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Haptoglobin is an Exercise-Responsive Acute-Phase Protein

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1. Introduction

The nomenclature of haptoglobin (Hp) was from the character of conjugation [hapto] with hemoglobin [globin] of red blood cells. Human Hp is one of the largest proteins in the plasma originally synthesized as a single polypeptide and has been thought to be derived primarily in liver, adipose tissue, brain, lung, and kidney (Peters & Alper, 1966). Following post-translational protease cleavage of Hp, α- and β-chains are formed and then linked by disulfide bridges to generate the matured Hp form (Kurosky et al., 1980). Human Hp gene located in chromosome 16q22.1 is characterized by two common alleles *Hp 1* and *Hp 2* respectively corresponding to α1-β and α2-β chain, and resulting in three main phenotypes: Hp 1-1, 2-1 and 2-2. All the phenotypes share the same β-chain containing 245 amino-acid residues. As shown in Figure 1A, the α1-chain contains 83 amino-acid residues possessing two "free" –SH groups. The one at the –COOH-terminus always cross-linked with a β-chain to form a basic α-β unit, and the other at the NH_2-terminus linked with another $(\alpha\text{-}\beta)_1$ resulting in a Hp dimer $(\alpha1\text{-}\beta)_2$ or a Hp 1-1 molecule. In contrast, the α2-chain containing a tandem-repeat of residues 12-70 of α1 with 142 amino-acid residues is "trivalent" providing an additional free –SH (Cys-15) that is able to interact with another α-β unit. As such, α2-chains can bind to either α1-β or α2-β units to form large polymers $[(\alpha1\text{-}\beta)_2\text{-}(\alpha2\text{-}\beta)_n$ in Hp2-1 and $(\alpha2\text{-}\beta)_n$ in Hp2-2] as shown in Figure 1B (Wejman et al., 1984).

Hp is a highly conserved acute phase protein (responsive to infection and inflammation) that is present in the plasma of all mammals (Raijmakers et al., 2003, Wang et al., 2001, Yerbury et al., 2005). A recent study has found that Hp also exists in lower vertebrates, bony fish but not in frogs and chickens (Wicher & Fries, 2006). The human *Hp 2* allele has been proposed to be evolved from *Hp 1* about 2 million years ago and then gradually displaced *Hp 1* as a consequence of a non-homologous crossing-over between the structural alleles (*Hp 1*) during meiosis, which is remarkable for being the first example in partial gene duplication of human plasma proteins (Maeda, 1985, Maeda et al., 1984, McEvoy & Maeda,

