

Review Article

Interplay between heat shock proteins, inflammation and cancer: a potential cancer therapeutic target

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Received December 21, 2018; Accepted December 28, 2018; Epub February 1, 2019; Published February 15, 2019

Abstract: The historical relationship between cancer and inflammation has long been evaluated, and dates back to the early work of Virchow (1863), where he hypothesised that chronic inflammation as a direct cause of tissue injury and infection, could actually promote tissue proliferation. At that period in time however, the exact mechanisms that mediated this relationship were little understood. Subsequent studies have since then demonstrated that chronic inflammation plays significant roles in microenvironments, mostly in the progression of tumours, probably, through over-secretion of proinflammatory cytokines and other immune-killing apparatus such as reactive oxygen species (ROS) which cause damage to normal cells leading to DNA damage and increased cellular mutation rates. Recently, the identification of DNA lesion 5-chlorocytosine (5-CIC) created by hypochlorous acid (HOCl) secreted to nullify or kill infectious agents and toll-like receptor 4 (TLR4)-mediated chronic inflammation in the human gut, has become the latest evidence linking inflammation directly to cancer. The key to cellular survival and adaptation under unfavourable or pathological conditions is the expression of heat shock proteins (HSPs) also called molecular chaperones. These proteins play essential roles in DNA repair processes by maintaining membrane integrity, orderliness and stability of client proteins that play prominent roles in DNA repair mechanisms. More so, HSPs have also been shown to modulate the effects of pro-inflammatory/apoptotic cytokines through the inhibition of cascades leading to the generation of ROS-mediated DNA damage, while promoting the DNA repair mechanism, thus playing prominent roles in various stages of DNA repair and cancer progression. Hence, studies targeting HSPs and their inhibitors in inflammation, DNA damage, and repair, could improve current cancer therapeutic efficiency. Here the focus will be on the relationship between HSPs, inflammation and cancer, as well as roles of HSPs in DNA damage response (DDR).

Keywords: Heat shock proteins, inflammation, cancer, DNA damage response, 5-chlorocytosine, hypochlorous acid

Heat shock proteins

Due to continuous exposure to cellular stressors (e.g. heat, heavy metal stress, viral and bacterial infections, nutrient deficiency, exercise, oxidative stress, cold, acute or chronic inflammatory diseases, ischemia injury, drought, UV-light), cells frequently produce a family of evolutionary conserved proteins termed heat shock proteins (HSPs) or molecular chaperones [1, 2]. These proteins enable cell survival under pathological conditions, metabolic changes and environmental adaptation, which may lead to protein aggregation and denaturation thus resulting in several neurodegenerative

disorders such as motor neuron, frontal temporal lobar degeneration, Alzheimer's, Huntington's and Parkinson's diseases, as well as aging and cancer [3-5]. Although most of these polypeptides are generally expressed upon thermal induction and stress, some that are involved in the folding of nascent proteins, signal transduction and translocation of organelles across cellular membranes, are constitutively expressed under physiological states and are termed heat shock cognate (Hsc) proteins [6-8]. These constitutively expressed HSPs perform important 'housekeeping' activities, which are critical in maintaining cellular homeostasis [9].

HSPs were first identified in the salivary glands of *Drosophila* larvae by Ritossa in the early 1960s and are broadly categorized into two main groups: high molecular weight and small heat shock proteins. High molecular weight HSPs (hHSPs) range from 40 to 110 kDa, (including HSPs 110, 100, 90, 70 and 60), and are ATP-dependent. They bind nascent and non-native proteins, and actively refold them into their 3-D structure. They also direct irreparable proteins to proteasomal degradation [9]. Small molecular weight HSPs (sHSPs) on the other hand, range from 8 to 30 kDa (including HSPs 40, 27, 15, 10 and ubiquitin), and are ATP-independent. These proteins, especially those which are encoded by *HSPB* genes, are structurally classified by flanking C- and N-terminal residues characterized by the existence of well-preserved α -crystallin and β -sandwich domains [10]. They are involved in the refolding of misfolded peptides, degradation of irreversible proteins and prevention of stress labile polypeptide aggregations [11]. More so, these proteins have been shown to be involved in complex immune responses to diseases such as cancer, as well as participate in the modulation of several inflammatory cascades, especially in the microenvironment [10].

