BBA - Reviews on Cancer 1869 (2018) 161–174

Contents lists available at ScienceDirect

BBA - Reviews on Cancer

journal homepage: www.elsevier.com/locate/bbacan

Review

Chaperoning the guardian of the genome. The two-faced role of molecular chaperones in p53 tumor suppressor action

Bartosz Wawrzynow[a], Alicja Zylicz[b], Maciej Zylicz[b,*]

[a] Institute of Biochemistry and Biophysics, PAS, Warsaw, Poland
[b] International Institute of Molecular and Cell Biology, Warsaw, Poland

ARTICLE INFO

Keywords:
Tumor suppressor p53
Heat shock proteins
Mutant p53 gain of function
Chemoresistance
Carcinogenesis

ABSTRACT

Organized networks of heat shock proteins, which possess molecular chaperone activity, protect cells from abrupt environmental changes. Additionally, molecular chaperones are essential during stress-free periods, where they moderate housekeeping functions. During tumorigenesis, these chaperone networks are extensively remodeled in such a way that they are advantageous to the transforming cell. Molecular chaperones by buffering critical elements of signaling pathways empower tumor evolution leading to chemoresistance of cancer cells. Controversially, the same molecular chaperones, which are indispensable for p53 in reaching its tumor suppressor potential, are beneficial in adopting an oncogenic gain of function phenotype when *TP53* is mutated. On the molecular level, heat shock proteins by unwinding the mutant p53 protein expose aggregation-prone sites leading to the sequestration of other tumor suppressor proteins causing inhibition of apoptosis and chemoresistance. Therefore, within this review therapeutic approaches combining classical immuno- and/or chemotherapy with specific inhibition of selected molecular chaperones shall be discussed.

1. Introduction

1.1. The concept of p53 tumor suppressor protein

The p53 protein is a pivotal tumor suppressor, termed “guardian of the genome” on account of its role in maintaining genomic stability and inhibiting tumorigenesis of the cell [1,2]. Under normal conditions the level of genotypic wild type p53 (WT p53) protein is tightly controlled (maintained at low levels) through proteolysis mediated by the ubiquitin-proteasome pathway, intricate translation control, dynamic subcellular relocalization and numerous interactions with other components of transcriptional machinery [3]. Upon stress conditions such as: DNA damage, oncogene activation, telomere erosion, hypoxia, heat shock or ribosomal stress, the p53 protein is stabilized and activated (Fig. 1). Following its activation p53 induces a variety of processes primarily acting as a transcription factor (through the activation and/or repression of specific promoters). Furthermore, it directly interacts with key regulator proteins or is involved in maturation of miRNA regulators. These actions of p53 tumor suppressor protein can lead to cell cycle arrest, initiation of DNA repair processes, metabolic pathway(s) refinement, cellular senescence, autophagy, inhibition of cell invasion and metastatic potential culminating in the induction of apoptosis (Fig. 1) (for review see [4]). In addition to tumor suppressive activity, p53 has been shown to be associated with normal development and cell differentiation, including proper regulation of self-renewal and differentiation of embryonic stem cells (ESC) and adult stem cells (ASC) [5,6]. Moreover, p53 was shown to inhibit cellular transformation within the population of damaged stem cells by selectively inducing apoptosis [7].

A prerequisite for tumor development is often the disruption of normal p53 function. Thus, mutations in the *TP53* gene are acutely common in cancer cells [2,8]. > 70% of them are missense mutations, which result in a single amino acid substitution clustered in the DNA binding domain of the p53 protein [8]. These mutations can be dichotomized into at least two classes: these which disrupt the global conformation of the DNA binding domain (structural mutations), and those that affect DNA binding without affecting the conformational stability of the domain (contact mutations). The inactivating missense mutations of *TP53* are advantageous during cancer development due to their action as trans-dominant inhibitors of WT p53. Moreover, p53 tumor-associated mutants, apart from the canonical loss of tumor suppressor activity, gain new oncogenic functions (GOF) (Fig. 1). This GOF phenotype broadly manifests itself in site-specific regulation of cancer metabolism, malignant progression including increased tumorigenesis and metastasis [9,10]. Within the GOF spectrum, mutant p53 may operate alone or in complex with other proteins. One such group