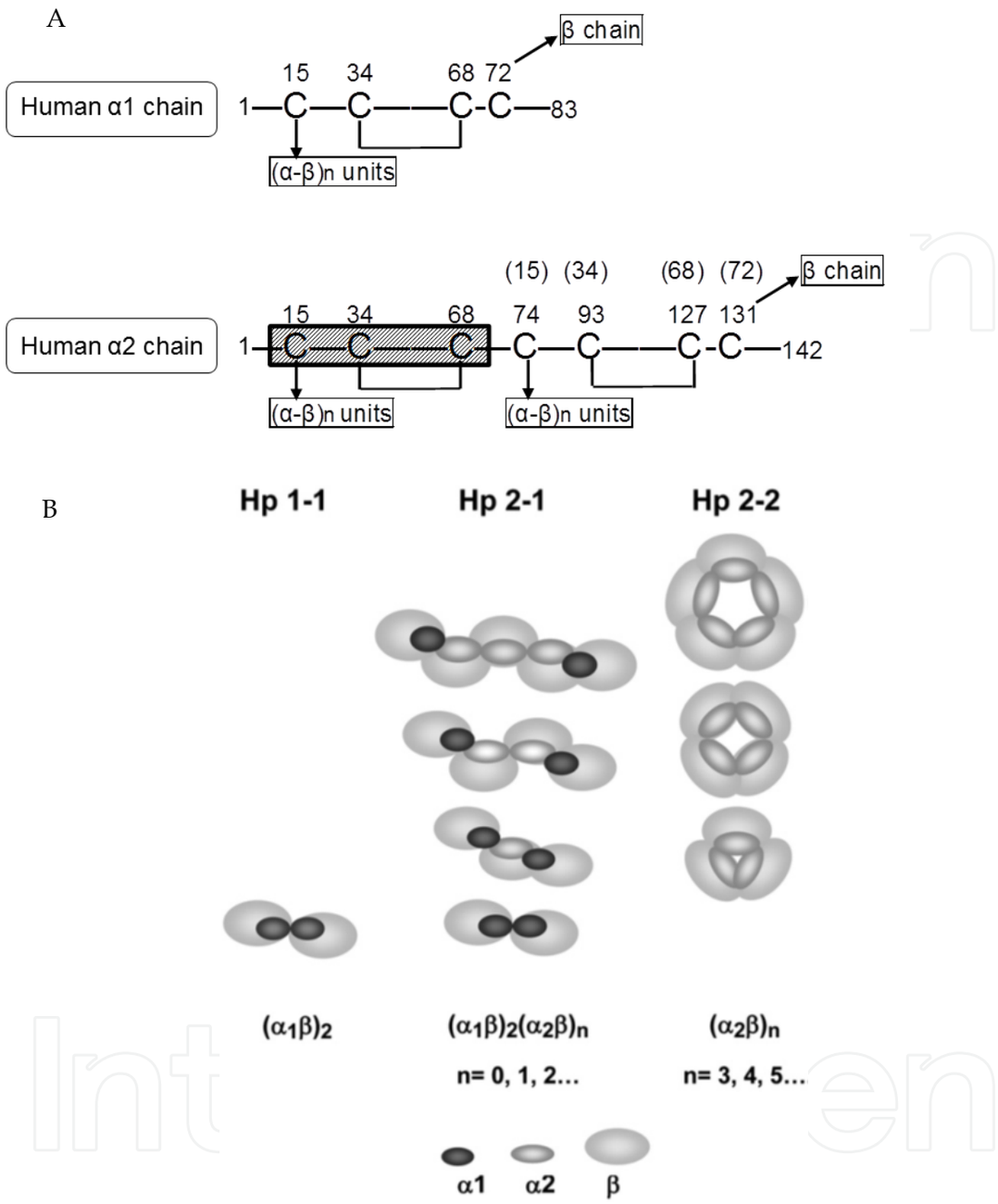

Fig. 1. A schematic model illustrating the structure of human Hp phenotypes. Panel A depicts the backbone of the amino acid sequence for α1-chain with 83 amino-acid residues and for α2-chain with 142 residues containing a 59 amino-acid tandem repeat (residues 12-70) (shown in shaded block). Panel B shows the secondary structures of Hp: Hp 1-1 represents a homodimer, the simplest combination of dimeric α1β chains $(\alpha 1\beta)_2$; Hp 2-2 is heterogeneous in size, starting with cyclic trimeric α2β chains, $(\alpha 2\beta)_3$, and other cyclic polymers; Hp 2-1 is also heterogeneous, but composed of simple homodimer $(\alpha 1\beta)_2$, a linear trimeric αβ chain, $(\alpha 1\beta)_2(\alpha 2\beta)$, and other linear polymers. All types share a common structure of the β chain.

1988). Thus, only humans possess additional Hp 2-1 and 2-2 phenotypes. However, more recently we have found that all the ruminants belong to Hp 2-2 phenotype, which was evolved during at least 20 million years (Lai et al., 2008). In general, individuals with polymeric structure of Hp 2-2 are dramatically more prevalent in certain clinical disorders, such as diabetes and inflammation-related diseases (Hochberg et al., 2002, Langlois & Delanghe, 1996, Levy et al., 2002, Miyoshi et al., 1991). Because Hp 1-1 molecule inhibits the inflammatory cascades more effectively than Hp 2-2, it is commonly assumed that patients with Hp 2-2 phenotype would expose to higher risk for poorer outcomes once suffered from diabetes and inflammation related diseases. Extrahepatic source of Hp has recently been recognized to be present in the body fluids; its regulation could be totally different from the liver -secreted Hp. For example, mononuclear cells secrete Hp when stimulated with all trans-retinoic acid (ATRA) to activate protein kinase C-δ, one of the major signal transductions (Kim et al., 2001). While tumor necrosis factor-α (TNF-α) can induce Hp release in neutrophils during the precursor stage (promyelocyte) at the condition of acute inflammation (Nakagawa-Tosa et al., 1995, Theilgaard-Monch et al., 2006).

The most-noted biological functions of Hp are to capture released hemoglobin (Hb) for accelerating the Hb degredation during an excessive hemolysis and participate in scavenging free radicals during oxidative stress (Bernard et al., 2003, Langlois & Delanghe, 1996). More recently, we have shown that Hp is an extremely potent antioxidant, which directly prevents low-density-lipoprotein (LDL) from Cu2+-induced oxidation. The potency is markedly superior to probucol, one of the most potent therapeutic antioxidants (Lai et al., 2007, Tseng et al., 2004). Transfection of Hp cDNA into Chinese hamster ovary (CHO) cells protects them against oxidative stress (Tseng et al., 2004). This finding can explain, at least in part, that the hypoxia-inducible factor-1α may enhance Hp expression (Oh et al., 2011).

Meanwhile, the concentration measurement of different Hp phenotypes is somewhat difficult hence there are limited reports showing the correlation between the Hp levels and inflammatory-related diseases in human subjects. Using an ELISA with phenotype-matched Hp standards, it becomes possible to accurately measure the Hp 1-1, 2-1, and 2-2 plasma levels and to define the response pattern to several diseases such as in patients with atherosclerosis (Cheng et al., 2007). Furthermore, the reference levels of Hp were significantly different in patients with different phenotypes. Increasing plasma Hp levels up to 2-4 times upon the inflammation or infection are considered to be a sound acute response. A human study of 10 healthy volunteers recently disclosed an elevation of Hp levels in bronchoalveolar lavage fluid (BALF) from the lung stimulated with lipopolysaccharide (LPS). We demonstrated that Hp 1 is a more dominant allele than Hp 2 based on the Hp mRNA expression (Cheng et al., 2007). Thus, subjects with Hp 1-1 and 2-1 have higher baseline levels of plasma Hp and possess stronger antioxidant activity relative to those Hp 2-2 individuals (Tseng et al., 2004).

Some conditions that commonly lead to substantial increase in plasma Hp include infection, trauma, surgery, burns, tissue infarction, various immunologically mediated inflammations, and some advanced malignant tumors. However, reports with respect to the relationship between exercise and Hp levels are rarely limited. Spitler et al. disclosed a significantly lower Hp level and a higher turnover rate of erythrocytes in subjects practicing high frequency fitness as compared to those with low frequency of practice. One reasonable explanation is that exercise induces a chronic hemolytic response (Spitler et al., 1984). It was thought that the stress due to exercise caused intra-vascular hemolysis with the consumption of Hp. This notion is consistent with reported observation that Hp was decreased after a 10-month period of repetitive treadmill program that included 11 male

medium-distance runners (Wolf et al., 1987). Nevertheless, there are still controversial debates about the exercise effect on Hp expression. Hp levels remained unchanged in 12 healthy male volunteers undergoing a maximal aerobic capacity (Vo2 max) every week for 3 weeks (Cordova et al., 1992). Further, the transcriptional levels of Hp and proinflammatory cytokine genes after exercise have never been reported. We attempted to explore a possible effect of a single short-term exercise on the plasma levels of Hp in the present study.

