Chapter 3

The Role of Haptoglobin and Its Genetic Polymorphism in Cancer: A Review

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1. Introduction

1.1. The acute phase response (APR) and haptoglobin (Hp)

Acute phase response is a stereotyped innate nonspecific reaction of the body proceeding specific immune reactions. It´s a systemic homeostatic reaction of the organism to local and or systemic disturbances caused by infections, tissue injury, trauma, immunologic disorders and neoplasias (Ron D *et al* 1990, Trautwein C *et al* 1994, Gruys E *et al* 2005). Proinflammatory cytokines are released at the place of tissue injury, diffuses locally and systemically to the vascular system and activates receptors on different target cells resulting in the activation of hypothalamic-pituitary-adrenal axis (HPAA), results in the production of growth hormone secretion and induces changes in the concentration of several plasma proteins (Ron D *et al* 1990, Trautwein C *et al* 1994, Gruys E *et al* 2005).

These acute phase proteins (APPs) can be positive (higher levels in plasma) or negative (lower levels in plasma). The alteration on mRNA in hepatocytes is due to simultaneous influence of systemic cytokines (IL1, IL6 and TNFα), glucocorticoids and catecholamines (Bowman BH 1993, Ron D *et al* 1990, Trautwein C *et al* 1994).

Haptoglobin together with fibrinogen, α-globulins with antiprotease-activity and lipopoly-saccharide binding protein belong to the group of positive APPs that increase 3-fold in mammals (Trautwein C *et al* 1994, Gruys E *et al* 2005).

Haptoglobin (Hp) is an acute phase α2 plasma glycoprotein that is a component of innate immunity, which also may influence acquired immunity. Through both types of immunity,

Hp is involved in the pathogenesis of tumours and infections (Langlois MR and Delanghe JR 1996, Van Vlierberghe H. *et al* 2004, Levy AP *et al* 2010).

2. Haptoglobin (Hp) synthesis, gene structure, variants and its geographic distribution

Haptoglobin locus is on chromosome 16q22 and its gene is transcribed and translated into a single peptide which undergoes post-translational processing resulting in a smaller α-chain and a longer β-chain linked by disulphide bridge (Giblett ER 1968, Langlois MR and Delanghe JR 1996, Wicher KB and Fries E 2007).

In 1955, Smithies, using thin layer starch gel electrophoresis identified the three phenotypes of Hp (1-1, 2-1, 2-2), corresponding to the α-chain length interindividual genetic variation.

The three genotypes are shown in electrophoresis in polyacrylamide gel electrophoresis (PAGE) (fig 1).

This genetic variation results from an internal duplication of a gene segment (exons 3 and 4), correspondent to α-chain of Hp1 giving rise to a larger one, characteristic of Hp2 (Maeda *et al* 1984, Wicher KB and Fries E 2007).

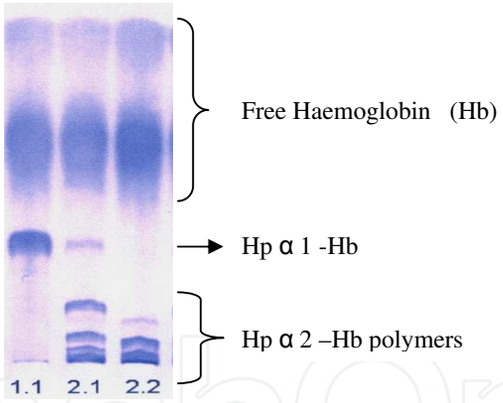

Figure 1. Typical pattern of haptoglobin bands in a polyacrylamide gel electrophoresis (PAGE). Shown are the phenotypes: Hp 1-1, is characterized by a fast migration band; Hp 2-2 is characterized by slower multiple bands; Hp 2-1, characterized by a mixed pattern of two allelic forms. The ultrafast bands are no haptoglobin bound haemoglobin chains (Linke RP 1984, Guerra J *et al* 1997).

This inter-individual variation is found only in humans and aroused about 100,000 years ago in Southeast Asia. The great majority of other mammals have only one band corresponding to the human Hp1-1, except the sheep, deer and cows (Ruminantia), which have only slow bands corresponding to Hp2-2 (Bowman BH and Kurosky A 1982, Wicher KB and Fries 2007).

The appearance of Hp2 can represent an important evolutionary genetic contribution for interpopulational diversity in human pathology (ER Giblett 1968, Maeda et al 1984, Wicher KB and Fries 2007). This allele is predominant in the human population (about 80% in some

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ethnic groups) and Hp1 allele is more predominant in populations subjected to malaria burden (Giblett ER 1968, Langlois MR and Delanghe JR 1996, Wobeto VP et al 2008, Levy AP et al 2010).

