The value of immunohistochemical research on PCNA, p53 and heat shock proteins in prostate cancer management: a review

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This review addresses the significance of the expression of proliferating cell nuclear antigen (PCNA), p53 and some heat shock proteins (Hsps) in prostate carcinoma (PC). In fact, PCNA and p53 are two widely discussed tools in PC diagnosis, mainly because of the controversy regarding the significance of their expression during prostate cancer development and progression. At the same time, only few studies have shown the potential role of Hsps in carcinogenesis and their overexpression in pre-neoplastic and neoplastic lesions of the prostate. We briefly describe the physiological roles of Hsps in normal cells, and the significance of their immunohistochemical detection in PC as well as in pre-cancerous lesions of the prostate. We will also discuss the possible functional interactions of these molecules in both dysplastic and neoplastic cells.

Key words: Prostate cancer, prostatic intraepithelial lesions, PCNA, p53, heat shock proteins

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Prostate carcinoma (PC) is one of the most commonly diagnosed carcinomas in the world and is the second leading cause of cancer-related deaths in men (Boring *et al.,* 1992). This statistic has spurred greater interest in PC research as a means to find posssible diagnostic approaches and therapeutic interventions.

At the same time, PC is considered to be the most frequently undiagnosed or under-diagnosed tumour (Sakr *et al.,* 1993). Over the past 20 years, the overall survival rates for all stages of prostate cancer combined have increased from about 60% to up to 97%, probably due to its early detection (Giard *et al.,* 1998, Tricoli et al. 2004). For patient outcome prediction, it is important to establish the grading of the carcinoma, which is done according to Gleason's system (GS), based on a low magnification image of the cancerous gland (Gleason, 1966 and 1977). GS has two main advantages for clinicians: i) it is easy to learn and apply, and ii) it has been demonstrated to be correlated with the prognosis (Kramer *et al.,* 1980). Nevertheless, there are some drawbacks: i) the grade may be under- or overestimated when a minimal amount of malignant cells are present in the biopsy, and ii) the multifocality of the PC with a simultaneous variety of differentiation may complicate the evaluation of neoplastic gland size and shape. These problems have been described as especially important to identify grade 6, the most commonly diagnosed PC, since, in the past, GS grades from 5 to 7 were considered to be intermediate grades of differentiation; however, McNeal et al. (1990) and Epstein et al. (1996) have reported that GS 7 may be more aggressive than grades 5 or 6.

The spectrum of PC is additionally complicated by the existence of prostatic intraepithelial neoplasm (PIN), a fundamental step during prostate tumourigenesis (McNeal and Bostwick, 1986).