2. Changes of human plasma Hp levels after exercise

2.1 One-time explosive running and jogging accompanied with the elevation of human plasma Hp levels

First, we conducted a preliminary study to determine whether a physical endurance jogging or an explosive run may affect the plasma Hp levels. Twelve males (phenotypes Hp 2-1 and 2-2) with age matched were recruited (Hp 1-1 were excluded in this study due to the rare population in our local area, generally < 7%) and examined by performing these exercises. Jogging was performed as a single time for 60 min, while explosive run was to race 100-m also as a single time for about 15 sec. These two types of exercise were conducted among the same individuals with a resting period of 30 days apart. To determine the time-course changes in Hp levels after one-time exercise, the fasting blood samples were collected at days 5, 10 and 25 and Hp was then measured using an appropriated ELISA (Cheng et al. , 2007).

Our preliminary data revealed that Hp is elicited in response to exercise, depending on the type of exercise. It should be noted that the basal levels of Hp were different with respect to the Hp phenotype of the subjects, i.e. low in Hp 2-2 and high in Hp 2-1 subjects similar to a previous report (Cheng et al., 2007). Both Hp 2-1 and 2-2 subjects exhibited a significant Hp elevation in plasma under an explosive exercise (100-m run). Although the overall basal levels of Hp were low in Hp 2-2 subjects, their Hp levels were increased substantially by about 20 fold after explosive running. Interestingly, 60-min jogging seems not to cause marked changes in Hp levels as compared to 100-m racing over the Hp 2-2 subjects (Figure 2). Meanwhile, these exercises did not cause overall loss of body weight or adipose tissue mass (data not shown). It is of interest to note that in general the elevation of Hp responsive to exercise is rather slow being observed after 5 days with one-shot exercise.

Recent studies indicate that acute-phase proteins changes in exercise are associated with low-grade oxidative stress (Petibois & Deleris, 2003). Since Hp is an extremely potent antioxidant (Tseng et al., 2004), we anticipated that elevated Hp expression level may potentially play a protective role reducing the oxidative stress during the exercise. The mechanism involved in such exercise-induced Hp elevation is discussed below.

2.2 High levels of plasma Hp is advantageous in patients with acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is a life-threatening severe inflammatory process in response to pneumocyte damages, including those mediated by free radicals. Because Hp is an anti-inflammatory and antioxidant molecule, it may be relevant in preventing against inflammation in patients with severe oxidative damage. To test whether plasma Hp levels are associated with the outcome in ARDS patients, we evaluated 88 patients with ARDS. Of remarkable interest, we have observed (unpublished data) that plasma Hp levels are greatly increased in patients affected with ARDS. Hp 2-1 patients with high Hp basal levels appear to have a much better prognosis relative to those with Hp 2-2 (Figure 3). Low Hp levels were found to be associated with multiple-organ dysfunction and

independently predict 28-day mortality of those patients with ARDS. Hp 2-2 patients have unfavorable ARDS outcomes.