In close linkage with haptoglobin gene there is another one, 2-2 Kb downstream from Hp locus, coding for Hp related (Hpr) plasma protein with 91% sequence identity to Hp1. The α-chain of Hpr contains a hydrophobic signal peptide that may explain its association to lipoprotein particles (HDL) or membranes (Kuhajda FP *et al* 1989 a, b).

3. Haptoglobin locals of its synthesis and regulation

The Hp gene is expressed primarily in hepatocytes and more recently has been described in other locations, such as keratinocytes, airway epithelial cells of lung, leucocytes, fibrocytes, adipocytes and endometrial cells, particularly during the blastocyst implantation (Friederichs WE *et al* 1995, Olson EG *et al* 1997 Wang *et al* 2005, Shaw JL *et al* 2007, Yang F 2000 *et al*, Larsen K *et al* 2006, and Theilgaard-Mönch K *et al* 2006).

Haptoglobin synthesis is induced by cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1) and tumour necrosis factor (TNFα) released by the macrophages, after activation of the innate immunity cells by PAMPs (pathogen associated molecular patterns) such as lipopolysaccharide, a TLR4 (Toll Like Receptor) activator (Raynes JG et al 1991, Kaisho T and Alkira S 2002).

Glucocorticoids and catecholamines activate haptoglobin synthesis previously induced by interleukins (increased), whereas insulin exerts an opposite action, despite the presence of these interleukins (Ron D et al 1990, Campos SP and Baumann H 1992 Nascimento CO et al 2004, Gruys E et al 2005 and XiaLi-xin et al 2008). Hypoxia also induces indirectly its synthesis (Wenger RH et al 1995, Oh Mi-Kyung et al 2011).

4. Haptoglobin metabolism, actions and respective mechanisms

Haptoglobin has a pronounced anti-inflammatory action, which is explained by its ability to bind to heme of haemoglobin, forming a Hp-Hb complex. This is characterized by stability and high affinity to its specific type scavenger receptor (CD163) located in the hepatocyte and the phagocytic-type cells such as circulating monocytes, resident macrophages (M2) and liver Kupffer cells. The CD163 is a membrane protein 130-kDa, whose long extracellular region has nine cysteine-rich domains of scavenger-type receptor (Graversen JH *et al* 2002, Nielsen MJ *et al* 2010, Akila P *et al* 2012). The expression of receptors (CD 163), Hp and hemoxygenase (HO-1), is strongly activated by antinflammatory cytokines, such as interleukins (IL6, IL10), growth factors (M-CSF) and glucocorticoids (Moestrup SK and Møller H 2004). In contrast CD 163 is down regulated by IL4 and GM-CSF, Interferon γ and TNF (Nielsen MJ *et al* 2010, Vallelian F *et al* 2011 and Akila P *et al* 2012).

After binding to its receptor the Hp-Hb complex is internalized in the form of endosome, followed by fusion with lysosomes, proteolysis of globin and intracellular release of heme to

hemoxygenase (HO-1) with concomitant formation of biliverdin that is converted in bilirrubin, CO (carbon monoxide) and release of iron to ferritin where is compartmentalised (Graversen JH *et al* 2002, Nielsen MJ *et al* 2010, Vallelian F *et al* 2011, Akila P *et al* 2012).

The small protein Hp1-1 is excreted in the urine when occurs kidney damage, however, the Hp2-1 and Hp2-2 are always retained (Fagoonee S 2005). The clearance of free haemoglobin (Hb) after intravascular haemolysis by the haptoglobin is higher in individuals carrying the Hp1 allele (Giblett ER 1968, Langlois MR and Delanghe JR 1996, Moestrup SK and Møller H 2004, Nielsen MJ *et al* 2010, Vallelian F *et al* 2011, Akila P *et al* 2012).

The free Hb has the ability to catalyse the formation of hydroxyl radicals (OH·), from the hydrogen peroxide, with highly damaging effects to the cellular constituents and extracellular macromolecules (Sadrzadeh SMH 1984, Gutteridge JMC 1987).