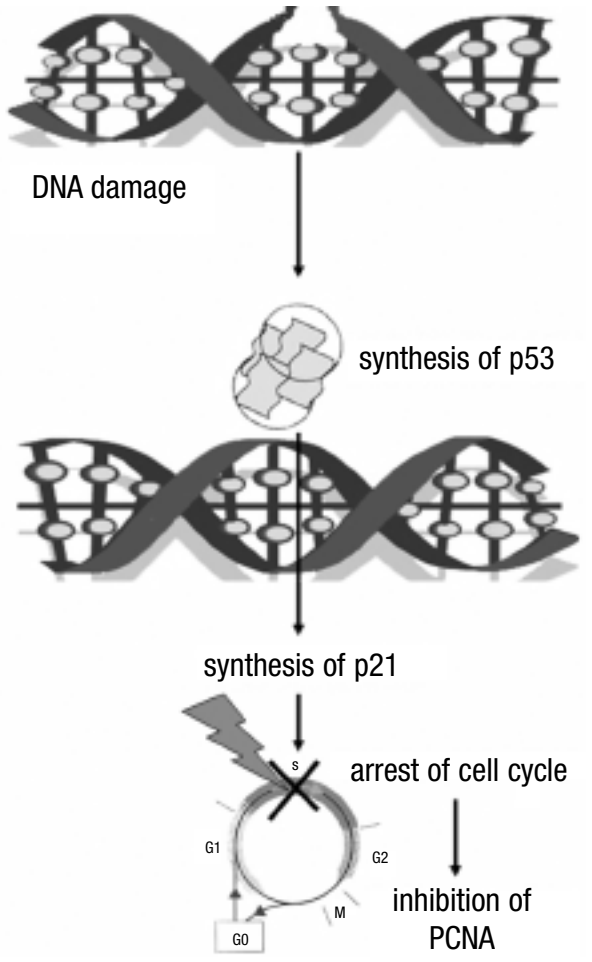

Figure 1. This scheme depicts the functional interaction between p53 and PCNA. DNA damage induces the synthesis of p53 which, in turn, determines p21 production and the arrest of the cell cycle, with consequent inhibition of PCNA.

PINs are well recognised as being pre-malignant (dysplastic) lesions of the prostate which were previously classified in three categories, depending on the level of dysplasia: mild (PIN-1), moderate (PIN-2) and severe (PIN-3). Nevertheless, more recent clinical evidence has prompted pathologists to further divide PINs into two groups, low- and high-grade PIN (respectively L-PIN and H-PIN). Although it has also been proposed to combine PIN-1 and PIN-2 as L-PIN (Montironi *et al.,* 1990; Crissman *et al.,* 1993; Jones and Young, 1994), it is now well recognised that PIN-2 and PIN-3 should be considered as H-PIN (Drago *et al.,* 1989; Epstein *et al.,* 1995).

Many researchers have hypothesised that the tumour progression from L-PIN to invasive carcinoma follows a predictable natural course (Bostwick and Brawer, 1987; Brawer, 1992). On the other hand, the molecular mechanisms at the base of this progression have not been well elucidated to date, although numerous papers have shown the expression of several biological markers during prostate carcinogenesis, identified their role during carcinogenetic steps, and tested them as diagnostic and prognostic tools (Sakr *et al.,* 2000; Alsikafi *et al.,* 2001; Prange *et al.,* 2001; Sakr and Partin, 2001).

In this review, we speculate on the clinical value of two well-known biological markers of carcinogenesis, PCNA and p53, as well as some novel biomarkers of PC progression, specifically Hsps, since only recently has their overexpression been shown in PC. Their role in normal cells and their possible involvement in prostate carcinogenesis are briefly described; finally, we postulate some possible molecular interactions among some of these proteins during the development and progression of PC.

PCNA and p53 interactions in normal cells

Proliferating cell nuclear antigen (PCNA) is a eukaryotic protein involved in DNA repair, replication, post-replication modifications and chromatin assembly. Active PCNA is a trimeric protein forming a sliding clamp around DNA. In immunohistochemical staining, PCNA is commonly found in G1- and G2-phases of the cell cycle. PCNA interacts with eukaryotic DNA polymerase to form a *replisome*. The interaction of cell cycle regulatory proteins, which make up a part of the p53 response pathway (i.e. p21 with PCNA), may be fundamental for cell survival, since it represents the link between the DNA damage response and the regulation of DNA replication and repair. When this mechanism is disrupted, mutations accumulate, genetic integrity is lost, and the cell cycle is deregulated (Jonsson and Hubscher, 1997).

p53 was first discovered and identified as a tumour suppressor gene (Lane and Crawford, 1979); later it was found to participate in almost all cell activities. The p53 tumour-suppressor protein controls the expression of the gene encoding the p21-regulatory protein of cyclin-dependent kinase. During p53-mediated suppression of cell proliferation, p21 and PCNA are involved in coordinating the repair of damaged DNA (Levine *et al.,* 1991) (Figure 1).

The p53 gene is frequently mutated in a number of malignant human tumours (Oren, 1992;

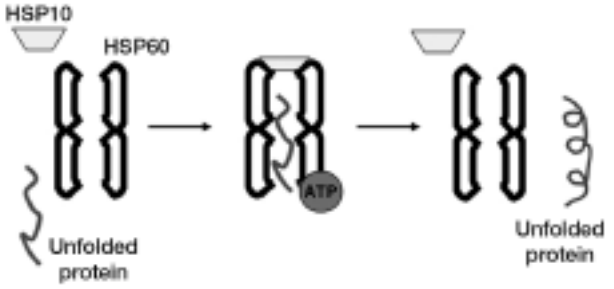

Figure 2. HSP60 and HSP10 form a complex inside mitochondria which acts in an ATP-mediated mechanism in protein folding.