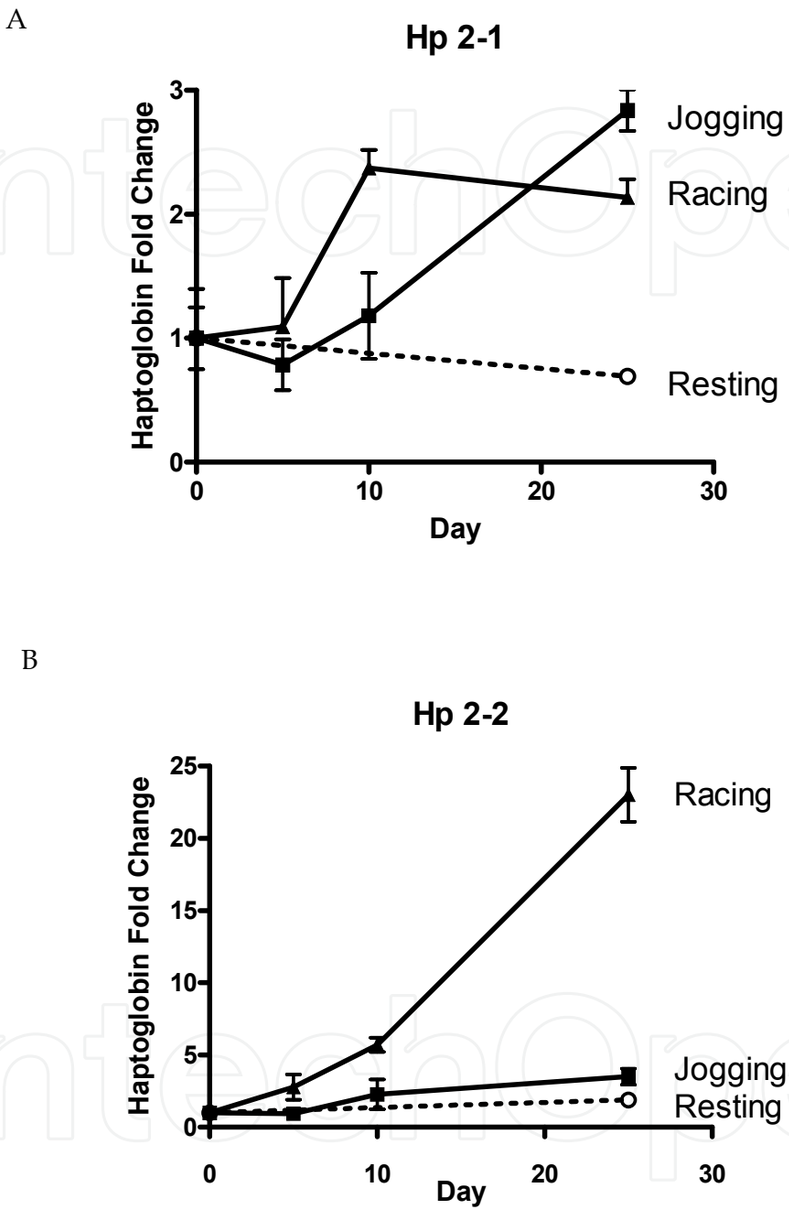

Fig. 2. Changes of plasma Hp levels in fold after one single exercise. Twelve males received a running program with endurance exercises (jogging for 60 min) with a 30-day resting period and followed by an exposing run (100-m for about 15 seconds). In 6 individuals with Hp2-1 (A), the Hp basal levels were relatively higher than those with Hp 2-2. Hp 2-1 levels increased 2.8-fold at day 25 with the mean ± SD from 1.3 ± 0.6 mg/ml for jogging ($p=0.063$). In 6 individuals with Hp 2-2 (B), the Hp basal levels were relatively low, but markedly increased by about 20-fold at day 25 from 0.09 ± 0.13 mg/ml for racing ($p<0.001$).

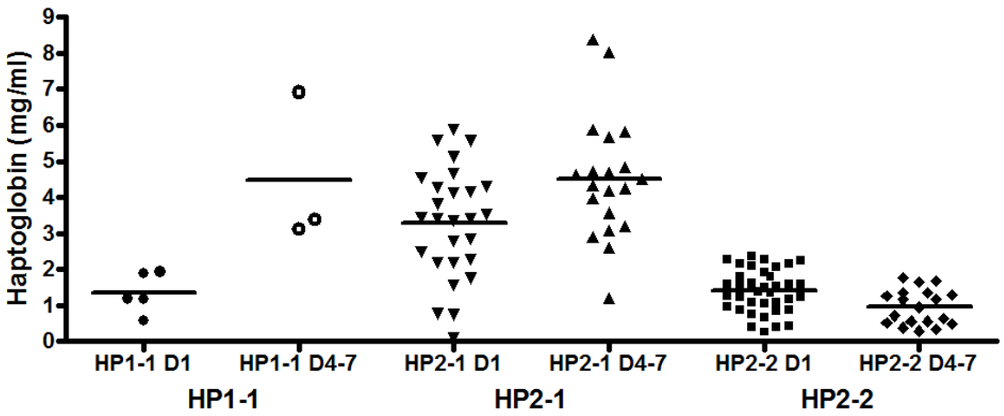

Fig. 3. Hp levels are various in septic patients with different phenotypes. Hp levels in 88 patients with sepsis-related acute respiratory distress syndrome measured on day 1 and days 4-7 are shown. Horizontal bar indicates the mean values. Patients with Hp 1-1 and 2-1 have higher Hp levels at days 4-7 relative to those with Hp 2-2 at the same period.

3. Source of elevated Hp levels in plasma and its underline mechanism involved after exercise

The rationale by which exercise induces the increase in plasma Hp is not clear. Initially, we attempted to address the source of elevated plasma Hp after exercise. By immunocytochemical staining, we show that neutrophils and monocytes in plasma, but not lymphocytes, are the two major cell types to express Hp (Figure 4). We therefore hypothesized peripheral white blood cells being responsible for the increased Hp levels at least in part.

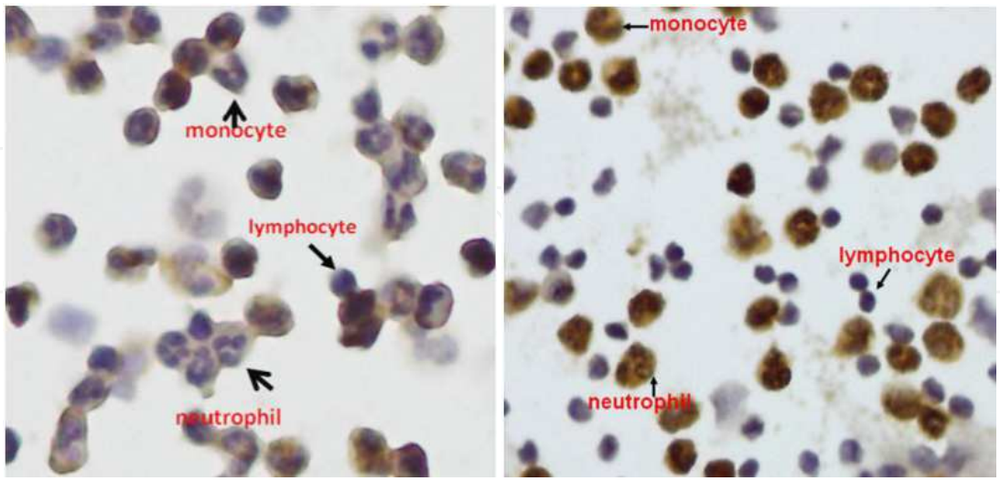

Fig. 4. Immunocytochemical analysis of Hp expression in human leukocytes. A representative staining of 3 healthy human subjects is shown. Left panel (control) displays the cells stained with hematoxylin and normal mouse serum. Right panel displays the cells stained with hematoxylin and a mouse anti-human Hp monoclonal antibody. Intracellular Hp is primarily expressed in mononuclear cells and neutrophils instead of lymphocytes.