The Hp-Hb complex, reduces the loss of Hb in urine and concomitant loss of iron and its transport is done mainly to the liver. As a result, the removal of free Hb has much important consequences for the organisms, preventing renal injury that may occur when the free Hb passes through the glomerular filter (Fagoonee S *et al* 2005). Also Hp prevents the promotion of free radicals and its accumulation in endothelial cells, catalysed by heme, where it causes vessel injury (Nielsen MJ *et al* 2010, Vallelian F *et al* 2011 and Akila P *et al* 2012). However, there is a great variability in these responses, which is dependent of Hp polymorphism having individuals with the Hp2-2 a lower antioxidant capacity than those with other phenotypes. Furthermore at the extra-vascular interstitial level, the antioxidant capacity of carriers of Hp2-2 is lower, because of its higher molecular mass that restricts its extravascular diffusion (Langlois MR and Delanghe JR 1996, Van Vierberghe *et al* 2004, Fagoonee S. *et al* 2005, Levy AP *et al* 2010).

Levels of haptoglobin in plasma or serum are lower in healthy infants than adults whose concentrations are between 0.38 and 2.08g/l (Langlois MR and Delanghe JR 1996). These steady state levels are consequence of haptoglobin half-life of 3.5 days and Hp-Hb complex of ten minutes (Sadrzadeh SMH and Bozorgmehr J 2004). The Hp can also be detected in urine and other organic fluids (Langlois MR and Delanghe JR 1996, Sadrzadeh SMH and Bozorgmehr J 2004). The half-life of Hp-Hb complex is phenotype dependent being Hp1-1 shorter than Hp2-2 (Levy AP *et al* 2010). Plasma concentrations are also phenotype dependent, people with Hp1-1 having the highest, Hp2-1 intermediate and Hp2-2 lesser concentrations in plasma (Langlois MR and Delanghe JR 1996).

Haptoglobin levels are quantified by chemical and immunochemical methods, from these the most utilised are the immunonephelometric and immunoturbidimetric methods that are automated (Langlois MR and Delanghe JR 1996, Sadrzadeh SMH and Bozorgmehr J 2004).

The haptoglobin polymorphism is most commonly determined by starch or polyacrylamide electrophoresis (Fig 1). When plasma levels are lower than 0.10g/l PCR based assays are utilised (Linke RP 1984, Langlois MR and Delanghe JR 1996, Guerra A *et at* 1997, Levy AP *et al* 2010). More recently in both, levels measurement and phenotype, are utilised new proteomic methods based on two dimensional gel electrophoresis and quantitative determination by mass spectrometry (MALDI-TOF-MS and SELDI-TOF-MS) methods (Gast M-C *et al* 2008, Chen C-B *et al* 2008).

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The Hp-Hb complex also binds nitric oxide or nitrogen monoxide (NO), produced by cytokine activated macrophages, thus preventing their physiological and pathological actions (Langlois MR and Delanghe JR 1996, Azarov I *et al* 2008, Alayash A 2011). Also this action is phenotype dependent, because Hp2-2/Hb complex scavenge more NO than Hp1-1/Hb due to its longer half-life (Azarov I *et al* 2008, Levy AP *et al* 2010, Alayash A 2011).

The Hp is also a potent endogenous inhibitor of prostaglandin synthesis, resulting in anti-inflammatory action. The inhibitory effects of Hp2-2 and Hp2-1 are less pronounced than those of Hp1-1 (Kendall PA *et al* 1979, Langlois MR and Delanghe JR 1996, Saeed SA *et al* 2007).

Haptoglobin has also bacteriostatic effects, because the capture and compartmentalization of the iron of Hb made it no longer available for bacterial growth. The Hp 2-2 is more efficient than the other phenotypes in this action against S*treptococcus*. There are also microorganisms that can remove iron from the Hp-Hb complex (Langlois MR and Delanghe JR 1996, Weinberg ED 1996, Van Vlierberghe *et al* 2004).

The role of Hp in angiogenesis has been identified as one of the factors for modulation of differentiation and proliferation of endothelial cells during the formation of new vessels (Cid MC *et al* 1993, Park SJ 2009). Free Hb can promote indirectly carcinogenesis through the iron that is necessary for cell growth. The withholding of iron inhibits cell growth and depresses the immune system (Langlois MR and Delanghe JR 1996, Weinberg ED 1996).

The local increased concentration of Hp in chronic inflammatory processes is important for the ischemic tissue reparation, promoting collateral vessel formation. Of the three genetic forms Hp2.2 is the most angiogenic (Cid MC *et al* 1993).

In resident tissues macrophages (M2 type), carbon monoxide (CO) resulting from the intracellular degradation Hp-Hb complex appears to be involved in anti-inflammatory effects of interleukin 10 (IL-10). The suppression of these immune and inflammatory responses results from its ability to decrease the antigen presentation and cytokine synthesis. This mechanism of regulation is more active in patients with the Hp1-1 phenotype that has a greater clearance of their complexes with their CD163 receptors present on monocytes, than for those carrying the phenotype Hp2-2 (Nielsen MJ *et al* 2010, Vallelian F *et al* 2011 and Akila P *et al* 2012).

