEM WORLDWIDE

According to the World Health Organization (WHO) there were 500 000 new cases of cervical cancer in 2005, and if was responsible for over 260 000 deaths[1,2]. Currently cervical cancer is the second most common form of cancer in women and it represents a severe threat to women's lives. It is estimated that there are over 1 million women worldwide with cervical cancer and most of them have not yet been diagnosed or have no access to screening or treatment[2,3].

There are huge differences between developed or developing countries in what concerns to cervical cancer rdistribution. Cervical cancer has a high correlation between incidence and mortality rates, being extremely common in countries from Central and South America, Eastern Africa and South-East Asia (Figure 1)[2]. In developed countries, screening programs such as *Papanicolaou* smear and colposcopy have reduced the incidence of cervical cancer, with impact on health quality status of women[4]. Many countries have been trying to implement screening programs in their health services, while others seem to be waiting for the introduction of vaccines in the market to start preventing cervical cancer occurrence[3].

Cervical cancer etiology

Cervical cancer has been studied since the 19th century and the etiological factors were unknown until early 90s, when it was established that the persistent infection by the oncogenic types of the Human Papillomavirus (HPV) was the main etiological factor for its development[5-7].

Only a minority of HPV genotypes are able to infect cervical epithelium, although studies estimated that 30-60% of sexually active women might be infected with HPV,