3.1 Exercise using mice as an animal model

Since all the animal species belong to Hp 1-1 phenotype except ruminants (Lai et al., 2008), the response of Hp levels following the exercise should be more uniform in animals than that in human subjects as mentioned above. To this end, mice were chosen as an animal model to substantiate the hypothesis mentioned above. First, we tested whether exercise may raise the Hp levels in mice. They were divided as four groups (n=24 in total). The control group (n=6) received no exercise, while the rest of the tested groups (n=6 in each) received a passive exercise with mild horizontal movement at a frequency of 60 times per min for 30 min, twice a day and last for one, two, and three weeks, respectively. All the groups were kept for the same period of time (3 weeks) and simultaneously sacrificed at day 21. For examples, the one-week group started to exercise at day 14 and ended at day 21, while the 3-week group started at day 0 and ended at day 21 as shown in Table 1. The body weight of each respective group (including the control) increased progressively over 21 days, but there was no significant difference between each group during the exercise period.

Days	**Exercised Group**			
	Week 0	Week 1	Week 2	Week 3
0	31.4 ± 2.4	31.4 ± 0.7	33.3 ± 1.0	31.4 ± 0.8
7	34.9 ± 1.8	33.9 ± 1.4	35.8 ± 1.0	33.0 ± 0.9
14	36.8 ± 2.5	35.6 ± 1.5	37.3 ± 1.0	34.2 ± 1.2
21	37.0 ± 2.8	36.3 ± 1.1	37.8 ± 1.0	36.4 ± 1.0

Shaded area represents the time to start the exercise

Table 1. Body weight of the mice underwent passive exercise. There was no significant difference during the 3-week period when compared between the mouse groups (week 0-3) at the same day.

3.2 Elevation of plasma Hp in mice after exercise

Using the Hp-hemoglobin complex formation method (Yueh et al., 2007), we show plasma Hp levels after exercise being progressively increased over time (Figure 5). At week 3, the levels significantly went up to about 2.67 fold ($p<0.005$). The data are consistent to the denseness measurements using a Western blot analysis (data not shown). By RT-PCR analysis, the Hp mRNA levels in total white blood cells were also significantly elevated at week 3 with about 6 fold (Figure 6) ($p<0.005$). Thus, it suggests that the Hp increase in plasma is contributed from the white blood cells at least in part. Figure 6 also shows that the Hp mRNA levels in response to exercise is rather slow and consistent to that human study (Figure 2).

3.3 Changes in cytokine levels of leukocytes in mice after exercise

Since IL-6 has been reported to be a factor to stimulate the Hp biosynthesis in cultured hepatocytes, we tested whether there was a change in IL-6 of leukocytes following the exercise. Figure 7 shows that both IL-6 and IL-1β mRNA levels were increased in some extent, but not IL-10 and TNF-α, using a RT-PCR analysis. The finding postulates that there might be other factors involved in stimulating the biosynthesis of leukocyte's Hp.