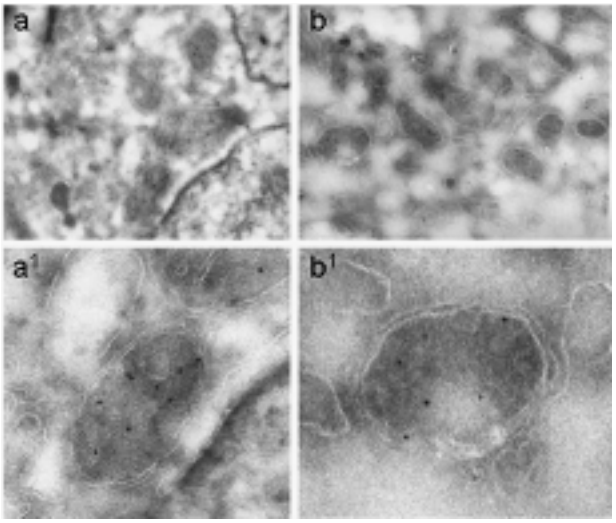

Figure 3. Transmission immunoelectron microphotographs showing intramitochondrial location of HSP60 (a) and HSP10 (b) in CHO cells. Higher magnifications show that only few molecules of HSP60 (a1) and HSP10 (b1) are present inside mitochondria.

Cappello *et al.,* 2002a). In the case of DNA damage, the abnormal p53 protein produced by a mutant gene is ineffective (and often more stable) than the wild-type protein; it becomes less sensitive to proteolysis and tends to accumulate in the nucleus, being easily detected by classic immunohistochemical techniques (Bruner *et al.,* 1993).

Heat Shock Proteins in normal and tumour cells

Hsps (heat shock proteins), discovered over 40 years ago (Ritossa, 1962), comprise several highly conserved families of functionally related proteins, most of which are affiliated with the large and diverse group of molecular chaperones that are defined by their capacity to recognize and to bind substrate proteins that are in an unstable or inactive state (Ellis, 1990). Among them, Hsp60, Hsp10 and Hsp90 are constitutively expressed in mammalian cells, while Hsp27 and Hsp70 are commonly induced by stresses (Garrido *et al.,* 2001). Hsps have different functions inside normal cells, such as prevention of the aggregation of denatured polypeptides (Burel *et al.,* 1992), interorganellar transport (De Nagel and Pierce, 1991), and antigen processing and presentation (Li *et al.,* 1997). Moreover, most Hsps have been proposed to regulate apoptosis. Hsp70, Hsp90 and Hsp27 are considered as antiapoptotic, since they bind to some pro-apoptotic molecules, including cytochrome c and Apaf (Li *et al.,* 1997). In contrast, Hsp60 and Hsp10 were firstly described as proapoptotic, although this opinion has been recently capsized (Gupta and Knowlton, 2005).

Hsp60 and Hsp10 are localized mostly in the mitochondria of normal eukaryotic cells. They interact in a two-step process of protein folding (Figure 2) (Richardson *et al.,* 1998). Protein folding is likely to occur within the cavity of cylindrical Hsp60/Hsp10 complexes in a so-called infinite dilution cage where no intermolecular interactions interfere with the folding process (Martin, 1997, Bukau and Horwich, 1998). The Hsp60/10 machine may also actively unfold kinetically-trapped intermediates, which creates a second chance of proper folding for the protein (Sigler *et al.,* 1998; Voos and Rottgers, 2002). The Hsp60/10 complex works in an ATP-dependent manner: a single protein undergoes multiple rounds of binding and is released from the complex before it reaches the final native state conformation (Bukau and Horwich, 1998). Due to the physiologically low amount of these Hsps in normal cells, research using immunohistochemistry is sometimes not sensitive enough, and more sophisticated techniques, such as immunogold-staining, may be necessary to study their cellular localisation in normal tissues (Figure 3). By contrast, their expression may be increased in a number of pathologic conditions, such as tumour cell tranformation (Cappello *et al.,* 2002b; 2003a; 2003b).