In macrophages, after the endocytosis of the Hp-Hb complex and CD163, increased levels of cytoplasmic iron ocurr, inducing the synthesis of ferritin, a primary iron storage, which can subtract it from inflammation site (Cozzi *et al* 2004). The activation of the CD 163 also induces a signal mediated by protein tyrosine kinase, leading to the secretion of anti-inflammatory cytokines and giving rise to a connection between the clearance function of the Hp and their immunomodulatory functions (Van Vlierberghe *et al* 2004, Guetta *et al* 2007, Nielsen MJ *et al* 2010, Vallelian F *et al* 2011 and Akila P *et al* 2012).

Haptoglobin can also modulate the immune response by binding to receptors on immune cells, such as CD22 on B lymphocytes and β2 integrin (CD11b/CD18) in neutrophils or LFA-1 (lymphocyte function associated antigen-1) in T lymphocytes (EL Ghmati SM *et al* 1996, Giannoni E *et al* 2003, Bottini N *et al* 2005). The Hp may bind to neutrophils, inhibiting NADPH oxidase activation and the production of reactive forms of oxygen associated with inflammation (Moestrup SK and Møller H, 2004, Guetta *et al* 2007).

Changes of the ratio of lymphocytes Th1 and Th2 are important for the determination of susceptibility to viral and parasitic infections, for allergies, for antitumor responses and autoimmunity (Gleeson ME 2006, Clerici M *et al* 1998). It was shown that Hp plays a modulating role of the Th1/Th2 ratio, promoting a Th2 dominant response, which is more pronounced in patients with the Hp1-1 and 2-1 phenotypes (Bottini N *et al* 2005, Guetta *et al* 2007).

The objective of this chapter is to review the scientific evidence of haptoglobin role, as an immune innate protein in the several aspects of cancer biology and its possible clinical importance as a genetic and a circulating biomarker for that pathology.

The methodology for this review is based in the search in the literature of relevant studies in cancer concerning both the circulating levels of haptoglobin (including the recent described fucosylated glicans), haptoglobin related (Hpr) and the genetic variation studies, in the Medline Data Bases and the related papers, since the first reports in the sixties of the last century until actuality. A special attention will be a consideration of cancer associated with human papillomavirus (HPV). The keywords used in the search will be haptoglobin, cancer genetics, circulating levels and clinics.

5. Haptoglobin (Hp) and its related pathway as biomarkers in cancer

Genetic polymorphism of haptoglobin leads to its functional differences resulting in interindividual variation of the related intermediate phenotypes at the different biological levels that can constitute circulating biological markers of clinical importance not only for the susceptibility but also for the prognostic and response to treatment at the diverse levels of natural history of the neoplasia disease (Bicho MC 2011). We will review by organs and systems the studies that evidence those aspects.

In table 1, we describe the association of Hp polymorphism in several populations with CNS head and neck, lung, blood and skin malignancies.

For the central nervous system it was demonstrated that haptoglobin is transcribed and expressed (proteomic methods) in human glioblastome cells and it is significantly associated with greater plasmatic levels in the higher grades compared with lower ones and those of control subjects (Sanchez DJ *et al* 2001, Kumar DM *et al* 2010). Also it was demonstrated that Hp increases in vitro glioblastome cell migration (Kumar DM *et al* 2010), table 1.

Head and neck squamous cell cancer (HNSCC) is a term that collectively refers to cancer of oral cavity, salivary glands, larynx and pharynx. After a first study the authors whose objective is discovery of circulating biomarkers associated with those tumours, demonstrate in HNSCC in general and nasopharynx in particular, the haptoglobin overexpression, in a stage and tumour volume dependency (Chen C-B *et al* 2008, Lee CC *et al* 2009). Another group confirmed the involvement of the Hp phenotype in infection with Epstein-Barr virus (EBV) that is associated with nasopharynx carcinoma (Speeckaert R *et al* 2009).

