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REVIEW

Hypoxia-inducible Factor 1 as one of the "Signaling Drivers" of Toll-like Receptor-Dependent and Allergic Inflammation

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Abstract Hypoxia-inducible factor 1 (HIF-1) is a heterodimeric transcription complex which plays a crucial role in cellular adaptation to low oxygen availability. In the last years there has been increasing evidence about the role of this factor in inflammatory/innate immune reactions. It has also been found to contribute to different types of allergic inflammation. In this review the current knowledge about the accumulation and role of HIF-1 in Toll-like receptor-mediated and allergic inflammation is summarized. Differential biochemical mechanisms employed to stabilize the protein in different cases are discussed.

Keywords Inflammation · Allergy · Toll-like receptors · Hypoxia · HIF-1

Toll-like receptors (TLRs) are pattern-recognition receptors (PRRs) that allow host mammalian immune cells to specifically recognize different molecular patterns shared by pathogens (bacteria, fungi, viruses) and induce inflammatory/innate immune reactions to them (Akira and Takeda 2004; Beutler 2004; Gay and Gangloff 2007). TLRs therefore lie at the core of resistance to infectious disease. The discovery of the TLRs as sensors of pathogen-associated molecular patterns transformed the views of discrimination between "self" and "nonself", a key requirement of any immune system. TLRs are now considered the key PRRs that allow mammals, whether immunologically naive or experienced, to detect pathogens (Akira and Takeda 2004; Beutler 2004; Gay and Gangloff 2007; Iwasaki and Medzhitov 2004). Noninfectious stimuli that have been used for many years to study inflammatory mechanisms can activate the proteins that belong to the TLR family (Gay and Gangloff 2007). In addition, it is now clear that many inflammatory processes, both sterile and infectious, may depend on TLR signaling (Akira and Takeda 2004; Gay and Gangloff 2007). Examples of such components include lipopolysaccharides (LPS, recognized by TLR4), lipopeptides (by cooperation of TLR2 with TLR1 or TLR6), viral single- or double-stranded RNA (by TLR7/TLR8 and TLR3, respectively), bacterial or viral DNA containing CpG motifs (by TLR9), flagellin (by TLR5), protozoan profilin-like protein, and unidentified ligands of uropathogenic bacteria (TLR11) (Beutler 2004; Gay and Gangloff 2007; Medzhitov et al. 1997; Medzhitov and Janeway 2000; Yarovinsky et al. 2005). TLR activation results in the recruitment of signaling intermediates, which include myeloid differentiation factor-88 (MyD88), Toll-interleukin (IL)-1 receptor (TIR)-associated protein (TIRAP, also known as MAL), TLR-associated activator of interferon, TLR-associated molecule, IL-1 receptor-associated kinases (IRAK), and tumor necrosis factor (TNF) receptor-associated factor 6 (Akira and Takeda 2004; Gay and Gangloff 2007). The significance of TLRs in the activation of adaptive immunity is also well investigated; TLR-mediated activation of dendritic cells (DCs) is a crucial step in this process (Akira and Takeda 2004; Gay and Gangloff 2007; Iwasaki and Medzhitov 2004). The control exerted by TLRs in linking innate and adaptive immunity is instrumental in the efficacy of vaccines that contain TLR ligands. TLRs are expressed in many leukocytes and tissue cell types; however, the key effectors of inflammation/innate immunity are myeloid macrophages, neutrophils, as well as DCs (Akira

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and Takeda 2004; Gay and Gangloff 2007; Iwasaki and Medzhitov 2004).