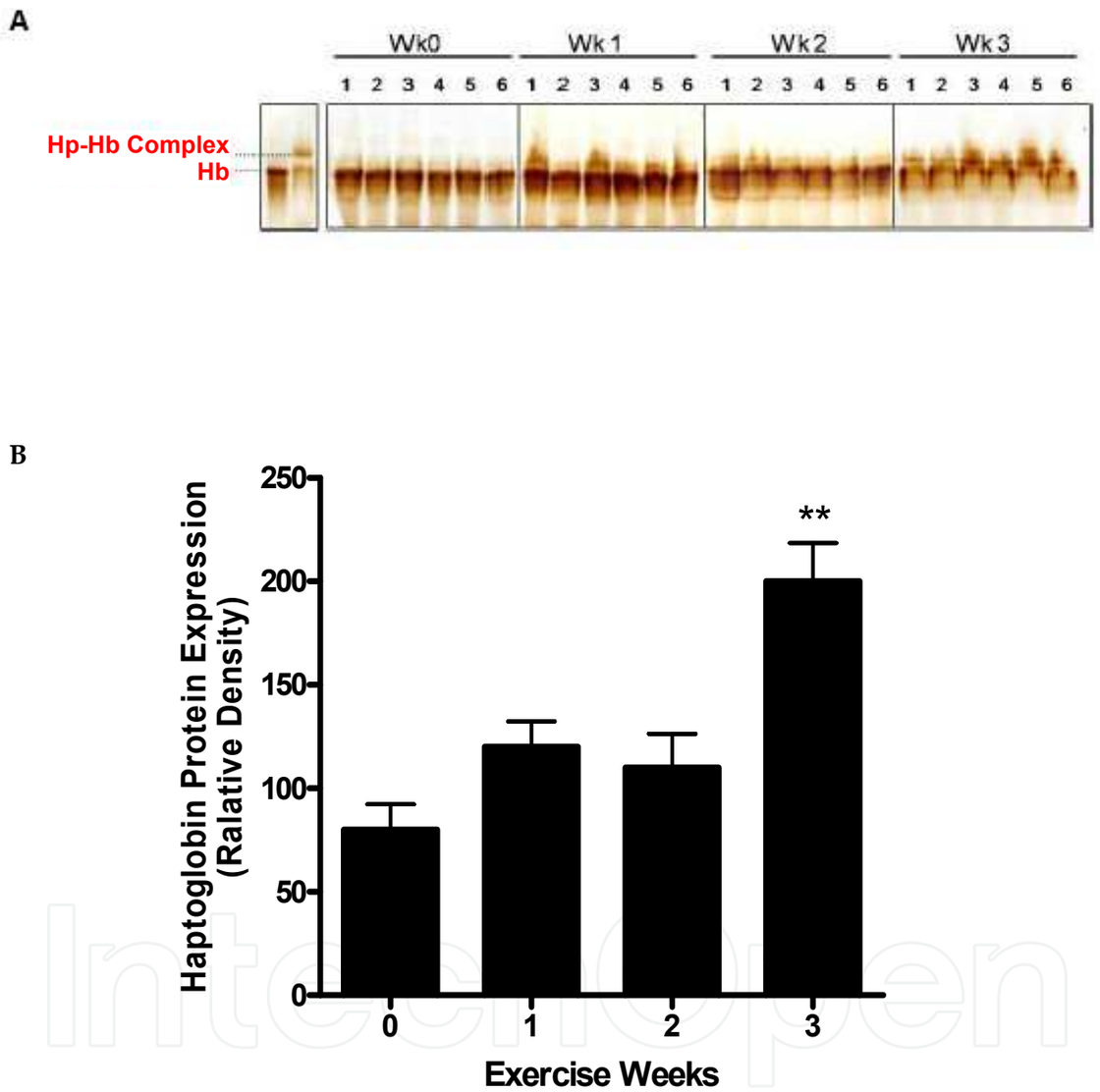

Fig. 5. Hp levels in mice with and without exercise. A: Representative native gel showing complex formation between mouse plasma Hp and added hemoglobin (Hb).
B: Chromogenity of formed Hp-Hb complex determined by a scanning densitometry.
**Hp levels in mice exercised at week 3 reveals a significant elevation relative to week 0 ($P<0.005$).