Although Hsp60 and Hsp10 have been recognised as key factors in protein folding within the mitochondria, it has now become evident that significant amounts of these chaperones may also be found in extra-mitochondrial locations in normal cells (Soltys and Gupta, 1996; Khan *et al.,* 1998; Sadacharan *et al.,* 2001). Both extra-mitochondrial Hsp60 and Hsp10 have been proposed to act as

anti-apoptotic molecules (Samali *et al.,* 1999; Knowlton and Gupta, 2003), although the role of the Hsp60/10 complex outside the mitochondria has not been fully elucidated to date. It is possible that the Hsp60/10 chaperone machine does not operate as a single unit, but as a part of a cell signalling network in the cytoplasm (Dubaquie *et al.,* 1998). It has also been reported that some Hsps, including Hsp60, Hsp70, and Hsp90 are capable of inducing the production of proinflammatory cytokines by the monocyte-macrophage system and the activation and maturation of dendritic cells (Tsan and Gao, 2004).

Involvement of Hsp60 and Hsp10 in the apoptotic pathway

Samali (1999) and Xanthoudakis (1999) were the first to demonstrate an interaction of Hsp60 and pro-caspase 3 in the mitochondria of HeLa and Jurkatt cells as well as the disruption of this complex and the dissociation of p20 and p17 (active caspase fragments) from Hsp60 with the simultaneous release of proteins (cytochrome c, adenylate kinase) from the intermembranous space of mitochondria. These authors hypothesised that Hsp60, due to its function as a 'foldase' chaperone, accelerates caspase-3 maturation by folding pro-caspase 3 into a protease cleavage-favouring conformation (Samali *et al.,* 1999; Xanthoudakis *et al.,* 1999). On the other hand, Gupta and Knowlton (2005) suggest that cytosolic Hsp60 could act as an anti-apoptotic protein, since Hsp60 associated with BAX sequester the latter away from the mitochondria thus preventing the onset of apoptosis. When the Hsp60 level was experimentally reduced, BAX protein was found to be synthesized and bcl-2 protein to be degraded, which, in coherence with translocation of BAX to mitochondria, contributed to cytochrome c release and apoptosis progression (Gupta and Knowlton, 2002; Kirchhoff *et al.,* 2002). In our studies, mutated p53 was only found in advanced carcinomas; by contrast, Hsp60 and Hsp10 overexpression was an early event in the development of prostate cancer (Cappello *et al.,* 2003c; Cappello *et al.,* 2003d). This leads us to query the mechanisms that allow the cell to overcome the cell cycle control in order to divide continuously despite the fact that the main tumour suppressor gene is not mutated and should, therefore, arrest the cell cycle and prohibit excessive proliferation. We postulate that this could be due to an interaction between the Hsp60/10 machine and p53, analogously to that already suggested for Hsp70. In fact, it has already been demonstrated that Hsp70 family members interact with the p53 C-terminal domain, playing a role in regulating the equilibrium of p53 translocation between the nuclear and cytoplasmic compartments (Wadhwa *et al.,* 1998; Wadhwa *et al.,* 2002); analogously, recently it has been proposed that other molecular chaperones, such as Hsp70, could be involved in the regulation of p53 localization (Zylicz *et al.,* 2001). In our opinion, the Hsp60/10 complex and p53 could also be considered in equilibrium for triggering apoptosis (Figure 4).

PCNA is currently the best marker in prostate cancer management

The differentiation and proliferative activity of tumour cells are important predictors of the aggressiveness of a carcinoma (Sakr *et al.,* 1993; Cher *et al.,* 1995). PCNA-positive immunostaining has been demonstrated to be related to the grade of the carcinoma (Visakorpi, 1992a; McNeal *et al.,* 1995). In particular, it has been postulated that the PCNA index can be used as an objective and quantitative means for evaluation of the malignancy of PC (Nemoto *et al.,* 1993; Naito *et al.,* 1994; Cappello *et al.,* 2003c). Moreover, the evaluation of the PCNA amount by immunohistochemistry may be particularly useful in diagnosis based on small-needle biopsies where the assessment of the grade may be difficult because the available tumour tissue is limited (Spires *et al.,* 1994; Limas and Frizelle, 1994).