Another type of mammalian/human inflammatory reaction is the noninfectious allergic inflammation, which is considered as an important pathological feature of a number of disorders such as allergic asthma, atopic dermatitis, allergic rhinitis, and several ocular allergic diseases (Crivellato et al. 2009). The key effectors of allergic inflammation are mast cells and basophils (Galli et al. 2008; Crivellato et al. 2009). Both mast cells and basophils are granulated cells which play complex and partially overlapping roles in adaptive and innate immunity. This includes both effector and regulatory activities. Mast cells are known to express a number of pro-angiogenic factors during inflammation that stimulate the process of angiogenesis (Crivellato et al. 2009; Gould et al. 2003; Grimbaldeston et al. 2006). Recent evidence clearly demonstrated that basophils also play a role in inflammation-related angiogenesis, principally, but not exclusively, through the expression of several forms of vascular endothelium growth factor (VEGF) and its receptors (Crivellato et al. 2009; Falcone et al. 2000; Min et al. 2004; Min and Paul 2008; Prussin and Metcalfe 2003; Sumbayev et al. 2009). Basophils and mast cells are considered as distinct hematopoietic lineages that can express complementary or overlapping functions during acute and chronic immunoglobulin E (IgE)-associated allergic reactions (Crivellato et al. 2009; Falcone et al. 2000; Min et al. 2004; Min and Paul 2008; Prussin and Metcalfe 2003).

Both mast cells and basophils express the tetrameric form of the cell membrane-associated high-affinity receptor FcεRI for IgE on their surface and both kinds of cells are crucial effectors in T-helper 2 (Th2) cell-dependent IgE-associated allergic disorders. Due to its affinity to FcεRI, IgE possesses a crucial role in the hypersensitivity response, but other IgE-independent mechanisms, such as TLR activation processes, may intervene. Activated mast cells and basophils express and release Th2 cytokines (IL-4, IL-5, IL-9, and IL-13) that polarize the immune reaction and produce biochemical mediators such as histamine as well as lipid metabolites, which are critical for vasoactive, immunoregulatory, and chemotactic functions (Crivellato et al. 2009; Falcone et al. 2000; Gould et al. 2003; Grimbaldeston et al. 2006; Min and Paul 2008; Schroeder et al. 2001). In both cases, the inflammatory process assumes several crucial stages:

(1) recognition of the pro-inflammatory ligand (TLR ligands or IgE) by the specific membrane-associated or endosomal receptor;
(2) cellular stress (pro-inflammatory stress caused by induction of the catalytic activity of dozens of kinases and molecular oxygen-consuming enzymes);
(3) adaptation of the effector cells to stress: the effector cells employ the intracellular signaling mechanisms which protect them against death, allowing such cells to properly induce inflammatory reactions;
(4) inflammation: the expression/release of pro-inflammatory cytokines that induce further reactions;
(5) programmed death of the effector cells: the inflammatory process culminates in the programmed death (apoptosis) of the effector cells.

One of the most important stages is the adaptation of the effector cells to pro-inflammatory ligand-induced stress. During such stress, many kinase cascades become activated, which eventually leads to the expression of pro-inflammatory cytokines. This type of inflammatory stress is always associated with decreased oxygen availability due to the accumulation of immune cells in the injured tissue (Walmsley et al. 2005). In addition, inflammatory stress leads to an increase in intracellular oxygen consumption and therefore could quickly lead to the depletion of ATP followed by the death of the effector cells (Cramer et al. 2003). Recent evidence has clearly demonstrated that immune cells employ hypoxia-inducible factor 1 (HIF-1) transcription complex (Cramer et al. 2003; Walmsley et al. 2005, Zarember and Malech 2005) during the inflammatory process. In the present review we aim to summarize the current knowledge about the functional role of the HIF-1 transcription complex in TLR-mediated and allergic inflammation.

Biochemistry of HIF-1 Transcription Complex and its Accumulation

HIF-1 is a heterodimeric transcription complex consisting of two subunits, HIF-1α and HIF-1β. HIF-1β (also known as aryl hydrocarbon receptor nuclear translocator or ARNT) is a common binding subunit of not just HIF-1α, but also many basic helix-loop-helix heterodimeric transcription factors with Per-Arnt-Sim domains. HIF-1β is constitutively expressed in the cells (Semenza 2002). HIF-1α is the oxygen-regulated subunit which rapidly accumulates in cells exposed to hypoxia. Under well-oxygenated conditions, HIF-1α protein undergoes rapid ubiquitination followed by proteasomal degradation. HIF-1α interacts with the von Hippel-Lindau protein (pVHL), which binds directly to its oxygen-dependent degradation domain and targets it for proteasomal degradation. VHL is associated with elongins B and C, cullin-2, and likely other factors that constitute part of an E3 ubiquitin ligase that functions as a multiprotein complex. Interaction between pVHL and the oxygen-dependent degradation domain of the HIF-1α subunit is regulated