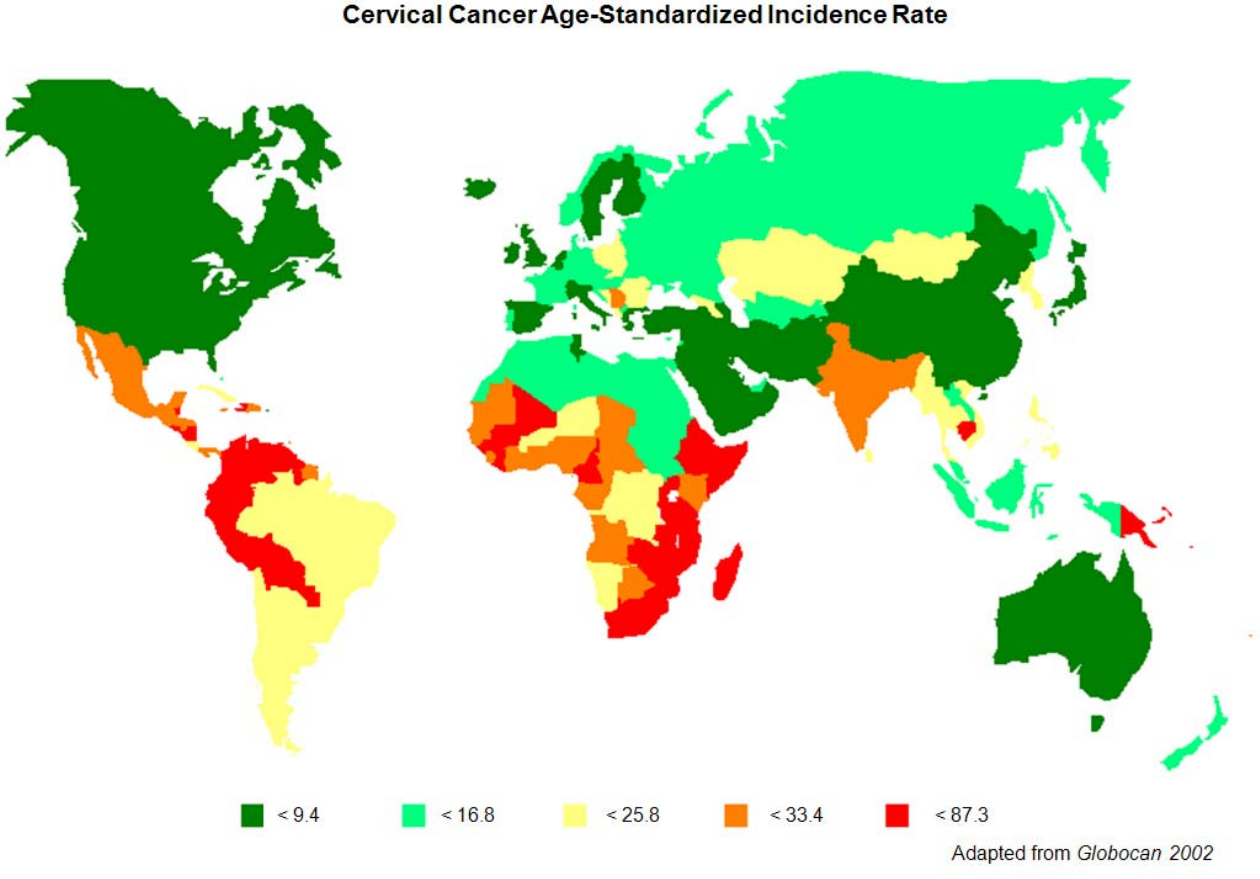

Fig. 1 – *Age-Standardized Cervical Cancer incidence Rate*

and most of them become infected shortly after beginning their first sexual relationship, with the highest prevalence seen in women < 25 years of age. Most of these infections will be transient and self limiting, however, persisting infection with the high-risk genotypes of HPV (types 16,18,31,33,35,39,45,51,52,56,58,59 and 68) is associated with over 99% of invasive cervical cancers[8-10].

Small lesions of the cervix may regress spontaneously and only a small percentage will progress into cervical intra-epithelial neoplasia (CIN)[11]. Depending on its severity, CIN lesions are histologically classified in 3 different groups (I, II and III), where the most severe can lead to invasive cervical cancer (ICC).

Several studies have been focusing on the role of risk factors that influence acquisition of persistent HPV infection or that mediate progression from pre-invasive lesions to cervical cancer. HPV is not sufficient for cervical carcinogenesis, and epidemiological studies have consistently associated the development of cervical cancer with measures of sexual activity (number of sexual partners, age at first sexual intercourse and sexual behaviour of male partners), parity (> 3 children), tobacco and alcohol consumption, co-infection with other sexually transmitted agents, as well as immunologic and host genetic factors[8,12-16]. Many efforts have been made to study the role of genetic factors in cervical cancer development, and currently there is still a great discussion on their potential.

HPV carcinogenesis

The high-risk HPVs access the basal cell layer of the cervical epithelium through microabrasions and establish a latent infection without clinical evidence of disease[3]. As these transient cells start to proliferate, viral DNA is maintained as an episome and is replicated in synchronization with the host DNA. In some cases the infection results in the integration of the viral episome into the host DNA providing a phenotypic modification on the cells. This integration frequently disrupts the HPV genome within the E2 region, leading to the loss of E2-mediated control of oncogene expression, therefore it has been suggested as a marker for