* Corresponding author at: International Institute of Molecular and Cell Biology in Warsaw, 4 Ksiecia Trojdena Street, 02-109 Warsaw, Poland.
E-mail address: mzylicz@iimcb.gov.pl (M. Zylicz).

https://doi.org/10.1016/j.bbcan.2017.12.004
Received 17 October 2017; Received in revised form 28 December 2017; Accepted 29 December 2017
Available online 31 January 2018

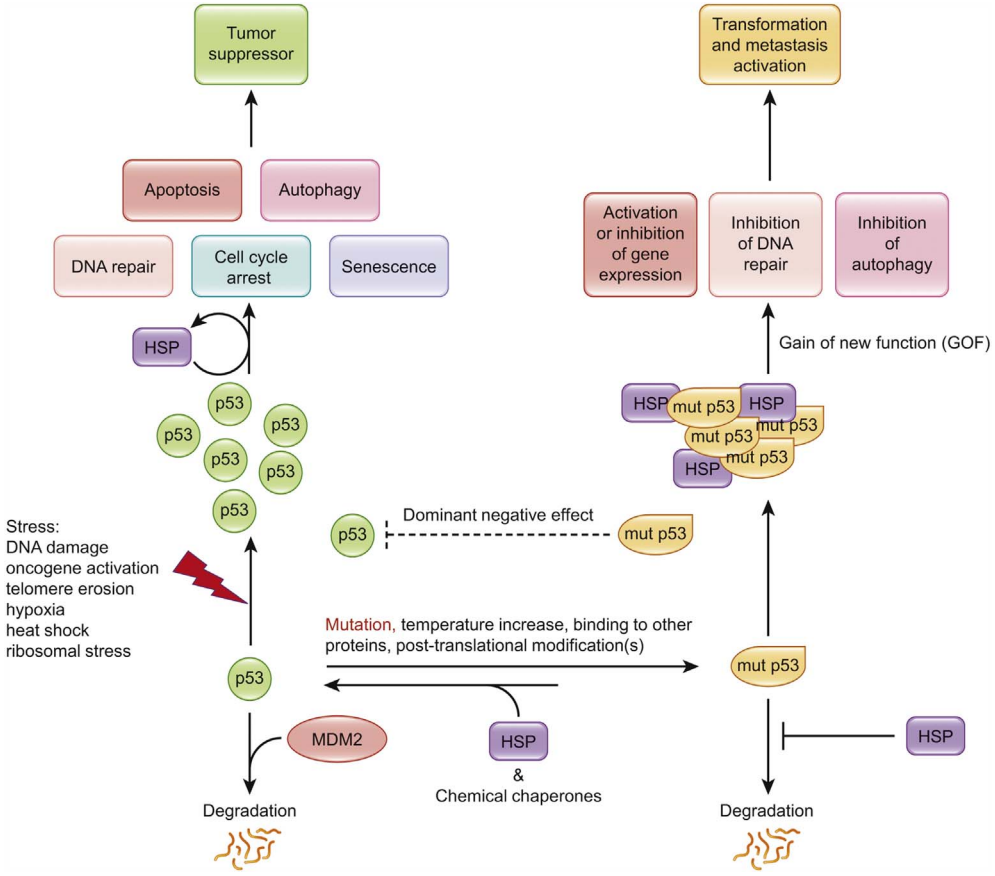

Fig. 1. Tumor suppressor versus oncogene, chaperoning the p53 protein. Detailed description of the figure is presented in the text (Sections 1.1 and 3). Briefly, due to its labile thermodynamic nature, the p53 polypeptide at physiological conditions is in equilibrium between native - wild type and mutant conformations. Molecular chaperones through transient cyclic bind-unwind-release reactions shift this state, so that p53 can adopt its proper tertiary and quaternary structure and carry out its tumor suppressor role. Chemical chaperones such as divalent cations or small molecule agents have a similar end effect. Nevertheless, this dynamic state can be shifted through internal and external stimuli, as depicted. Molecular chaperones in this case, through stable non-cyclical binding, stabilize mutant p53, prevent it from proteasomal degradation, stimulate its dominant negative properties and facilitate the formation of non-canonical quaternary arrangement. In effect, being sequestered themselves to these structures. In other words, the involvement of molecular chaperones belonging to the heat shock protein family, is indiscriminate between p53 tumor suppressor and its pro oncogenic gain of function counterpart. The prime difference is the network organization in which these chaperones act.

comprises of molecular chaperones, which belong to the heat shock family of proteins [11–13].

