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Mini-review

Heat stress: A risk factor for skin carcinogenesis

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ABSTRACT

Recent evidence suggests that heat stress may also be a risk factor of skin carcinogenesis. Heat stress causes activation of heat shock proteins (HSPs), chaperone proteins which prevent cells from undergoing apoptosis and ensuring their cellular function. However, HSPs recruitment may also have deleterious effects particularly if the cells rescued from apoptosis carry oncogenic mutations. We hypothesise that exposures to both heat and UV induce skin cancer(s) by concomitant expression of HSPs and oncogenic mutant proteins. Here we review studies demonstrating that heat stress-activated heat shock proteins such as HSP72 and HSP90 can influence signalling pathways such as MAPK, JNK and p53, which are all involved in regulating cell proliferation, survival and apoptosis.

1. Introduction

Increasing global temperature as a result of climate change is a significant primary environmental issue likely to impact on future climates worldwide. In fact, the Intergovernmental Panel on Climate Change (IPCC), a global organisation dedicated to monitoring climate change, suggested that if global warming continues, the ambient global temperature can be expected to rise between 2 - 4.5 °C by 2100 [1]. This means that arid areas in Australia, which have average temperature ranges of 36–38 °C [2], may normalise at 40–42 °C in the next few decades. This is alarming not only in terms of global ecology but also because it could pose a significant health hazard. There is the possibility that exposure to such extremes of temperature may result in increased incidences of cancer, particularly of the skin.

The core body temperature of 37 °C sustains activity and transcription of genes that are vital for maintenance of cellular homeostasis as well as differentiation and proliferation [3–7]. However, as the body is constantly exposed to the environment, some cells, particularly those located in the skin, may be subjected to increased temperatures with deleterious effects [8]. Exposure to temperatures of 39 °C and above (heat shock), can cause morphological damage to cells. For example, heat-exposed keratinocytes have enlarged nuclei with dispersed chromatin changes [9]. Furthermore heat causes the enlargement of the cytoplasm of melanocytes, as well as an increase in the number and size of their dendritic processes [10].

Higher temperatures can trigger extensive denaturation, degradation and aggregation of critical intracellular proteins triggering cell death pathways [4,11]. The deleterious consequences of increased temperatures are prevented, to some extent, by an adaptive response that ensures cell survival in the presence of heat [12]. The survival pathway activated by heat is the heat shock response, a cascade of events that lead to induction of heat shock proteins (HSPs) which minimise acute cell damage (reviewed by [13]).

Several studies have documented the major pathways involved in the heat stress response in various cells, including epidermal cells [4,14,15]. A major effect of the heat stress response on cells is prevention of apoptosis [16]. As a decreased rate of apoptosis is also a hallmark of cancer, it is possible that heat stress may be a risk factor for cancer, particularly of the skin, since epidermal cells can be constantly exposed to heat stress [17]. The fact that regulators of the heat shock response, namely heat shock factor-1 (HSF-1) and heat shock proteins (HSPs) [18], are commonly found upregulated in many cancer cells, including skin cancer, supports this notion. Furthermore, squamous cell carcinoma has been known to arise from lesions of the heat-induced skin condition called Erythema ab Igne (EAI) [19] which develops in the skin of people constantly exposed to intense heat such as bakers and glass blowers [10]. There is also an increased incidence of

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skin cancers among mine workers, constantly exposed to intense temperatures [20]. Taken together, these facts support the proposal that heat may pose an as yet unidentified risk factor for skin cancer [21].

2. Heat stress and the heat shock proteins

To ensure that cells are protected against environmental stressors, cells have developed protective mechanisms against cellular apoptosis. This protective mechanism is commonly referred to as the heat shock response (Fig. 1) [22,23], and is primarily controlled at the transcription level by the transcription factor heat shock factor-1 (HSF-1) [24]. HSF-1 is normally present in the cytoplasm as a monomer which has no DNA binding capability [25]. However, when cells are exposed to environmental stresses such as heat, monomeric HSFs combine to form trimers which translocate to the nucleus. Once in the nucleus, these transcription factors are activated by phosphorylation and bind to DNA heat shock elements (HSEs) [26]. These HSEs are consensus sequences of DNA located in the upstream promoters of genes responsive to HSF-1 [5,27] including HSPs [28].

The HSP proteins are highly conserved in different species and are expressed in all cells [29]. There are many types of heat shock proteins, but HSP72 and HSP90 are the key proteins involved in the heat shock response [14,30]. These peptides have important roles in various cellular processes but their main function is to act as a molecular chaperone, i.e. they bind to other proteins and mediate their folding, transport and protein–protein interactions [8]. In addition, these HSPs have the ability to direct re-folding of denatured proteins, damaged as a result of heat shock, thus suppressing further damage [11]. As a result, cells are stabilised and protected against heat-induced damage [22].