PCNA has also been found to be expressed in PIN, supporting the hypothesis that these are preneoplastic lesions (Myers and Grizzle, 1997). In particular, research on PCNA has shown that proliferative activity in H-PIN is increased when compared to L-PIN and normal tissue (Myers and Grizzle, 1996; Xie *et al.,* 2000). The discovery that PCNA in H-PIN has an intermediate expression between that of a benign and carcinomatous prostate also supports the claim that H-PIN is a fundamental step in prostate carcinogenesis (Tamboli *et al.,* 1996). Moreover, a study on the proliferation index for the peripheral and the transitional zone of the prostate showed a significant difference, supporting the hypothesis of a biologic difference between carcinomas arising in these different zones (Grignon and Sakr, 1994). PCNA may

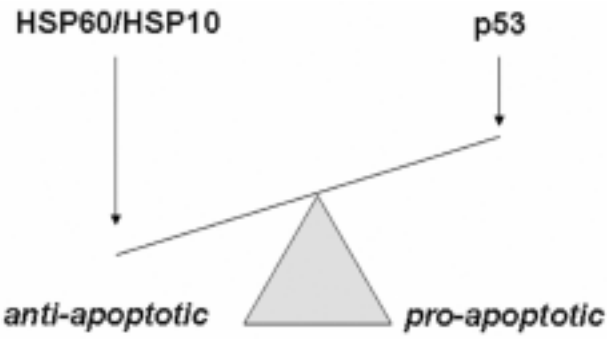

Figure 4. We hypothesise that the anti-apoptotic effects of the HSP60/10 complex may antagonise the pro-apoptotic effect of wild-type p53 during prostate cancer development.

help to predict prognosis, since the measurement of PCNA immunolabeling provides important prognostic information in T1-2 N0M0 tumours, in addition to the GS (Vesalainen *et al.,* 1994). Indeed, patients with a lower PCNA expression survive significantly longer than those with a higher one (Vesalainen *et al.,* 1994). PCNA levels have also been tested in post-radiotherapy prostate biopsies by correlating their staining with the clinical outcome, uncovering that PCNA negativity predicts an eventual recovery from the tumour, while PCNA positivity correlates with local failure (Crook *et al.,* 1994).

In the light of these data, PCNA immunostaining should be considered to be one of the best indices of PC behaviour. Although the proliferative activity may be variable in PC, it also seems to be correlated with p53 overexpression; indeed, PCNA has a significantly higher expression in tumours with p53-positive cells (Van Veldhuizen *et al.,* 1993; Kuczyk *et al.,* 1994; Leite *et al.,* 1999; Al-Maghrabi *et al.,* 2001; Cappello *et al.,* 2003d;). Consequently, p53 mutation could be an early event in at least a subset of PCNA-positive PC (Cappello *et al.,* 2003c).

The role of p53 mutation is still non-conclusive

Most authors believe that the mutation of the p53 tumour suppressor gene typically occurs in advanced stages of PC, but not in PINs (Navone *et al.,* 1993; Mottaz *et al.,* 1997; Myers and Grizzle, 1997; Cappello *et al.,* 2003d). Nevertheless, some authors have found p53 immunopositivity in H-PIN, with a pattern of expression similar to that found in PC, but significantly different from benign prostate neoplasms (Humphrey and Swanson, 1995; Tamboli *et al.,* 1998).