through hydroxylation of 402/564 proline residues by enzymes known as prolyl hydroxylases (PHDs) (Epstein et al. 2001; Huang et al. 1998; Ivan et al. 2001; Jaakkola et al. 2001; Maxwell et al. 1999, Semenza 2002; Sumbayev and Yasinska 2007). HIF-1α PHDs have a requirement for dioxygen, iron, 2-oxoglutarate (2-OG), and ascorbic acid. Under hypoxic conditions, prolyl hydroxylation of the HIF-1α subunit is suppressed, leading to stabilization/accumulation of the protein (Semenza 2002; Sumbayev and Yasinska 2007).

Hypoxia is a physiological environment for the host innate immune defense against pathogens. However, pro-inflammatory ligands could also induce the accumulation of HIF-1α and subsequently transactivation of the HIF-1 complex under normal oxygen availability. This factor is required for the promotion of angiogenesis, support of energy metabolism, and protection of the effector cells against quick programmed death induced by inflammatory stress (Cramer et al. 2003; Walmsley et al. 2005; Zarember and Malech 2005).

Biochemical Mechanisms Leading to the Accumulation/Activation of HIF-1α Protein During TLR-induced and Allergic Inflammatory Reactions

To date, a number of studies have reported the accumulation of HIF-1α protein and transactivation of HIF-1 transcription complex by different types of innate immune cells in response to stimulation with TLR ligands (Blouin et al. 2004; Oda et al. 2006; Walmsley et al. 2005; Peyssonnaux et al. 2007; Nicholas and Sumbayev 2009). Intriguingly, both membrane-associated and endosomal TLRs were found to trigger the accumulation of HIF-1α protein. Furthermore, experimental evidence has recently shown that HIF-1α protein is activated in primary human mast cells and basophils during pro-allergic responses. However, despite a number of similarities in signaling cascades employed in all of the above cases, HIF-1α is accumulated via differential mechanisms. Even membrane-associated and endosomal TLRs recruit, to some extent, different signaling systems to bring about HIF-1α protein accumulation.

At the moment, two types of membrane-associated TLRs (TLR4 and TLR2) are known to induce the accumulation of HIF-1α (Blouin et al. 2004; Djafarzadeh et al. 2008; Frede et al. 2006; Sumbayev 2008a). In addition, it was recently reported that HIF-1α coordinates the induction of TLR2 and TLR6 during hypoxia (Kuhlicke et al. 2007). However, the biochemical mechanisms leading to HIF-1α accumulation have been studied mostly for TLR4. In this case, a redox-dependent mechanism is the major player in the accumulation process (Nishi et al. 2008; Oh et al. 2008; Sumbayev 2008a). In addition, protein phosphorylation is also required for successful accumulation/transactivation of HIF-1α protein (Sumbayev 2008a). Furthermore, an increase in protein expression was found to take place (Blouin et al. 2004; Sumbayev 2008a). Upon interaction with the ligand (LPS), the intracellular TIR domain of the TLR4 recruits myeloid differentiation factor 88 (MyD88), which interacts with Bruton's tyrosine kinase (Btk). Btk has to be phosphorylated by Src and most likely other tyrosine kinases before it joins the pathway. Upon interaction with MyD88, Btk phosphorylates TIRAP, which gains affinity for and thus interacts with the MyD88 (Gray et al. 2006; Schwartzberg 2003). The MyD88-TIRAP complex is crucial for the main TLR4 downstream pathway leading to the activation of transcription factors (such as NF-κB and AP-1) and therefore the expression of pro-inflammatory cytokines (Akira and Takeda 2004). Btk at the same time phosphorylates PI-3-specific phospholipase C (PLC-1γ), which then gains catalytic activity (Gray et al. 2006; Schwartzberg 2003; Sumbayev 2008a). Active PLC-1γ indirectly leads to the activation of the protein kinase C (PKC) α and β isoforms (He et al. 2006; Sumbayev 2008a, b). PKCα/β could then phosphorylate the protein p47phox (Koff et al. 2006; Siow et al. 2006). After phosphorylation, the p47phox induces the assembly of the cell membrane-associated six-protein complex, which upon formation gains NADPH oxidase activity and the capacity to produce reactive oxygen species (ROS) (Koff et al. 2006; Nishi et al. 2008; Oh et al. 2008; Siow et al. 2006; Sumbayev 2008a), which are known to contribute to the accumulation of HIF-1α (Dehne and Brune 2009).