Inflammation

Inflammation, forms part of the non-specific immune system and is the first line of defense in response to all forms of cellular injuries (e.g. viral or bacterial infections, toxins and chemicals) and is identified normally by heat, pain, redness, and swelling in the inflamed area [12]. Inflammatory response clears cellular damage caused by cellular injuries and initiates cellular repair and healing. It can be broadly classified into two: acute and chronic inflammation. Acute inflammation is a short-term and a self-limiting response that occurs under physiological conditions. It is thought to be beneficial to the cellular system when short-lived, but if long-termed and uncontrolled, it could degenerate into chronic inflammation characterized by increased inflammatory mediators, acute-phase reactants, inflammatory signalling pathway activation and increased production of abnormal cytokines [13]. Chronic inflammation leads to the destruction of several healthy cells and tissues, and in most cases, degenerates into organ failure and mortality, as observed in several human inflammatory diseases (HIDs) and

cancer [14]. The major causes of chronic inflammation are currently still a topic of debate. Recent studies, however, have shown that inflammatory instigators such as microbial infections or bodily injuries are not the only causes. Hormonal imbalance and malfunctioned tissues caused by complications from other human diseases such as aging, HIDs and cancer also play a major role [15, 16].

Inflammatory response is normally mediated by proinflammatory signalling molecules as well as the secretion of proteins called cytokines. Cytokines are a large group of molecular proteins that are secreted normally by the Helper T-cells and macrophages. These molecules mediate specific interactions and communications between immune cells thus, stimulating inflammatory reactions and immune responses [17]. Generally, cytokines are named according to their mode of action and/or site of production; examples include interleukins produced by leukocytes, lymphokines produced by lymphocytes, chemokines produced to play chemotactic roles, monokines produced by monocytes and interferons [17, 18]. Interleukins (ILs) are the minute component of cytokines immunomodulatory proteins secreted by one leukocyte to act on neighbouring leukocytes, therefore acting as “second molecular messengers” which activate these cells during inflammation and immune response [19]. Unlike other amino acids and steroidal-derived hormones which act on the endocrine system, interleukins act in an autocrine or paracrine manner due to their effects on neighbouring cells. ILs can also act as both pro- and anti-inflammatory stimulators and have been reported to modulate immune cell activation, growth, and differentiation during inflammatory reactions, infection and regulation of neuronal proteins, cell injury and invasion [20]. Those ILs which can stimulate inflammation and immune response under both physiological and pathological conditions are grouped into classes (IL1-IL17) according to their common structural elements and peptide sequence conservation. This makes them ideal therapeutic targets in several human diseases [18].

Cancer

Cancer is a group of diseases caused by uncontrolled cell growth, proliferation and invasion, and has the ability to metastasize to other

parts of the body through the bloodstream and lymphatic nervous system [21]. Despite improvements in treatment modalities, this disease persists as one of the leading global health threats in both developed and developing countries. In the United States alone, cancer accounts for higher mortality rate more than heart diseases in individuals below the age of 85 years [22]. Furthermore, statistical and epidemiological studies compiled by the National Centre for Health Statistics (NCHS), National Cancer Institute (NCI), North American Association of Central Cancer Registries (NA-ACCR) and Centres for Disease Control and Prevention (CDC) have shown that 1 in every 4 deaths was as a result of cancer and 1,529,560 new cancer cases and 569,490 deaths were predicted to occur in 2010 [22].

Cancer can be broadly classified according to the tumour cells' originality; these include carcinoma, leukaemia, sarcoma, blastoma and germ cell tumour [23]. Carcinomas originate from epithelial cells such as colon, lung, breast, pancreas and prostate, and are most common in adults [24]. Leukaemia develops from the cell lining of the blood vessels, and they account for almost 30% of cancer cases in young children [25]. Sarcoma develops from connecting tissues outside the bone such as cartilage, nerve, fat and bone. Blastoma originates from immature cells or embryos and is more common in children than in adults [26]. Germ cell tumours originate from the gonads, testes and the ovaries [27].

Cancer and inflammation

Genetic mutations, environmental factors (e.g. ultraviolet radiation, air pollution, ionizing radiation, cancer-causing chemicals and occupational exposures), lifestyle (e.g. smoking, lack of exercise, imbalanced diet and excess alcohol consumption) and hormonal imbalance, have emerged as the major sources of cancer morbidity and mortality worldwide [28, 29]. Although bacterial and viral infections such as human papillomavirus (HPV) are now gaining momentum, persistence chronic inflammation resulting from long-term invasion of infectious (e.g. *Helicobacter pylori*) and non-infectious (e.g. chronic pancreatitis, esophagitis, Barrett's and metaplasia) agents contribute immensely towards the development of several cancer