Concerning PC development and progression, many authors have demonstrated a correlation between p53 immunoreactivity and high grade GS (Kallakury *et al.,* 1994; Myers *et al.,* 1994), but this datum is still under debate (Berner *et al.,* 1995; Dorkin *et al.,* 1997; Karaburun *et al.,* 2001). The p53 expression has also been correlated with both increased histologic grade and presence of metastases, suggesting that p53 expression may be linked to the tumour behaviour (Thomas *et al.,* 1993; Hughes *et al.,* 1995; Sasor *et al.,* 2000; Karaburun *et al.,* 2001). In particular, the p53 gene mutations seems to be associated with advanced stages, presence of metastases, loss of ability to differentiate, and transition from androgen-dependent to androgen-independent growth (Navone *et al.,* 1993; Vesalainen *et al.,* 1994; Voeller *et al.,* 1994; Brooks *et al.,* 1996; Uzoaru *et al.,* 1998; Cheng *et al.,* 1999). In contrast, some authors have reported that p53 mutations are infrequent in both primary and metastatic PC, and they could not find a correlation between p53 mutation and tumour metastases (Dinjens *et al.,* 1994; Stattin *et al.,* 1996). Other authors have postulated that p53 reactivity could be an independent prognostic indicator between low- and intermediate-grade carcinomas (Shurbaji *et al.,* 1995; Bauer *et al.,* 1995). The lower p53 expression in PC has also been related to a lower Gleason score, as well as to a lower expression of other markers of tumour growth and behaviour in both transition and peripheral zones (Erbersdobler *et al.,* 2002), but these data were not confirmed (Sulik and Guzinska-Ustymowicz, 2002). Nevertheless, patients with negative p53 neoplastic tissue obtained from a prostate biopsy are likely to have a good prognosis in prolonged follow-up (Bauer *et al.,* 1995; Stattin *et al.,* 1996; Erbersdobler *et al.,* 2002).

Concerning therapy, p53 abnormalities have been associated with lymph node metastases derived from PC patients who have not undergone hormonal treatment (Eastham *et al.,* 1995). Apakama and co-workers (1996) have proposed that the combined detection of p53 and bcl-2 overexpression predicts hormone resistance in PC. Also, an abnormal p53 finding in early and hormone refractory disease may be related to PC progression (Aprikian *et al.,* 1994; Henke *et al.,* 1994; Heidenberg *et al.,* 1995; Koivisto and Rantala, 1999). The p53 status

could also help to circumscribe a group of patients before radiotherapy, since p53 inactivation could produce radio-resistant tumours (Stattin *et al.,* 1996). At the same time, in other studies, p53 protein overexpression was not predictive of outcome in patients treated with radiation therapy (Incognito *et al.,* 2000). Another study showed that the accumulation of p53 detected by immunohistochemistry was an independent prognostic factor in patients with PC during follow-up (Borre *et al.,* 2000).

In our opinion, the wide discrepancy of p53 mutation in the reported studies may depend not only on the type of tumour, but also on the region of the tumour included in the study. Indeed, a heterogeneous topographical distribution of the mutant p53 has been observed, and analysis of the topographical distribution of the mutant p53 protein shows remarkable differences (Mirchandani *et al.,* 1995). P53-positive nuclei have also been noted in basal cells of benign glandular acini in regions flanking the tumour, supporting the notion that the mutation of p53 might play a role in the prostate carcinogenesis (Kallakury *et al.,* 1994). The mutation of p53 has also been associated with increased angiogenesis in PC (Yu *et al.,* 1997) as well as with the presence of post-atrophic hyperplasia, one of the patterns of prostatic atrophy considered to be a precursor of PC (Tsujimoto *et al.,* 2002). Finally, sarcomatoid carcinoma may develop from a high-grade PC if associated with a progressive accumulation of p53 (Delahunt *et al.,* 1999).

In conclusion, while many studies have demonstrated a strong relationship between p53 nuclear positivity and disease-specific mortality, they seem to be non-conclusive. We agree with Visakorpi et al. (1992a; 1992b) who hypothesised that p53 accumulation may confer a proliferative advantage for PC cells and may define a small subgroup of highly malignant carcinomas.

May Hsps detection help in the management of prostatic cancer?