In addition, the redox-dependent mechanism employed for HIF-1α accumulation is further supported by MAP kinase pathways. Apoptosis signal-regulating kinase 1 (ASK1), its downstream p38 MAP kinase, and ERK were found to contribute to the LPS-induced TLR4-dependent accumulation of HIF-1α protein (Frede et al. 2006; Sumbayev 2008a). We recently reported that LPS-dependent TLR4 signaling triggers cross-talk of ASK1 and HIF-1α protein (Sumbayev 2008a). ASK1 is selectively required for the activation of the p38 MAP kinase isoforms during TLR4 downstream signaling (Hayakawa et al. 2006; Matsuzawa et al. 2005; Sumbayev and Yasinska 2006). p38 is required for the stabilization of HIF-1α protein in different cases and was also found to directly phosphorylate the protein (Kwon et al. 2005; Sumbayev 2008a). This phosphorylation process takes place during LPS-induced HIF-1α accumulation (Sumbayev 2008a). Earlier reports clearly demonstrated that ERK is critical for TLR4-induced HIF-1α accumulation (Frede et al. 2006). ERK is also known to directly phosphorylate HIF-1α protein at least at two sites (Ser-641 and Ser-643) (Mylonis et al. 2006). However, ERK-dependent phosphorylation of HIF-1α has

not been yet investigated in the case of LPS-dependent accumulation of this protein. Therefore, ERK could possibly phosphorylate HIF-1α protein. On the other hand, it could influence expression of the HIF-1α gene. Blouin and coauthors found that the PI3 kinase (PI3K) pathway also contributes to the LPS-induced accumulation of HIF-1α protein (Blouin et al. 2004). Most likely, in this case, PI3K positively influences the expression of HIF-1α protein via NF-κB (Blouin et al. 2004). This hypothesis is further supported by the fact that IL-1β promotes HIF-1α accumulation in a PI3K/NF-κB-dependent manner (Jung et al. 2003). Since the intracellular signaling (TIR) domain of the IL-1β receptor is similar to that found in TLRs (Garlanda et al. 2009), their downstream signaling mechanisms are most likely similar in principle. We subsequently found that PI3K is critical for tracking ASK1 activity, which is important for protection of the cells against ASK1-induced programmed cell death (Sumbayev 2008b). Before that, Akt, the PI3K downstream kinase, was reported to specifically phosphorylate ASK1 on the Ser 83 residue, which down-regulates the activity of ASK1 (Kim et al. 2001). It is likely that this mechanism is employed to prevent the pro-apoptotic overactivation of ASK1. At later stages, S-nitrosation of ASK1 also takes place (Sumbayev 2008b). S-nitrosation of ASK1 could lead to a decrease in its catalytic activity (Park et al. 2004; Yasinska et al. 2004). Therefore, these two mechanisms (the PI3K pathway and S-nitrosation) possibly influence the activity of ASK1, allowing its pro-inflammatory function but preventing the enzyme from inducing apoptosis. This "anti-apoptotic" activity of PI3K could also possibly positively influence the activity of HIF-1α protein since apoptosis is normally associated with a decrease in HIF-1α accumulation/activity. One could also speculate about the role of HIF-1 in the downregulation of the ASK1 catalytic activity as the gene encoding ASK1 inactivating protein phosphatase 5 has hypoxia-responsive elements and is up-regulated by the HIF-1 transcription complex (Zhou et al. 2004). All the pathways described above are summarized in the Fig. 1a.