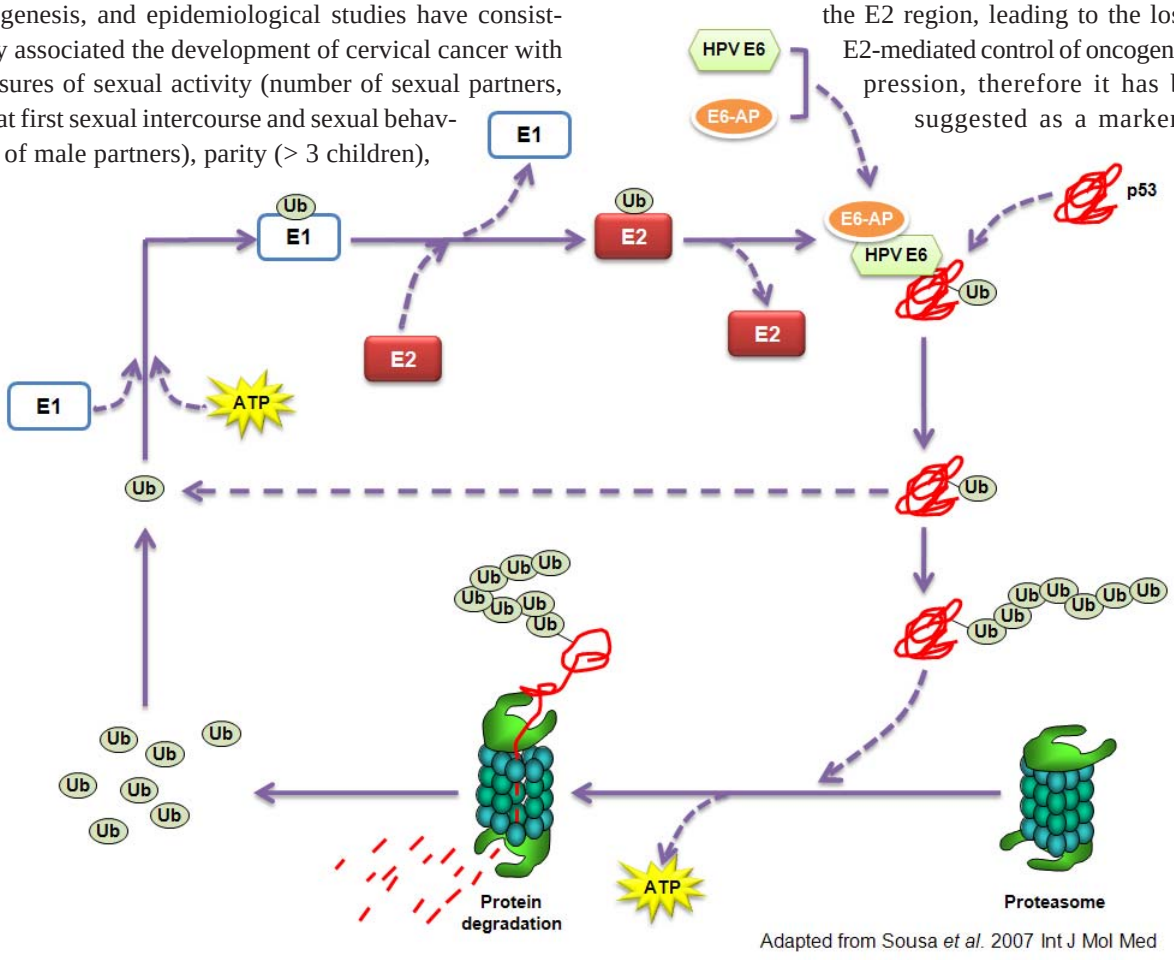

Fig. 2 – The HPV E6-mediated ubiquitin-proteasome degradation of p53
Ubiquitin (Ub) is a 76 amino acid protein highly conserved among eukaryotes involved in proteolysis and many other processes. Free ubiquitin is first activated by covalent attachment to E1 enzyme in an ATP-dependent reaction and subsequently, ubiquitin is transferred to an ubiquitin-conjugating enzyme (E2). In the end, high-risk HPV-E6 binds to the cellular ubiquitin-protein ligase E6-associated protein (E6-AP) that then binds to p53. Poly-ubiquitinated p53 is recognized and degraded by the proteasome and ubiquitin is regenerated.

cancer progression. The integration results in HPV E6 and E7 overexpression which promote genetic instability as a result of cell cycle de-regulation, by targeting the tumor suppressor protein p53 and the retinoblastoma protein p105RB, respectively, to degradation trough ubiquitin-proteasome system[17].