In the eighties several studies of association with cancer of acute phase proteins in particular haptoglobin were done, that is the case for the lung cancer in 309 Swedish patients where the

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Neoplasia	Population (N) (Control/Neo)	Conclusions	References
Human glioblastome	N=26/96 India	Hp2 allele higher grades	Sanchez DJ *et al* 2001; Kumar DM *et al* 2010
Head/neck squamous cell cancer	N=135/163	Hp2 allele tumour volume dependency	Chen C-B *et al* 2008
	N=134/49 Taiwan		Lee CC *et al* 2009
Nasopharynx carcinoma	N=918/208 Belgium	Hp1-1 and Hp 2-1 less prone to positive EBV serology	Speeckaert R *et al* 2009
Lung cancer	N=309 Sweden	Hp1 allele more frequent in adenocarcinoma in females	Beckman G *et al* 1986
Acute lymphoid leukemia	N=2331/110 Sweden	No association	Fröhlander N and Stendahl U 1988
Leukemias	N= 211 Israel	Associated Hp1-1 with ALL, AML, CML	Nevo S and Tatarsky I 1986
Acute myeloid leukemia	N=197/188 Brazil		Campregher PV *et al* 2004
ALL, AML, CML, IgA ML	N=134 Australia	Higher Hp 1-1 association	Mitchell RJ *et al* 1988 Germinis A et al 1983
Squamous cell carcinoma (SCC)	N=300 Belgium	Hp phenotype 1.1 more prone to develop SCC in kidney transplanted patients	Speeckaert R *et al* 2012
Kaposi´s sarcoma		Hp1.1 phenotype more prone	Speeckaert R *et al* 2011

Abbreviations: ALL-Acute lymphatic leukaemia; AML- Acute myeloid leukaemia; CML- Chronic myeloid leukaemia; CLL-Chronic lymphatic leukaemia; ML- Myeloma.

Table 1. Haptoglobin and Cancer: Various Tumours.

Hp1 allele is more frequent in women with adenocarcinoma (Beckman G *et al* 1986). More recently other group confirmed the association of local higher levels of the Hp l expression in pulmonary adenocarcinomas in opposition to squamous cell carcinomas (SCC) and small cell carcinomas (Abdullah M 2009).

There are five references for blood malignancies such as acute and chronic lymphoid leukemia and acute myeloid leukemia from three different ethnic groups Sweden, Israel and Brazil (Caucasians and Afro-descendants) and only one sample of Ashkenazy Jews (Germinis A *et al* 1983, Nevo S and Tatarsky I 1986, Mitchell RJ *et al* 1988, Fröhlander N and Stendahl U 1988, Campregher PV *et al* 2004).

Cutaneous malignancies and in particular squamous cell carcinoma (SCC)/Bowen´s disease are more frequent in kidney transplanted patients, that are more prone to disease when are

carriers of Hp 1.1 phenotypes particularly after ten years of the transplantation (Speeckaert R *et al* 2012). The same happens in the development of Kaposi´s sarcoma in HIV positive patients, even after adjustment for age, gender and AIDS status (Speeckaert R *et al* 2011).

Tumours of gastrointestinal tract where also studied and the single reference to haptoglobin polymorphism in colon cancer refers to one association in 184 Greek patients of Hp1-1 phenotype (Archimandritis A *et al* 1993), table 2.

More recently it was shown that Hp is produced in a large molecular complex with the beta chain of urokinase in cancer cells as well as in capillary endothelial cells (Harvey S *et al* 2009). This cancer-associated glycoform of Hp (β-chain) is a ligand for Galectin-3, a beta-galactoside binding protein implicated in tumour progression and metastases of colorectal cancers (Bresalier RS *et al* 2004).

Neoplasia	Population (N) (Control/Neo)	Conclusions	References
Colon cancer	N=2026/184 Greece	Association of Hp1-1 phenotype	Archimandritis A *et al* 1993
Gastric cancer	N=104/100 India	Risk for Hp2-2 carriers	Jayanthi M *et al* 1989
	N=114/2026 Greece	No association	Theodoropoulos G *et al* 1992
Oesophageal cancer		Higher risk for Hp2-1 phenotype	Jayanthi M *et al* 1989
Pancreatic cancer	N=11/11 China	Frequency of Hp 2-2 is higher	Deng R *et al* 2007

Table 2. Haptoglobin and Cancer: Digestive Tumours.

Geographic differences have been reported regarding the influence of the Hp alleles in cancer risk. In India, where the frequency of Hp2 allele is high at the population level (84%) the risk for gastric cancer of the Hp2-2 phenotype carriers is 4.04 and the risk for oesophageal is 3.86 for Hp2-1 phenotype carriers (Jayanthi M *et al* 1989). On the contrary in another geographic localization (Greece) a study of a similar number of gastric carcinoma patients didn't show any difference for the same polymorphism (Theodoropoulos G *et al* 1992).