In the case of endosomal TLRs (TLR7 and TLR8) it was found that differential mechanisms are employed to activate HIF-1α protein. In this case, a redox-dependent mechanism similar to that reported for TLR4 also takes place. However, at later stages, IRAKs 1 and 4 also seem to participate in the activation of NADPH oxidase and therefore to influence the generation of ROS (Nicholas and Sumbayev 2010). Earlier reports demonstrated the contribution of IRAK1/4 to the phosphorylation of the p47phox and consequently the assembly of the NADPH oxidase complex during TLR signaling (Pacquelet et al. 2007). It is most likely that this reaction takes place in the case of TLRs 7 and 8. Reactive nitrogen species (RNS) are also involved in the ligand-induced TLR7/8-mediated

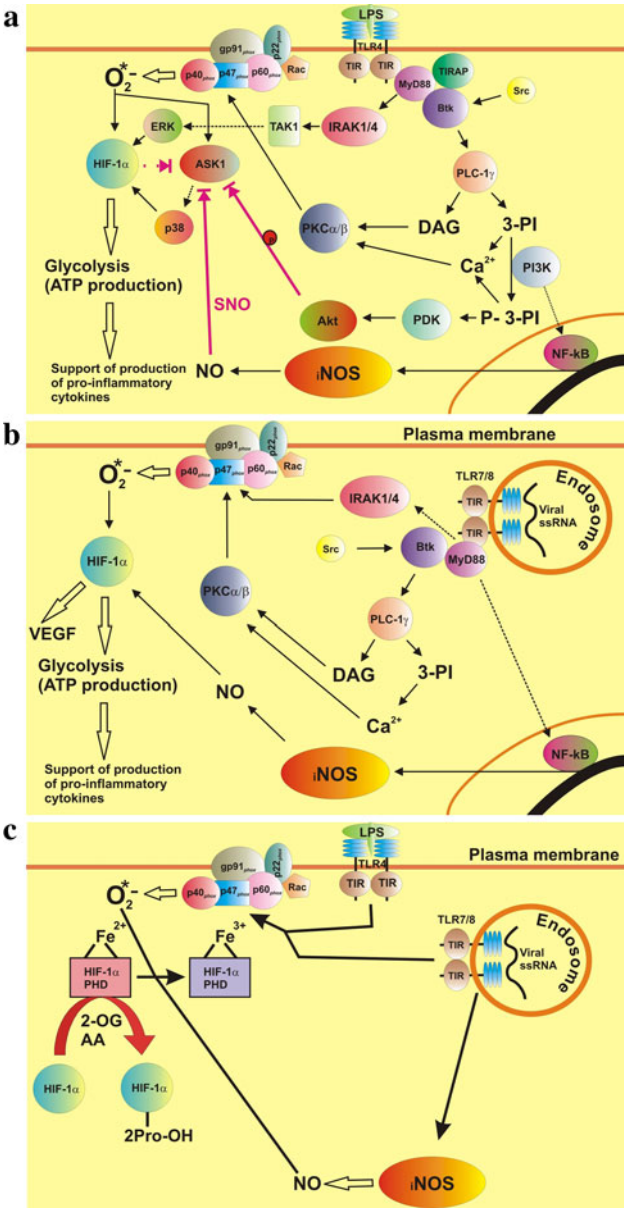

Fig. 1 Biochemical mechanisms of HIF-1α protein accumulation/activation during TLR signaling. Mechanisms leading to the accumulation and activation of HIF-1α protein during ligand-induced TLR4- (**a**) and TLR7/8- (**b**) mediated inflammatory process are presented. Proposed molecular mechanisms of TLR-dependent downregulation of HIF-1α prolyl hydroxylation are also outlined (**c**)

accumulation of HIF-1α protein (Nicholas and Sumbayev 2010). ASK1, PI3K, ERK, and p38 do not seem to influence HIF-1α accumulation/activation in this case (Fig. 1b) (Nicholas and Sumbayev 2010). HIF-1α protein is a known potential target for S-nitrosation (Sumbayev et al. 2003; Sumbayev and Yasinska 2007). However, further experiments clearly demonstrated that S-nitrosation is not the major player in TLR7/8-mediated HIF-1α accumulation (Nicholas and Sumbayev 2010). In the case of TLR4 only

ROS and in the case of TLR7/8 both ROS and RNS down-regulate HIF-1α prolyl hydroxylation, leading to the accumulation of the protein, which fails to interact with VHL protein (Nicholas and Sumbayev 2010). This correlates with a decrease in the content of intracellular Fe^{2+} (Nicholas and Sumbayev 2010). These results suggest that oxidation of the intracellular iron most likely leads to the down-regulation of Fe^{2+}-dependent enzymes (which include HIF-1α PHDs). Similar observations about inhibition of the VHL-dependent degradation were reported for the IL-1β-induced accumulation of HIF-1α protein (Jung et al. 2003).