HPV E6 and p53

High-risk HPVs encode E6 oncoprotein that targets p53 to degradation through ubiquitin-dependent proteolysis. The *TP53* gene encodes a nuclear phosphoprotein (p53) with critical functions in the maintenance of cellular integrity[18,19]. The p53 is considered to be the *guardian of the genome* due to its role on cell cycle arrest, DNA repair activation and regulation of apoptosis. When a cell is exposed to some genotoxic stress (such as genetic alterations, viral infections or oncogenic activation), p53 arrests cell cycle in G1 phase and induces DNA repair, nevertheless in severe cases p53 targets cells to apoptosis[20]. If a mutation occurs, the protein might not execute its tasks accurately, and the G1/S phase checkpoint is escaped, leading to cell proliferation and the accumulation of genetic alterations that may cause cancer development[20]. In fact, *TP53* gene is mutated in 50-55% of all cancer cases and it has been suggested that in 10-15% of other cases it is inhibited or down-regulated[18,19].

The mechanism through which HPV interacts with p53 has been intensely studied in the past decade, and it is assumed that the way HPV E6 mediates p53 to degradation is the essential mechanism of HPV associated carcinogenesis[21,22]. Only E6 proteins from the high-risk HPVs are able to bind the cellular ubiquitin-protein ligase E6-associated protein (E6-AP) and therefore induce p53 degradation. This E6/E6_AP complex binds to p53 and promotes its interaction with the ubiquitin-conjugating enzymes (Figure 2)[23-26]. This process is extremely well synchronized and once started all targeted proteins will be forced to poly-ubiquitination leading to its degradation through the proteasome system. This mechanism through which p53 can be inactivated, has similar functions as any mutation on the *TP53* gene that could affect the normal functions of p53[23-26]. This was a major finding that proved that the degradation of p53 is sufficient to promote the genetic instability that leads to cell proliferation and to the development of neoplasia.

p53 and codon 72 polymorphism

Genetic polymorphisms have been described as having an important role on cancer development[27-35]. *TP53* has been one of the most studied genes, which lead to the identification of numerous single nucleotide polymorphisms (SNPs) on its sequence, some of them seem to interfere with protein structure or stability[36-47].

p53 is a 393 amino acid protein with different domains with important remarks on conformation, structure and function: an N-terminal transactivation domain (TAD; amino-acid 1-40), a proline-rich domain (PRD; residues 61-94) adjacent to the TAD with important conformation elements, a large DNA-binding domain (DBD; residues 100-300), a tetramerization domain (4D; residues 324-355) and a basic C-terminal domain (CTD; residues 360-393). Also remarkable is the existence of a nuclear localization signal (L) between the DBD and the 4D, and a nuclear export signal (E) embedded in the 4D. The amino acid sequence of p53 has several conserved serine, threonine and lysine residues that have potential regulatory significance. Moreover, the PRD has shown to be extremely important in the regulation of p53 stability and activity[48].

One of the most studied SNPs is located on exon 4 of the *TP53* gene. This SNP causes an amino acid replacement from Arginine (Arg) into Proline (Pro) at p53 codon 72[40,49]. This SNP is located at the PRD of the protein and several studies have confirmed that it might interfere with protein stability. Although there is no obvious impact of an arginine amino acid at this position[50], this polymorphism seems to confer two different structural and functional forms of p53[51-53]. These evidences lead to a large investigation on the role of this polymorphism in the development of different neoplasias such as cervical cancer[32,33,54-57], bladder cancer[58,59], colorectal cancer[60], breast cancer[61], nasopharyngeal cancer[62], ovarian carcinoma[34] and lung adenocarcinoma[63].