Deng R *et al* demonstrated in 2007 that, in pancreatic carcinoma patients, the frequency of Hp 2-2 is higher compared with chronic pancreatitis patients and normal controls. Haptoglobin of these patients is not elevated in serum, but it is abnormally fucosylated in β-chain that has four N-glycans sites, the same happens but not so extensively in hepatocellular, gastric and colorectal carcinomas. The fucosylation of Hp seems to be induced by a factor secreted by these tumours itself (Nakano et al 2009, Miyoshi E, Nakano M 2008)

Early references of the distribution of haptoglobin polymorphism in Greek patients with prostate carcinoma compared with prostate benign hypertrophy (BPH) patients failed to

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demonstrate any association (Germenis A *et al* 1983, Dimopoulos MA *et al* 1984). These results were consistent with a recent report from an association study realized in an African population where the Authors didn´t also demonstrate any association of the Hp polymorphism with PSA (Prostate Specific Antigen) and prostate cancer patients survival (Mavondo GA *et al* 2012). However there were demonstrated higher circulation levels of monoclonal antibodies against glycosyl epitopes presents in the beta chain of Hp in prostate carcinoma compared with BPH that decreased after radical prostatectomy (Saito S *et al* 2008), table 3.

Serum levels of haptoglobin were elevated in kidney and bladder cancer concomitantly with a metabolite of Prostaglandin F2α, however only in bladder cancer was demonstrated in 264 Germans a statistically significant lower frequency of Hp2-2 genotype (Dunzendorfer U *et al* 1981; Bemkman HG *et al* 1987).

Neoplasia	Population (N) (Control/Neo)	Conclusions	References
Prostate cancer	N=155/115 Greek patients	Failed to demonstrate any Hp association	Germenis A *et al* 1983; Dimopoulos MA *et al* 1984
	N=122/74 Africa, Botswana Zimbabwe	Any association of the polymorphism with PSA and survival	Mavondo GA *et al* 2012
Bladder cancer	N=264 Germany	Lower frequency of Hp 2-2	Benkman HG *et al* 1987

Table 3. Haptoglobin and Cancer: Urological Tumours.

For breast cancer despite consistency of overrepresentation of Hp 1 allele in three earlier studies (Tsamantains C *et al* 1980, Kaur H *et al* 1984, Bartel U *et al* 1985) and only one negative study (Hudson BL *et al* 1982) a more recent study demonstrate that Hp phenotype distribution in patients is family history-dependent. For these authors the frequency of Hp 1-1 and Hp 2-1 phenotypes is higher in the familial group and the opposite for the no familial group (Awadallah S and Atoum MF 2004). Moreover, in the recent study whose objective was to search for circulating proteins, predictive of recurrences and free survival of high risk primary breast cancer, with proteomic techniques (SELDI-TOF-MS) the authors, based on disturbances of iron (low levels of ferritin light chain is associated with good prognosis), identified Hp 2 allele as risk factor, nonetheless validated in an independent, sample and technique group of patients (Gast M-C W *et al* 2008). Also, it may have clinical important value, as a biomarker for recurrence in early breast cancer patients, the haptoglobin related (Hpr) protein in tissues and plasma (Kuhajda FP *et al* 1989 a-b).

The first references from the sixties of the last century about gynaecologic tumours indicate contradictory results between the authors when they were analyzed as a whole in what concerns to the frequency of Hp1 allele (Larkin MF 1967, Milunicova A *et al* 1969). However, a posterior reference of Bartel U et al 1985 confirms a higher Hp1-1 genotype frequency in 246

German patients with gynaecological and breast tumours. When only ovarian cancer samples were considered, two references, one Polish and another Swedish, indicate they are associated respectively with Hp 1 allele and Hp2-1 phenotype in patients with family history (Dobryszycka W and Wavas M. 1983, Fröhlander N and Stendahl U 1988).

Cervical neoplasia is a good model that illustrates haptoglobin and its polymorphism influence in the several steps of its natural history interacting with oncogenic and non-oncogenic HPV (Human Papillomavirus) and other co-factors such as sexual steroid hormones and smoking habits (Bicho MC 2011).

Preliminary reports on the role of this haptoglobin polymorphism in the development of cervical cancer were conflicting, with two authors (Milunicova and Bartel) indicating that Hp1 allele carriers were at risk of cancer development. In opposition, Larkin et al report the Hp2 allele as the most represented in their cervical cancer cases (Milunicova A *et al* 1969, Bartel U *et al* 1985 U, Larkin M 1967). Those reports were published previous to the, nowadays confirmed, association of oncogenic HPV types as the primary etiologic factor of cervical cancer and the HPV effect was not evaluated in the control populations. However, HPV is a necessary but not a sufficient cause of cervical cancer and it is also important the presence the other co-factors host related. One of these co-factors can be the immune response of the host. It has been proposed a role for haptoglobin a one of such co-factors (Mahmud SM *et al* 2007, Bicho MC *et al* 2006 and 2009).