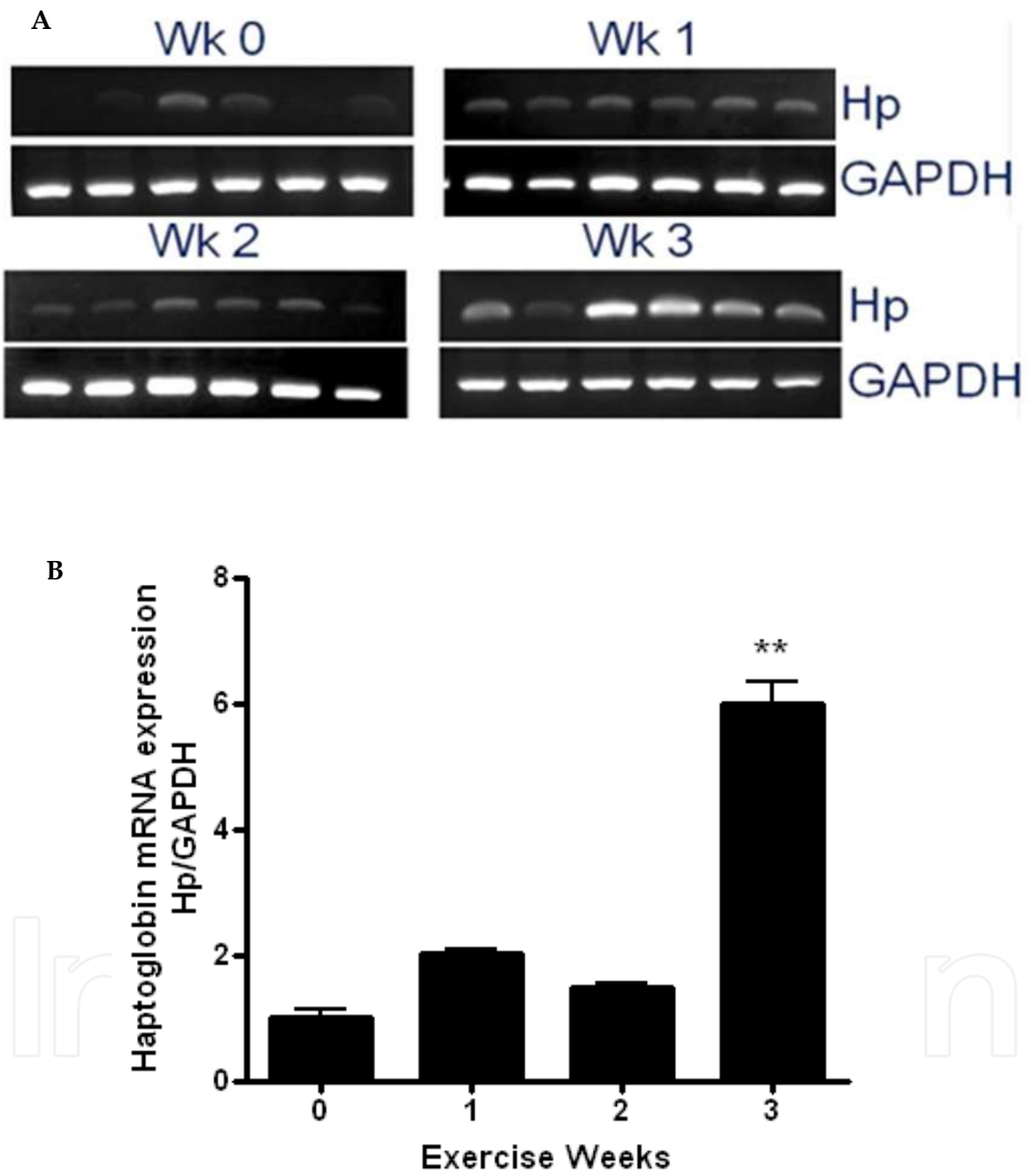

Fig. 6. Effect of exercise on Hp mRNA expression in leukocytes from different mouse groups assessed by a RT-PCR. A: Hp mRNA expression from each group (n=6). B: Mean ± SD of the density from RT-PCR results (from A) determined by a scanning densitometry. A significant increase in Hp mRNA expression levels is observed after 3 weeks of exercise ($p<0.005$). Each group was sacrificed at the same day.

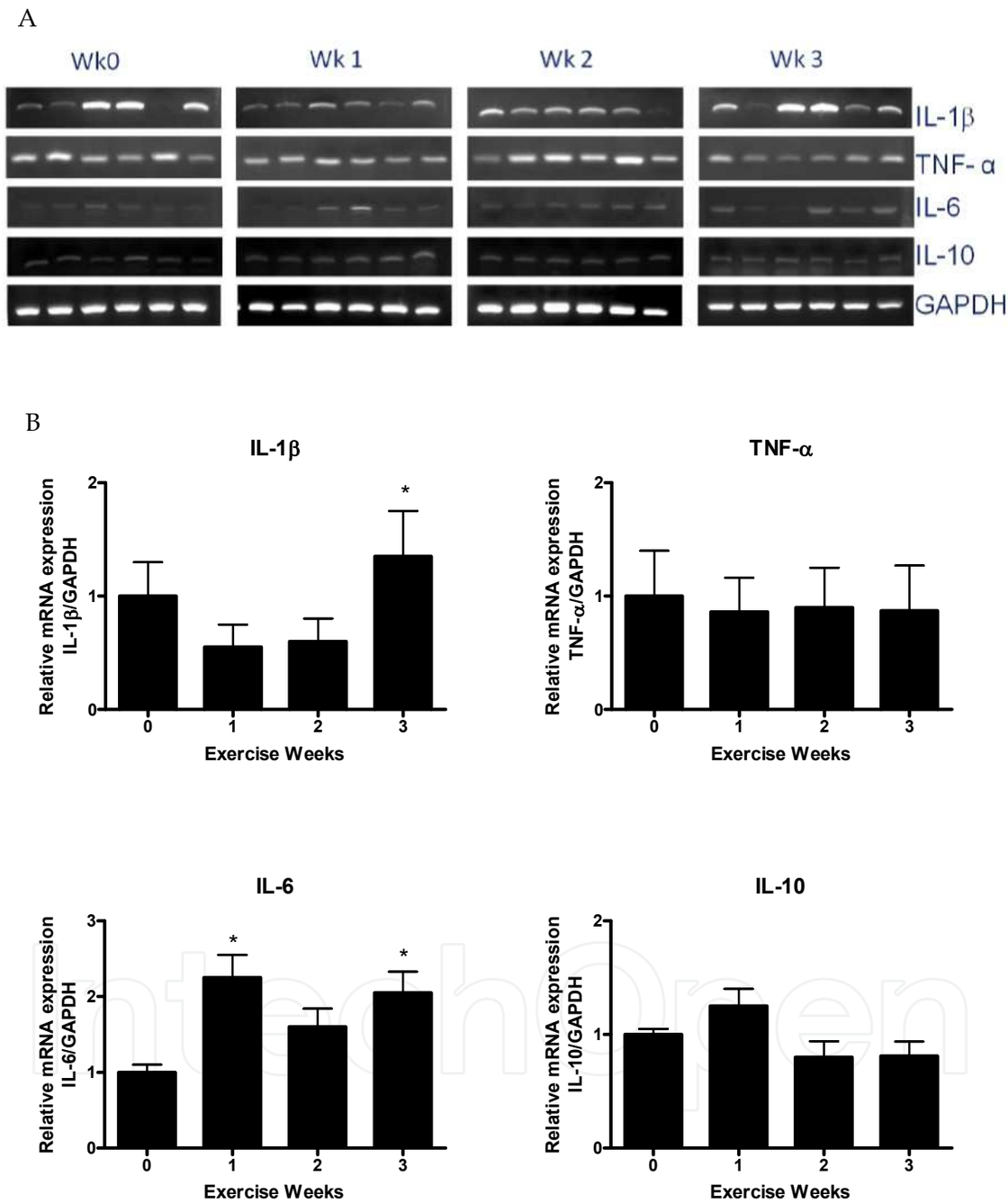

Fig. 7. Effect of exercise on mRNA expression of the cytokines, IL-1β, TNF-α, IL-6, and IL-10 in mouse leukocytes. A: mRNA levels corresponding to each cytokine after exercise (n=6 for each respective group). B: Mean ± SD of the density from RT-PCR results (from A) determined by a scanning densitometry. *$p<0.05$ as compared to week 0. Each group was sacrificed at the same day.

3.4 Hp mRNA levels of liver remaining unchanged in mice after exercise

To test whether exercise can affect the expression of hepatic Hp mRNA levels over time, we analyzed the mouse liver samples using a RT-PCR. Figure 8 shows that Hp mRNA levels were not altered during the three-week exercise suggesting that the elevated levels of plasma Hp were not derived from the livers.