types [30]. In fact, it is estimated that nearly 25% of all cancer cases are connected to chronic inflammation due to infectious or physico-chemical agents, with persistence *H. pylori* and hepatitis A and C promoting the risk of stomach and hepatocellular carcinoma, respectively [31]. This could be due to improper stimulation and regulation of inflammatory cytokines, as well as immune cells leading to DNA damage and mutation of oncogenes, which in turn leads to tumour development. An adequate stimulation of inflammatory response can lead to quick clearance of the immune cell apparatus and inflammatory cytokines (e.g. chemokines, interleukins) via phagocytosis and apoptosis, immediately after acute inflammation [32]. The phagocytosis of apoptotic factors by phagocytes further supports anti-apoptotic action by promoting the production of anti-apoptotic transforming growth factor- β (TGF- β). Transforming growth factor- β in complex with a serine/threonine kinase binds to TGF- β receptors to trigger signalling cascades that regulate chemotaxis, cell differentiation, proliferation and several immune cell activators resulting in the inhibition of cancer progression [33, 34]. However, inadequate regulation of inflammatory response results in chronic inflammation characterized by massive cellular and tissue destruction and neoplastic transformation, which may lead to cancer progression and other inflammatory diseases [35, 36].

Link between HSPs, inflammation and cancer: a potential cancer therapeutic target

The link between chronic inflammation and cancer has long been an area of debate. Nevertheless, the precise mechanisms by which persistence inflammation leads to cancer are now beginning to unfold. A DNA lesion or site of structural damage in the DNA called 5-chlorocytosine (5-CIC) created by inflammatory cells during the inflammatory response, has been identified as a major DNA mutant that links chronic inflammation to cancer. In response to infectious agents, biological systems stimulate the synthesis of the immune apparatus referred to as "battery of chemical warfare" with the aim of killing infectious agents and initiating cellular repair. These immune apparatus includes T- and B-lymphocytes, leukocytes, interleukins, cytokines, chemokines, reactive nitrogen species (RNS) (e.g. hydrogen peroxide, hypochlorous

acid, and nitric oxide) and ROS. The reactive oxygen molecules designed to nullify the effects of invading pathogens can also in the process cause collateral damage to normal healthy cells resulting in irreparable DNA damage and mutation [37].

For instance, hypochlorous acid (HOCl) generated from the oxidative reaction between H_2O_2 and chloride ions (Cl⁻) catalysed by the heme enzyme myeloperoxidase, plays major roles in the killing of foreign pathogens [38]. However, when in excess and under acidic conditions, this molecule is capable of chlorinating cytosine on the DNA strand to form 5-chlorocytosine, resulting in a lesion seen at the inflammatory site and present during inflammatory-related diseases such as atherosclerosis [39, 40]. Furthermore, because 5-chlorocytosine is relatively unstable, its conversion to 5-chlorouracil either spontaneously or through enzymatic deamination, causes irreparable damages and mutations in DNA which can lead to cancer [41, 42].

The other mechanism directly linking inflammation to cancer is the incidence of toll-like receptor 4 (TLR4) expressions in colon cancer [43]. TLR4 plays a significant role in activating the immune system, inflammatory response, as well as clearance of invading pathogens; however, this receptor can also sustain chronic inflammation, for example, the TLR4 response to bacteria found in the human gut, due to frequent food intake. These bacteria constantly gets replenished, therefore, cannot be completely cleared by the immune response. In this way, TLR4 can sustain persistent chronic inflammation, which is not only involved in cancer formation but also promotes different phases of cancer progression [44].

Moreover, one of the key factors of cellular survival under stressful conditions is the expression of highly regulated and conserved proteins termed HSPs. These proteins are upregulated in response to stress signals such as inflammation and the onset of tumours. Therefore, it is not surprising that these proteins are elevated in every facet of cancer development and inflammatory reactions. According to recent studies, HSPs form part of an immune-inflammatory complex that responds to infectious agents, cellular damage as well as DNA breaks [16]. The DNA is frequently subjected to lesion-