It is important to note that intense temperatures, particularly above 45 °C (hyperthermia), can lead to the impairment of HSPs and lead to cell death [31]. The exact mechanism by which hyperthermia induces cell death is not clear [32]. However, the general consensus is that death occurs due to the irreversible, unfolding of a significant number of proteins. Resultant protein denaturation leads to defective DNA replication, transcription and repair [33–35], with improper processing of DNA fragments, which results in genomic instability and cell death [36].

By contrast at temperatures between 39 and 43 °C, HSPs protect cells from apoptosis [37], by inhibiting cell death-signalling pathways, c-Jun NH_2 terminal kinase (JNK) and p53 pathways [16,38]. In fact, when HSP72 is overexpressed, the activity of death signalling pathways such as JNK and p53 are decreased [26]. Inhibition of apoptosis may allow DNA damaged cells to survive and proliferate thus contributing to cancer initiation [39,40]. Furthermore, HSP90 has been found to stabilise mutant B-RAF and N-RAS proteins, which normally are controllers of cell proliferation, however when activated by mutations they are constitutively activated leading to oncogenesis [41]. Thus, HSP90 would support their constant activation and oncogenic activity. Interestingly, overexpression of HSPs, particularly the major chaperone proteins HSP72 and HSP90, is common in most cancers including BCC, SCC and melanoma [42–45].

2.1. HSPs and inhibition of cell death-inducing pathways and activation of survival pathways

HSP72 (or HSP70) is part of a family of proteins with the molecular weight of 70 kDa [11]. It is one of the most abundant HSPs and accounts for approximately 2% of all cellular proteins [4]. As mentioned above, expression of HSP72 is very important for the regulation of the heat shock response, and these proteins can transiently interact with various signalling pathways and negatively regulate their function in order to prevent apoptosis [46]. The c-Jun N-terminal kinase (JNK) signalling cascade is one pathway inhibited by heat induced HSPs [47]. This pathway is responsible for activation of apoptosis in damaged cells [48].

JNK is a member of an evolutionarily conserved sub-family of mitogen-activated protein (MAP) kinases. Normally, cellular damage activates JNK, which then induces cleavage of the pro-apoptotic protein Bid and/or phosphorylation of anti-apoptotic proteins Bcl-2 and Bcl-xl, leading to the efflux of cytochrome c from the mitochondria [49]. The efflux of cytochrome c activates caspase 9 and caspase 3, which are members of the caspase family of proteases involved in the activation of cell apoptosis.

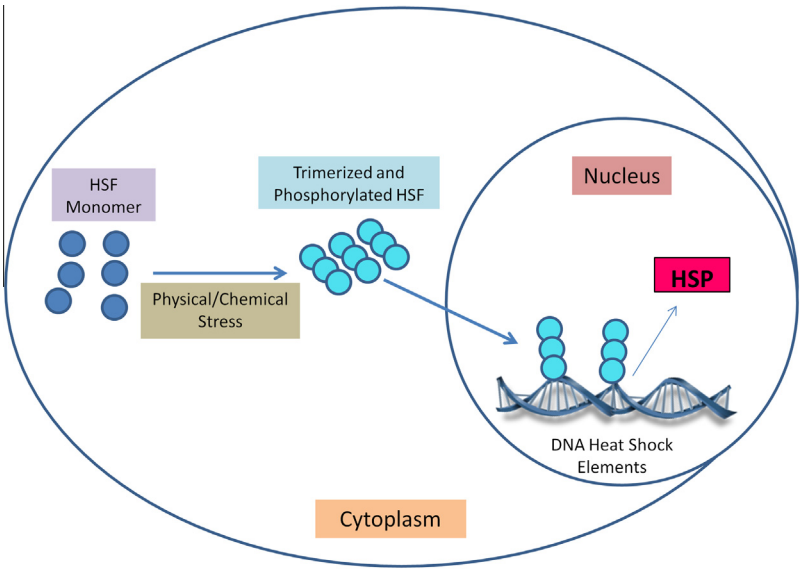

Fig. 1. The heat shock response (adapted from [38]). The heat shock response is activated upon exposure to environmental and chemical stressors. It is initiated by the translocation of phosphorylated, trimeric heat shock factor (HSF) into the nucleus where it binds to heat shock elements promoters leading to expression of chaperone proteins called heat shock proteins (HSPs).