In the case control study conducted in Canada (307 cases vs 358 control women), Mahmud et al examined the association of Hp phenotype with high grade cervical intraepithelial neoplasia (CIN III), a precursor lesion of invasive carcinoma (ICC). The control group had to present a normal cytology and HPV genotyping was performed to evaluate the HPV oncogenic type status. Accordingly, only when the risk analysis is restricted to the HPV positive women, an association was observed and Hp 1-1 carriers have almost a threefold increased susceptibility to the development of CIN III (OR=2.7, 95% IC: 1.0-7.2) (Mahmud SM et al 2007). In a recent study, we report an increased susceptibility for women that are Hp 1-1 carriers to develop ICC (OR=4.62, 95% IC: 1.86-11.48) (Bicho MC 2011). These results are consistent with another study performed in a different geographic localization (Ghana) and indicating a significant protective effect for the Hp2 allele in homozygous women (Quaye IK et al 2009). In another report, we studied the influence of Hp polymorphism on the risk for the development of HSIL and ICC (n=196) under the influence of sex steroid hormones. We found that the risk for an interaction is proportionally higher with the number of Hp 1 allele presents (Bicho MC et al 2009). However, when the interaction between Hp polymorphism with smoking habits was studied the Hp 2 allele in homozygoty increased the risk to develop HSIL and ICC (Bicho MC et al 2006).

6. Discussion

During the first thirty years (from the sixties to nineties of the last century) of cancer association studies, genetic blood markers, including haptoglobin were concomitantly studied with

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Neoplasia	Population (N) (Control/Neo)	Conclusions	References
Breast cancer	N=109 Greece	Overrepresentation of Hp 1 allele	Tsamantains C *et al* 1980
	N=50/50 India	Overrepresentation of Hp 1 allele	Kaur H *et al* 1984
	N=246 Germany	Overrepresentation of Hp 1 allele	Bartel U *et al* 1985
	N=129/200 Jordania	Higher frequency of Hp 1 allele	Awadallah S
	Familial (N=42) Non familial (N=86)	Higher frequency of Hp 1 and Hp 2 alleles	Atoum MF 2004
	USA	No association	Hudson BL *et al* 1982
	N=371 USA	No association	Gast M-C W *et al* 2008
Ovarian cancer	N=114/132 Polland	Associated Hp 1 allele	Dobryszycka W and Wavas M. 1983
	N=182 Swedish	Associated Hp2-1 phenotype with family history	Fröhlander N and Stendahl U 1988
Cervical cancer	N=170/85 Checoslovakia	Hp1 allele carriers at risk	Milunicova A *et al* 1969
	N=430/526 Germany	Hp1 allele carriers at risk	Bartel U *et al* 1985
	N=430/526 USA	Hp2 allele as the most represented	Larkin M 1967
	N=358/307 Canada	In HPV positive women, risk for Hp 1-1 is higher CIN III	Mahmud SM *et al* 2007
	N= 396/196 Portugal	In ICC women the risk for Hp 1-1 carriers is greater in steroid hormone ingestion	Bicho MC 2011
	N=120/60 Ghana	Protective effect of the Hp2 allele in homozygoty	Quaye IK *et al* 2009

Table 4. Haptoglobin and Cancer: Gynaecological Tumours.

descriptive studies of allele distribution in the different populations (Giblett ER 1968, Langlois MR and Delanghe JR 1996, Wobeto VP *et al* 2008, Levy AP *et al* 2010). These preliminary reports usually were cross-sectional case control studies, that didn't enter in consideration with the biological plausibility in cancer linked to the genetic variation. Diverse geographic regions, with very different distribution of alleles, various genetic variations backgrounds and above

all have different environments that interacts with genomes to give highly variable phenotypes, may explain controversial results.

Moreover, the lack of reproducibility of the several studies may also reflect methodological differences in the criteria of case definitions and selection of controls, and in what concerns to the influence of environment of factors such as microbiological (HPV, EBV, M. tuberculosis, H. Pylori, Plasmodia), smoking habits, sun exposition, xenobiotic and sex steroid hormones (Beckman G *et al* 1986, Benkmann HG *et al* 1987, Bicho MC *et al* 2006 and 2009, Mahmud *et al* and 2007, Abdullah M *et al* 2009, Speeckaert R *et al* 2011 and 2012).