NADPH oxidase-derived ROS were reported to down-regulate the HIF-1α prolyl hydroxylation/VHL interaction in other cases (for example, intermittent hypoxia) (Yuan et al. 2008). Earlier reports suggested that exposure of human myeloid macrophages to LPS in the presence of the proteasome inhibitor MG132 is associated with the presence of both stabilized non-ubiquitinated HIF-1α and poly-ubiquitin HIF-1α (Frede et al. 2006). This might mean that the interaction of hydroxylated HIF-1α with VHL followed by ubiquitination still exists when the cells are exposed to LPS. It might also mean that LPS treatment induces the accumulation of HIF-1α, which is both dependent and independent of VHL binding. The possibility of affected PHD activity was supported in experiments demonstrating decreased expression of these enzymes in cells exposed to LPS (Peyssonnaux et al. 2007) and was further confirmed by our experiments that demonstrated decreased but not attenuated HIF-1α prolyl hydroxylation in human myeloid macrophages when exposed to LPS (Nicholas and Sumbayev 2010). Recent evidence suggested that LPS induces an oxidative burst via activation of NADPH oxidase, which generates superoxide that is further converted into other ROS (Nishi et al. 2008; Oh et al. 2008; Sumbayev 2008a). This leads to changes in the intracellular redox status and to an increase in iron (II) oxidation to the iron (III), affecting the catalytic activity of iron-containing enzymes such as PHDs (Dehne and Brune 2009; Nicholas and Sumbayev 2010; Sumbayev and Yasinska 2007). These biochemical mechanisms of the TLR-mediated downregulation of HIF-1α prolyl hydroxylation are summarized in the Fig. 1c.

During allergic inflammation, HIF-1α protein is also known to be stabilized in mast cells as well as in basophils (Lee et al. 2008; Sumbayev et al. 2009). Recent evidence has indicated that an increase in HIF-1α expression occurs in mast cells in response to stimulation with ovalbumin. This is achieved via the PI3K pathway (Lee et al. 2008). In primary human basophils it has also been found that HIF-1α protein becomes accumulated in an IgE-dependent manner (Sumbayev et al. 2009). However, in this case ERK and p38 MAP kinase contribute to the protein accumulation. Interestingly, ASK1, ROS, and PI3K did not influence anti-IgE-induced HIF-1α accumulation in primary human basophils (Sumbayev et al. 2009). A further report demonstrated that the contact allergen nickel induces the accumulation of HIF-1α protein in primary endothelial cells (Viemann et al. 2007). In this case, activated p38 MAP kinase does not interfere with the accumulation of HIF-1α protein, but modulates HIF-1α-dependent transactivation (Viemann et al. 2007). Based on the above statement one could conclude that HIF-1α protein is accumulated in the immune cells during allergic inflammation. Overall, HIF-1α protein is accumulated in the cases of infectious TLR-mediated inflammatory reactions as well as during allergic inflammation. However, in each case differential biochemical mechanisms are involved in the HIF-1α accumulation/activation process. However, the detailed biochemical mechanisms of the accumulation process remain unclear and further detailed investigations have to be performed to clarify it.