inducing agents, it exogenous (genotoxic chemicals, UV or ionizing radiation) or endogenous (reactive oxidants), which subsequently leads to the generation of several DNA lesions including 5-CIC, double-stranded breaks, single-stranded breaks, and single base modifications. In the case where these errors are not properly repaired, they may lead to genome instability which increases the risk of oncogenesis, as a result, multi-dangerous gene mutations [45]. The evidence of heat shock proteins in reducing mutation frequency in *Saccharomyces cerevisiae* responding to elevated temperature, as well as the elevation of HSP70 in glioblastoma cell lines induced by UV or γ -rays interaction with p53, may however suggest their functions in apoptosis, cell cycle control and DNA repair processes [46, 47]. Furthermore, HSP70 and HSP27 in particular have demonstrated association with base excision repair (BER) enzymes such as human AP endonuclease (APE1) and uracil DNA glycosylase (UDG). This observation suggests the significant roles of HSPs in DNA repair mechanisms, as well as presenting HSPs as modulators of certain DNA repair systems; and since most therapies targeting cancer exert their action by disrupting the normal integrity, structure, and functions of DNA, proper DNA repair mechanisms mediated by HSPs are therefore crucial in maintaining genome stability, integrity and orderliness, which may increase cancer therapeutics efficiency [48, 49].

Interestingly, scientific evidence exist showing that HSPs interact with and stabilize key client proteins that play crucial roles in DNA damage response (DDR) mechanisms and cancer progression. DDR mechanisms refer to pathways that are involved in cell-cycle checkpoints, activation of signalling networks, detection of DNA damage, and induction of cell death or DNA repair [50]. The mechanisms that are involved in the DNA repair processes include base excision repair (BER), direct DNA damage reversal and nuclear excision repair (NER). The ability of DDR to respond to DNA damage is controlled by the balancing act between client protein synthesis and their degradation mediated by HSPs. HSP90 in particular binds to DDR proteins and prevent them from E3 ubiquitin-CHIP (chaperoning) mediated ubiquitination and degradation [49]. These proteins include checkpoint