Storey et al suggested that the Arg p53 variant is seven times more susceptible to E6-mediated degradation than the Pro, and thus women with Arg/Arg genotype had increased risk for cervical cancer development[54]. Furthermore, *in vitro* studies revealed that the E6 protein seems to bind more efficiently to the Arg p53 variant at position 72, than the Pro, leading to an higher ability to promote degradation of p53 through the ubiquitin proteasome pathway[23,24]. Since Storey's results, the Arg/Arg genotype has been considered as a potential susceptibility marker for cervical cancer development. However, several other studies have attempted to corroborate this association unsuccessfully[32-35,64,65].

p53 codon 72 polymorphism and cancer: biological plausibility

The great majority of p53 mutations found in neoplastic cells occur with more frequency in the DNA binding do-

main, and usually differ from the wild-type in only one amino acid residue. These mutant proteins are frequently functionally inactive due to their incapacity to bind DNA[51].

Matlashewslki et al showed that the p53 codon 72 polymorphism leads to an aminoacid change which results in a structural change in the p53 protein[40]. The SNP is located on the proline-rich domain (PRD; residues 61-94), and the proline at residue 72 constitutes one of the five PXXP binding motifs in PRP[66]. Interestingly, the presence of arginine at this position does not seem to interfere with the wild type structure of the protein since they have similar ability to bind the p53 DNA recognition sequences[40]. Both protein variants are structurally wild type, although, recent studies have shown that there are subtle differences in their transcriptional activities and apoptosis activation[51]. The fact that p53 variants are not functionally equivalent, may be important in the management of patients with wild-type p53 tumors, depending on their p53 genotype.

Several data from *in vitro* and *in vivo* models suggest that not only a single mutation of a single residue within the TAD, PRD or CTD can induce a selective advantage to cells. The same studies refer that maybe the combined mutation of several modified residues could cause a more pronounced effect on p53 activity[67]. However, multiple mutations are not very common in spontaneous tumours, and therefore the role of single mutations on cancer susceptibility are likely to be more important when considering the interaction they can have with oncogenic proteins, such as the HPV E6 or E7[67].

The fact that the presence of an arginine at residue 72 could modify p53 activity has lead to the development of several studies regarding its role on cancer susceptibility. In fact, the arginine variant is more common in some populations, and therefore, several authors have studied the ethnic variations of this SNP in attempt to show that this could be a genetic marker for cancer susceptibility[35,50,68-70]. These studies revealed that the arginine variant is more common in Caucasian populations than African and Asiatic populations[35,50,68-72]. Beckman et al suggested that these genetic variants on p53 could represent a potential genetic marker for natural selection during intrauterine development and suggests that this p53 codon 72 polymorphism might balance natural selection[68]. Moreover, Sun et al and Bonafé et al have discussed about the potential role of the p53 codon 72 polymorphism in longevity, therefore acting as a genetic marker for natural selection[50,73]. These considerations might be of extreme importance, although, there are still some proteins with unexplained pathways that can interfere with p53 activity and the role of this SNP in cancer susceptibility.

CONCLUSION

The two p53 codon 72 variants seem to be differently degradated by HPV E6, therefore, there might be a biological plausibility for its association with development of cervical cancer. The more recent studies still confirm that the arginine variant is degradated with more efficiency than the proline, although, studies are not strong enough to prove this association. Some authors revealed that different HPV types can interact differently with p53 and this can be more important if we consider the association with different p53 variants.

The controversial data from Storey et al. is still being considered as important, and this controversy already lead to an increasing number of reviews on the subject. Up to date, it stills remains to establish the role of p53 codon 72 polymorphism on cervical cancer development[64,65,74]. A recently published meta-analysis review from our group considered all published papers on European populations regarding the role of this polymorphism in cervical cancer, considered geographical location as a marker for population genetic background, found that the arginine homozygous genotype is not a susceptibility risk marker for the development of both cervical intraepithelial lesions or invasive cervical cancer[35]. The same study also showed that there was a homogenous frequency of this genotype among European populations, and only populations from the edges of Europe have different frequencies. By comparing this data with the data from Beckman et al, it might be plausible that p53 codon 72 polymorphism has a distinct geographical distribution and therefore act differently as a genetic susceptibility marker[68]. Furthermore, future investigations require appropriate attention to design and methodological issues, mainly by considering larger sample size.

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