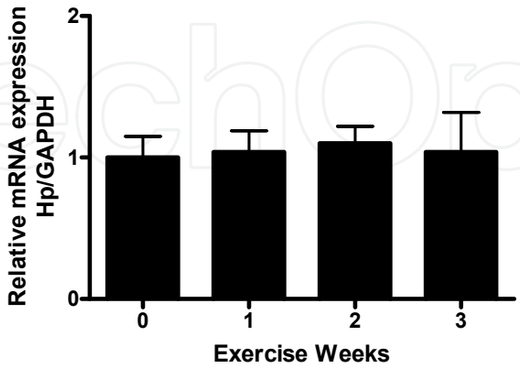

Fig. 8. Effect of exercise on mouse hepatic Hp mRNA expression over time. There are no significantly different between each group (n=6 for each respective group). $p>0.05$

3.5 Neutrophils is a major moiety responsible for the elevation of Hp in mice after exercise

Lymphocytes, neutrophils, and monocytes are taken account for the major types of white blood cells in plasma. Finally, we found only the number of plasma neutrophils being mostly increased after exercise, but not that of lymphocytes and monocytes (Figure 9). Thus,

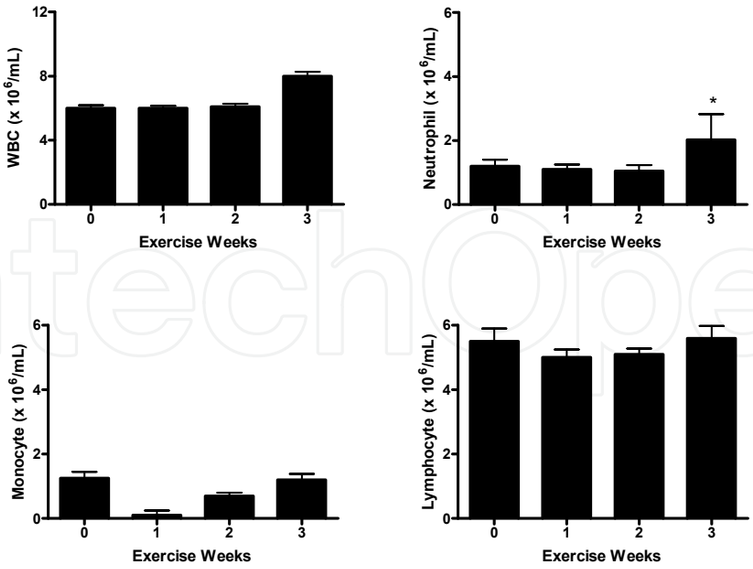

Fig. 9. Effect of exercise on the number of total leukocytes, neutrophils, monocytes, and lymphocytes in mice. Only neutrophils from the leukocytes are significantly increased as compared with the other cell types after 3-week exercise. *$p<0.05$ as compared with the week 0. Each group was sacrificed at the same day.

our results point out that the increase in neutrophils over the circulation is accompanied with the elevation of plasma Hp shown in Figures 5 and 6. Such correlation can be rationalized by the fact that exercise can induce a marked increase in blood neutrophils in human studies (Gavrieli et al., 2008, Laing et al., 2008, Weight et al., 1991). These neutrophils are then attributed for the release of Hp into the plasma shown in our study. A similar study was conducted by us in cows with mastitis, large accumulation of neutrophils in mammary glands resulted in a marked Hp increase in milk (Lai et al., 2009). We suggest that neutrophils are responsible for the elevated Hp levels in plasma following the exercise.

4. Conclusions

From the human study, we show that one short-term jogging and explosive run are able to induce the Hp plasma elevation, while the animal study revealed that a mild exercise induces marked increase in plasma Hp and neutrophil-dervied Hp mRNA or in leukocytes, but not in the hepatocytes. It is conceivable that although liver is a major organ responsible for the Hp biosynthesis, the net increase in plasma Hp, may be directly originated from the leukocytes (at least in part) following exercise. Clinically, increase in leukocytes count, particularly neutrophils, after microbial infection is very common. The present study provides evidence that a substantial elevation of Hp is associated with the neutrophil increase (mobilized from the lymphatic pool). These findings could be relevant for most inflammatory responses when neutrophils level increases in the circulation. It also suggests that Hp levels could be the marker for the neutrophil functional activity.

Given the ability of neutrophil to secret the anti-inflammatory molecule Hp into circulation, we suggest that neutrophil mobilization from the lymphatic system or bone marrow may play a role as a physiologic repair mechanism to inflammatory tissue injury. The application of mild exercise to actively elicit the plasma Hp expression in preventing infections or in reducing chronic inflammation needs further investigations.

5. Acknowledgments

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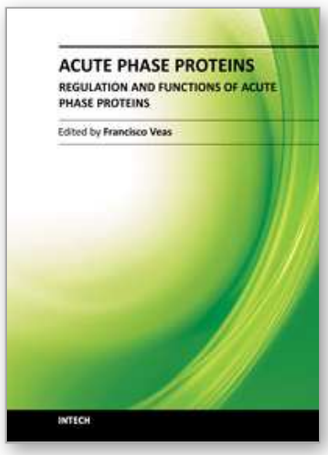

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The two volumes of Acute Phase Proteins book consist of chapters that give a large panel of fundamental and applied knowledge on one of the major elements of the inflammatory process during the acute phase response, i.e., the acute phase proteins expression and functions that regulate homeostasis. We have organized this book in two volumes - the first volume, mainly containing chapters on structure, biology and functions of APP, the second volume discussing different uses of APP as diagnostic tools in human and veterinary medicine.

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