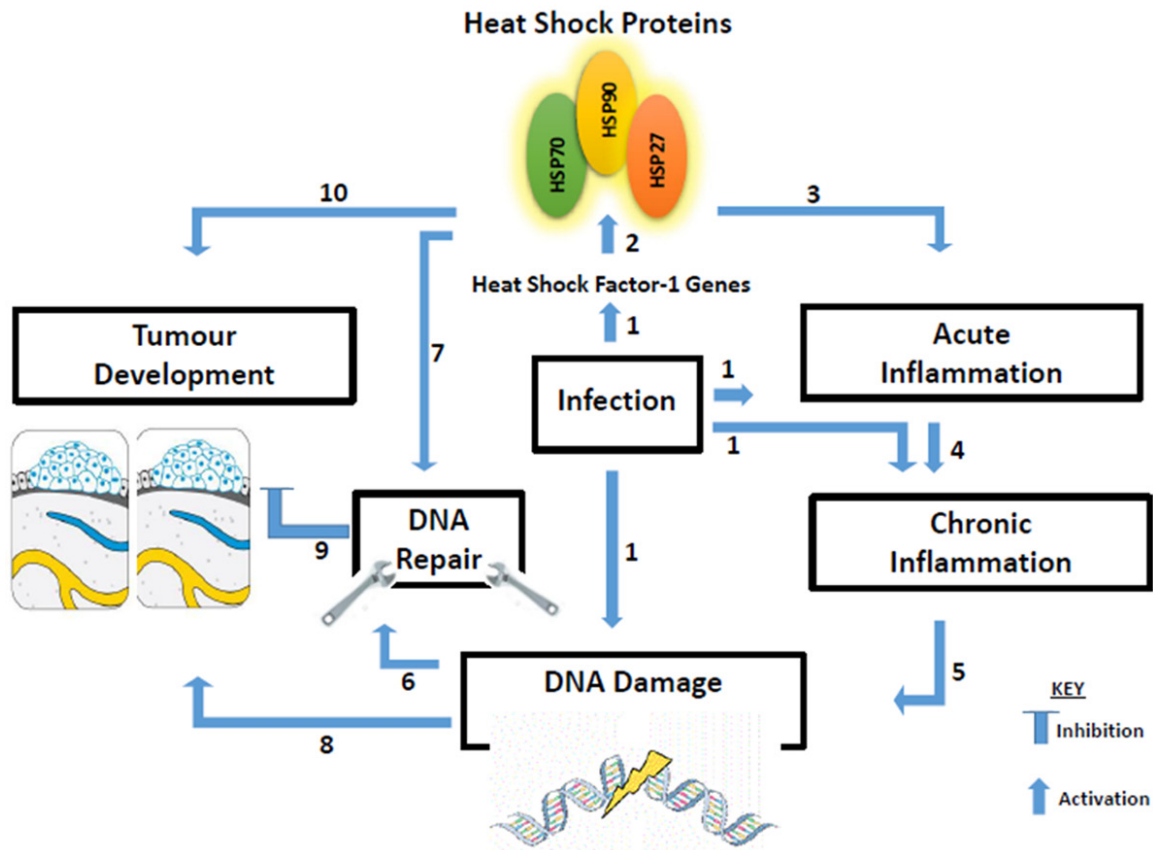


Figure 1. Proposed model showing biological cooperativity between heat shock proteins and inflammation as a promising target towards improved cancer therapeutics. (1) The presence of infection causes the transcription of the heat factor-1 (HSF) gene, which enhances the synthesis of heat shock proteins (HSPs). Infection could also activate acute inflammation, and sometimes initiate chronic inflammatory response and DNA damage directly; (2) Synthesis and activation of HSPs (70, 90, and 27); (3) HSPs together with several immune cells including macrophages, neutrophils, interleukins, and several cytokines as well as ROS (HOCl), form part of acute inflammation aimed at eliminating infectious agents and initiating cellular repair; (4) Nevertheless, if the immune cell apparatus, especially ROS (HOCl in particular) are not properly stimulated, inflammation could persist and degenerates to chronic inflammation. (5) Chronic inflammation is characterized by massive cells and tissue destruction, resulting in DNA damage; (6) DNA damage activates several DDR pathways which can repair DNA damage and prevent accumulation of damaged proteins and tumour development; (7) Central to DNA repair mechanism is the synthesis of heat shock proteins, which maintain and stabilize the DDR proteins and prevent peptides aggregation and cancer; (8) DNA damage and lesions created by chronic inflammation can directly lead to tumour development; (9) If the DDR mechanisms fail due to the presence of HSPs inhibitors, the result could be malignant cells progression; (10) Improper stimulation of HSPs during tumour formation can lead to tumour invasion, progression, and metastasis.

kinase 1 (CHK1), O⁶-meG-DNA methyltransferase (MGMT), MLH1 and MLH2, and APE1, among others.

Emerging evidence has shown that cells inability to repair DNA damage caused by stress has been associated with the loss of genomic integrity, organisation, structure, and function, which may increase the rate of tumour development [51]. These findings reveal the significant roles of HSPs in genetic stability, DDR and tumour progression [52]. Moreover, the roles of HSPs

in inflammation cascades have been well elucidated. According to Ikwegbue and co-workers, HSPs exert cytoprotection against inflammatory reactions through the modulation of inflammation cascades that lead to the activation of pro-inflammatory cytokines such as TNF- α , thereby attenuating chronic inflammation [16]. So far there is no study linking HSPs directly to 5-CIC lesion and DDRs, but it can be hypothesised that a similar mechanism observed in other DNA damages and DDRs is followed. Based on these findings, it is tempting to pro-

pose that any study that is targeting HSPs (especially HSP90) and their inhibitors in membrane and genetic stability, as well as inflammation, could give new mechanistic insight and may serve as a promising target to improve cancer therapeutics efficacy as proposed in the model (**Figure 1**).

Conclusion

Tremendous efforts have been made over the years in devising strategies to prevent, manage, cure and even vaccinate against cancer, yet with several unsatisfactory results. More so, recent studies have focussed on testing therapeutic efficacy of HSPs and HSP inhibitors in cells and animal models, while other efforts are focussed on conducting clinical trials using HSPs in different stages of cancer development. However, any study aimed at understanding the functions of excess HOCl during inflammatory response, and the roles 5-CIC lesion (created by HOCl) which links chronic inflammation to DNA damage, and crucial roles of HSPs in maintaining the integrity and stability of the proteins that are involved in DNA repair processes, could be promising targets in improving current cancer therapies. Based on this promising aspect of HSPs and its inhibitors in inflammation, DNA repair, and cancer, one can therefore be optimistic that improved therapies and a cure for cancer is to be expected soon.

Acknowledgements

Abidemi Paul Kappo is sincerely grateful to the National Research Foundation (NRF), South Africa for a Thuthuka Research Grant and to the University of Zululand Research Committee for funding (Grant No: C387). Paul Ikwegbue and Priscilla Masamba are equally thankful to the National Research Foundation (NRF), South Africa for postgraduate bursaries towards their studies. Londiwe Mbatha acknowledges the University of Zululand Research Committee for a Postdoctoral Research Fellowship, while Babatunji Oyinloye is grateful to Afe Babalola University for an educational advancement scholarship.

Disclosure of conflict of interest

None.

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