1.2. The concept of molecular chaperones

The specific three-dimensional fold of proteins governs their biological functions. Protein folding, maintenance of proteome integrity, and protein homeostasis (proteostasis) critically depend on a complex network of molecular chaperones [14–16]. Most molecular chaperones belong to the class of heat shock proteins (HSPs), originally identified as stress-responsive proteins required managing thermal and other proteotoxic stresses. Historically the nomenclature for HSPs was designated in accordance to their approximate molecular weight and consequently the main families of these proteins were distinguished: small HSP (sHPS), HSP40, HSP70, HSP90 and HSP60 (chaperonins). The human genome encodes 11 members of - sHSP (HSPB) with the molecular weight between 15 and 30 KDa, 13 members of the HSP70 (HSPA) family ranging from 66 to 78 kDa, 5 members of the HSP90 (HSPC) family with 85–100 kDa and roughly 14 members of the chaperonin and related cohort, HSP60 (HSPD1, HSPE1, CCT) with molecular weight around 60 kDa [17]. The most abundant group is the HSP40 (DNAJ) or J-like protein family. At present it is known that the human genome encodes 41 members of DNAJ family [18] with very broad range of molecular weight from 10 kDa (DNAJC19) to 254 kDa (DNAJC13) or 520 kDa for J-like protein, DNAJC29 (sacsin) [19].

The first *Hsp* gene [20] and its protein product [21] were identified and biochemically characterized as bacterial DnaK, later to be designated as a prokaryotic ortholog of the eukaryotic *HSP70* (*HSPA*) family. The amino acid sequence, as well as protein function, of HSP70 (HSPA) family members are highly evolutionary conserved [22]. All key biochemical properties of bacterial heat shock proteins such as: i) week ATPase activity of DnaK, which is stimulated by binding to the substrate [21] and by co-chaperone specificity factor DnaJ (HSP40), along with the nucleotide exchange factor GrpE [23], or ii) substrate specificity determined by DnaJ co-chaperone [24] were later confirmed in their eukaryotic orthologs [25,26]. Nucleotide exchange factors (NEFs) not only recycle HSPs bound to client polypeptide [23,27] but also are involved in selective recognition of the client polypeptide [26,28]. Moreover, they were shown to link the HSPA machinery to protein folding, protein disaggregation or proteolysis [14,15,29]. The co-chaperone HOP was demonstrated to link the HSP70 (HSPA) and HSP90 (HSPC) chaperone machines [30]. Apart from the HSPA/HSPC – dependent polypeptide folding, 10 to 15% of nascent polypeptide chains require chaperonins to reach proper native conformation (Hsp60; GroEL, GroES in prokaryotes and CCT (TRiC) chaperonins in eukaryotic cells [15]).

The functions of molecular chaperones, belonging to the HSP family, are very broad. Initially the first biologically relevant reaction utilizing molecular chaperones was described on the molecular level for bacteriophage lambda initiation of DNA replication [21,31]. Based on those findings and other data available at the time, such as: i) the discovery that, HSP upon stress is translocated from the cytoplasm to nucleus and subsequently catalyzes the re-assembly of damaged pre-ribosomes within the nucleoli, and probably other ribonuclear proteins (RNPs) after heat shock [32] and ii) that the BiP protein (HSP70 member residing within the ER) was shown to transiently interact with heavy chain immunoglobulins [33], Hugh R. Pelham published an article in Cell (1986) speculating on the role of heat shock proteins [34]. Astonishingly, all his predictions turned out to be correct. The data from several contributing laboratories, including our laboratory, has firmly supported the conjectures proposed by HR Pelham: i) HSP70 has a general affinity for polypeptides with hydrophobic amino acid residues, denatured and abnormal protein(s) [35], ii) HSP70 aids in the assembly of specific protein-protein complexes e.g. the preprimosomal