Functional Role of HIF-1 Protein in Inflammatory Reactions

The major function of the HIF-1 transcription complex in inflammatory reactions is the promotion of angiogenesis (Cramer et al. 2003; Walmsley et al. 2005). In all reported cases, HIF-1 activates the expression of VEGF isoforms and their receptors. This event is crucial for angiogenesis that allows the cells/tissues involved in the innate immune reaction to overcome the conditions of limited oxygen availability (Cramer et al. 2003; Walmsley et al. 2005). In addition, HIF-1 downstream genes include those involved in support of glycolysis and energy metabolism (Semenza 2002). Active immune cells normally become dependent on glycolysis due to decreased oxygen availability (Oda et al. 2006). The expressions of several glycolytic enzymes (glyceraldehyde-3-phosphate dehydrogenase, triosophosphate isomerase-1, lactate dehydrogenase) as well as glucose transporters 1/3 are controlled by the HIF-1 transcription complex (Walmsley et al. 2005; Zarember and Malech 2005). HIF-1 therefore supports glycolysis and energy metabolism, preventing ATP depletion and thus protects the cells against death and supports the production of pro-inflammatory cytokines (IL-6 and TNF-α in the case of TLR-mediated and IL-4 in the case of allergic inflammation) (Lall et al. 2008; Nicholas and Sumbayev 2010). Another report demonstrated the importance of HIF-1 for the LPS-induced production of TNF-α, IL-1, IL-4, IL-6, and IL-12 (Peyssonnaux et al. 2007). It is also important to mention that the HIF-1 transcription complex is crucial for the process of adhesion of the immune cells. The expression of CD18 β_2 integrins is also controlled by the HIF-1 transcription complex (Walmsley et al. 2005). Therefore,

independently of the molecular mechanism leading to the accumulation of the HIF-1α protein in the immune cells, one could define the following functions of the HIF-1 transcription complex during the process of infectious TLR-mediated and noninfectious allergic inflammation:

(1) promotion of angiogenesis;
(2) support of glycolysis and energy metabolism;
(3) protection of the effector cells against death;
(4) support of the expression of pro-inflammatory cytokines;
(5) adhesion of immune cells.

These results were obtained in both in vitro and, what is more important, in vivo studies. In vivo experiments have shown that HIF-1 is critical for the inflammatory response (Cramer et al. 2003; Walmsley et al. 2005). It was first found that activation of HIF-1 is essential for myeloid cell infiltration and activation via a VEGF-independent mechanism. Loss of VHL led to a large increase in acute inflammatory responses. HIF-1 was therefore considered essential for the regulation of glycolytic capacity in myeloid cells in vivo. Absence of HIF-1α led to a dramatic reduction in the intracellular ATP pool (Cramer et al. 2003). This metabolic defect resulted in profound impairment of myeloid cell aggregation, motility, invasiveness, and bacterial killing (Cramer et al. 2003). HIF-1 is therefore directly involved in the regulation of survival and function in the inflammatory microenvironment (Cramer et al. 2003). Further experiments suggested that HIF-1 is also critical for the maturation of DCs responsible for the presentation of the antigen (Jantsch et al. 2008). In addition, in in vivo experiments this transcription complex was found to be critical for the development of LPS-induced TLR4-mediated sepsis, a process which reflects a detrimental host response to infection in which bacteria or LPS act as potent activators of immune cells, including monocytes and macrophages (Peyssonnaux et al. 2007). Importantly, expression of HIF-1α protein was found to regulate the bacterial capacity (bactericidal activity) of phagocytes (Peyssonnaux et al. 2005).

It is important to mention that HIF-1α is a principle member of the HIF-family. The latter contains HIF-2α and HIF-3α, which have to some extent similar functions and a number of similar regulatory mechanisms to HIF-1α (Jelkmann 2004; Prabhakar et al. 2009). However, it is still unclear whether these other members of the HIF-family also contribute to the inflammatory/innate immune reactions in a manner similar to HIF-1.

Concluding Remarks

Overall, the HIF-1 transcription complex is an important "signaling driver" of the inflammatory process. As a hypoxia and stress-inducible transcription factor, HIF-1 controls the adaptation of effector immune cells to inflammatory stress, allowing them to survive and generate an inflammatory reaction (expression of the pro-inflammatory cytokines). Furthermore, HIF-1 supports energy metabolism in inflammatory leukocytes and, as such, prevents the depletion of the ATP. Finally, the HIF-1 complex is critical for adhesion of the immune cells, which is vital for the proper innate immune response and its correct linking to the adaptive immune reaction. HIF-1 also seems to play a similar role in allergic inflammation, as suggested by recent promising data. However, further investigations are required to better characterize the functional role of HIF-1 in allergic responses.

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