The usual cross-sectional approach of these studies didn´t take into account the somewhat different influences of the genotypes on the natural story of the cancer that courses in multistep way (Zur Hausen H 2002). The great majority of the studies were done in patients with distant phenotypes (advanced stage cancer) and take not in consideration the subclinical disease. This isn´t evidenced in those times by lack of knowledge of physiopathology and lack of reliable biomarkers (circulating and imaging) that gives a more dynamic picture of the situation.

It was not common, the realization of measurements of serum and plasma levels of the Hp independently of phenotype in part due too time consuming of the technics (Langlois MR and Delanghe JR 1996). In these cases, not even the local processes are reflected in circulation but also it is demonstrated the existence of a local tissue environment in what Hp functions in paracrine and autocrine way (Yang F *et al* 2000, Xie Y, *et al* 2000, Sharpe-Timms *et al* 2002, Wang H *et al* 2005, Shaw JLV *et al* 2007).

The natural history of cervical cancer seems to be dependent of genetic polymorphism of haptoglobin in its interaction with HPV and cofactors such as sex steroid hormones and smoking habits (Bicho MC *et al* 2006 and 2009, Mahmud *et al* and 2007).

Also there are reports of the different influences of Hp alleles in a context of familiar history for the breast and ovarian cancers (Fröhlander N and Stendahl U 1988, Awadallah S and Atoum MF 2004).

For the clarification of these issues a better knowledge of the physiopathology mechanisms of action of the Hp alleles is necessary.

Haptoglobin as a pleiotropic protein has several different functions being the Hp1 allele and correspondent genotypes Hp1-1 and Hp1-2, the more represented in the several cancers reviewed. The innate immune response of the host against the tumour is limited in the subject's carriers of the Hp1 allele through several mechanisms, already reviewed.

It is accepted, in this pathway, the role of Hp-Hb, CD163, HO-1, CO, bilirubin, activation of anti-oxidant intracellular systems (including ferritin), and extrusion of iron through ferroportin. This pathway is characteristic of immunosuppressive tumor macrophages M2 types that are more active in Hp1 carriers inducing a switch for a Th2 antinflammatory cytokine profile characteristic of lesser Th1 type cytotoxic immune antitumor mechanisms (Van Vlierberghe *et al* 2004, Guetta *et al* 2007, Nielsen MJ *et al* 2010, Vallelian F *et al* 2011 and Akila P *et al* 2012).

This switch can be also dependent of a stronger acute phase response characteristic of Hp1 carriers that can modulate immune cells activity after binding of Hp to its receptors CD22, β2

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integrin and LFA located respectively in B cells neutrophils and T cells (EL Ghmati SM *et al* 1996, Giannoni E *et al* 2003, Bottini N *et al* 1999 and 2005, Arredouani MS *et al* 2005, Lu JY *et al* 2007). A third mechanism can be the interaction of environmental factors such as sex steroid hormones and glucocorticoids that activates predominantly Th2 arm of acquired immunity in synergy with Hp1 allele as happens in cervical cancer (Gleeson M 2006, Bicho MC *et al* 2009, Akila P *et al* 2012).

An increased prevalence of Hp 2-2 genotype is observed in some tumours leading to the hypothesizes of haptoglobin involvement in the mechanisms associated with the carcinogenesis and tumorigenesis of the chronic inflammation (head and neck carcinomas, glioblastome, gastric carcinoma).

The lower antioxidative capacity and inhibition of prostaglandin synthase associated to the genotype Hp 2-2 are the best known explanatory mechanisms (Wen WN et al 2001, Saeed SA *et al* 2007). Indirect effects of prostaglandins on carcinogenesis are mediated through the stabilization of HIF1α and the resultant expression of angiogenic factors like EPO (erythropoietin), VEGF (vascular endothelial growth factor), that have synergic effects with Hp2-2 (Cid MC *et al* 1993, Liu XH *et al* 2002, Acs G *et al* 2003, Ye YN *et al* 2004, Mihailović M *et al* 2005, Palayoor ST *et al* 2009, Park SJ 2009).

Another mechanism involved is the withholding of iron in macrophages that is necessary for the proliferation of immune cell (Touitou Y *et al* 1985, Weinberg ED 1996, Cozzi A *et al* 2004).

The effects of smoking habits are modulated by Hp2-2, because the effects in the nicotine down regulation of haptoglobin expression and also the effects of CO producing local hypoxia and the immune depression (Ye YN *et al* 2005).

7. Perspectives

More studies are necessary to complete our understanding about the role of this important acute phase protein, its levels variations, particularly the fucosylated isoforms and its regulation, the Hpr and its polymorphism and its immunomodulation role in cancer. Finally, future studies may focus in the importance of haptoglobin polymorphism conducting to a pharmacogenetic approach to chemoprevention.

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