An increased expression of several Hsps has been reported in a number of tumours (Mosser and Morimoto, 2004; Ciocca and Calderwood, 2005). Some Hsps were found to be over-expressed in breast cancer, hepatomas and neuroectodermal tumours (Soti and Csermely, 1998). In particular, Hsp27 has been reported to be overexpressed in breast (Ioachim *et al.,* 2003) and endometrial (Zagorianakou *et al.,* 2003) carcinomas as well as in leukemia (Kasimir-Bauer *et al.,* 1998). Increased expression of Hsp70 has been reported in high-grade malignant tumours including breast, endometrial, lung, pancreatic, renal, bone, colon carcinoma and blood neoplasm (Soti and Csermely, 1998; Gaudin *et al.,* 1999; Zylicz *et al.,* 2001; Moalic-Juge *et al.,* 2002; Myung *et al.,* 2004). Hsp90 has been shown to be overexpressed in lung (Zhong *et al.,* 2003) and breast carcinomas (Neckers, 2002). Overall, the high expression of these Hsps have been associated with metastases, poor prognosis and resistance to chemotherapy and radiation therapy (Ciocca *et al.,* 1993; Fuqua *et al.,* 1994; Vargas-Roig, 1998; Cornford *et al.,* 2000).

We recently studied the expression of two Hsps in some different carcinogenetic models, the dysplasia-carcinoma sequence of the exocervix and colon (Cappello *et al.,* 2002b; 2003a; 2003b). This study showed an accumulation of cytoplasmic Hsp60 and Hsp10 in tumour cells and in the dysplastic elements, where they became easily detectable by immunohistochemistry when compared to controls. Such results have been confirmed by other studies (Yang *et al.,* 2004; Castle *et al.,* 2005).

A number of papers have delved on the role of the overexpression of several Hsps in prostate tumour cells *in vitro* (Harvey *et al.,* 2002; Sreedhar and Csermely, 2004). Indeed, it has been postulated that the overexpression of some Hsps, specifically Hsp27, Hsp70 and Hsp72 could become targets for multimodal anticancer treatments and for antitumoural immunity stimulation (Roigas *et al.,* 2002; Lipinski *et al.,* 2005). Only a few studies concern the expression of Hsps during prostate carcinogenesis *in vivo*. Hsp27 is one of the most studied Hsps in PC. Storm *et al.,* (1993) investigated the diagnostic and prognostic significance of Hsp27 in a series of PCs, finding that the expression of this molecule does not have any significance. In contrast, Cornford et al. (2000) demonstrated that Hsp27 expression is an independent predictor of clinical outcome for PC. An overexpression of Hsp90 and Hsp60 has also been found in PC (Alaiya *et al.,* 2000). Since PCs are hormone-dependent tumours that respond to drugs which prevent binding of androgens to their receptors (AR), and since AR exists in a complex with Hsp90, it has been suggested that inhibitors of Hsp90 may represent a novel strategy for the treatment of patients with PC (Solit *et al.,* 2003). However, clin-

ical trials to test this hypothesis have yet to be completed.

We explored the expression of both Hsp60 and Hsp10 during prostate carcinogenesis, finding an early overexpression of these molecules. A high cytoplasmic positivity for both of these markers was present in PIN lesions as well as in carcinomas. Moreover, their overexpression was not correlated with PCNA and p53 immunopositivity, since PCNA grew from PIN to carcinoma and p53 mutations were commonly reported as a late event (Cappello *et al.,* 2003d). Nevertheless, their prognostic and therapeutic roles still need to be evaluated.

Conclusions

The immunohistochemical evaluation of PCNA is currently considered to be a very useful index of PC behaviour. Since PCNA also has a significantly higher expression in tumours with p53-positive cells, the simultaneous validation of the expression of both markers may serve as a useful tool in the process of therapeutic strategy planning. By contrast, the significance of p53 status alone is still doubtful, although the presence of its mutation may help to make a prognosis. Finally, a few studies have investigated the prognostic role of Hsps overexpression and are as yet still inconclusive. Nevertheless, the analysis of this body of literature may allow us to postulate new hypotheses. Indeed, since a number of papers reported a possible involvement of Hsp60 and Hsp10 in the process of apoptosis, it is tempting to suggest a possible link between the Hsp60/10 machinery and the process tumourigenesis. Indeed, although the expression of Hsps should be a protective mechanism for stressed cells, we support the thesis that their overexpression during carcinogenesis may influence cell growth negatively and interfere with apoptotic pathways. This hypothesis, if confirmed *in vivo*, could help us to identify some Hsps, among which is the Hsp60/10 complex, as a molecular target for antitumoural therapies in multimodal treatment approaches.

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