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Review

Reassessing the role of p53 in cancer and ageing from an evolutionary perspective

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Abstract

The gene *p53* has been fashioned as the guardian of the genome and as prototype of the tumour suppressor gene (TSG) whose function must be inactivated in order for tumours to develop. The ubiquitous expression of truncated p53 protein isoforms, results in ''premature ageing'' of laboratory mouse strains engineered for expressing such isoforms. These facts have been construed in the argument that *p53* evolved in order to protect organisms with renewable tissues from developing cancer yet, because p53 is also an inducer of cellular senescence or apoptosis after extensive DNA damage, it becomes a limiting factor for tissue renewal by depleting tissues from stem/precursor cells thus leading to whole-organism ageing. From that point of view *p53* displays antagonist pleiotropy contributing to the establishment of degenerative diseases and ageing. Therefore, tumour suppression becomes a balancing act between cancer prevention and ageing. Nevertheless, here we present current evidence showing that the aforementioned argument is rather inconsistent and unwarranted on evolutionary grounds. The evolutionary perspective indicates that *p53* evolved so as to play a subtle but very important role during development while its role as a TSG is only important in animals that are protected from most sources of extrinsic mortality, thus suggesting that *p53* was primarily selected for its developmental role and not as a TSG. Therefore no real antagonist pleiotropy can be attached to p53 functions and their relationship with whole-organism ageing might be a laboratory artefact.

Keywords: Antagonist pleiotropy; Apoptosis; Development; Disposable soma theory; Tumour suppressor

1. Introduction

The gene *p53* and its product, the protein p53 have been the subject of continued research considering that *p53* is the gene most frequently mutated in human cancers (Hollstein et al., 1994). The protein p53 is able to transactivate genes whose products block the cell cycle in presence of DNA damage, and it is also involved in the regulation of DNA repair at different levels, as well as being an inducer of either apoptosis or cellular senescence in cells subjected to significant stress (Giaccia and Kastan, 1998; Sengupta and Harris, 2005). The gene *p53* is a constitutive but rather lowly expressed gene, yet after exposure of cells to different kinds of stress such as: ionising and UV-radiation, hypoxia, depletion of ribonucleotide pools, excess of reactive oxygen species (ROS) and over-expression of some cellular oncogenes, the protein p53 accumulates within the cell nucleus and its half-life increases by means of postranslational modifications such as phosphorylation and acetylation (Giaccia and Kastan, 1998; Motoyama and Naka, 2004). This information has been construed in a widely quoted argument according to which p53 is a molecular node linking DNA-damage-dependent signal-transduction cascades and different downstream responses that result in either arrest of the cell cycle in order to allow for DNA repair to occur or induction of cell apoptosis in case that the DNA damage is non-repairable (Lane, 1992; Sherr, 1998; Tyson, 2006). In both cases the apparent result is the preservation of the stability of the genome in such a way that mutations resulting from the previous DNA damage cannot be passed to the cellular progeny. Thus *p53* has been fashioned as the guardian of the genome and as prototype

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of the tumour suppressor gene (TSG) whose function must be inactivated in order for malignant tumours to develop (Gómez-Lozano et al., 2004). The high frequency of *p53* mutations observed either in biopsies of human tumours or cells derived from such tumours, and the correlation between *p53* germ-line mutations and elevated incidence of multiple types of cancer observed in families affected by the rare Li-Fraumeni syndrome (Hollstein et al., 1994; Olivier et al., 2003) support the role of *p53* as a TSG. Moreover, the fact that almost all laboratory mice null for *p53* develop malignant tumours clearly indicates that absence of p53 function favours tumour development (Donehower et al., 1992; Jacks et al., 1994).

On the other hand, reports in which the constitutive, ubiquitous expression of truncated p53 isoforms, results in ''premature ageing'' of laboratory mouse strains engineered for expressing such isoforms (Tyner et al., 2002; Maier et al., 2004), have been construed in a further argument according to which p53 function has evolved in order to protect organisms with renewable tissues from developing cancer yet, because p53 is also an inducer of cellular senescence or apoptosis after extensive DNA damage, it becomes a limiting factor for tissue renewal by depleting tissues from either stem cells or precursor cells, thus leading to whole-organism ageing (Donehower, 2002; Campisi, 2003, 2005). From this perspective *p53* becomes a prime example of a gene displaying antagonist pleiotropy (Williams, 1957), since the gene functions are useful early in life but then become deleterious for the organism with time by contributing to the establishment of degenerative diseases and ageing. Therefore, tumour suppression becomes a balancing act between cancer prevention and ageing (Campisi, 2003, 2005; Pelicci, 2004)

Such argument linking tumour suppression and ageing may only be sustained provided that *p53* has been positively selected and fixed within the mammalian genome for its tumour suppressive functions. However, if *p53* has been primary selected for other functions different from tumour suppression then the aforementioned argument is falsified. Hereunder we present and discuss current evidence indicating that *p53* has a very important role during development while its role as a TSG is only important in animals that are protected from most sources of extrinsic mortality and so display extended survival after the age of reproductive success (like modern human populations or laboratory mice), thus suggesting that *p53* was primarily selected for its developmental role and not as a TSG. From an evolutionary perspective the argument that links tumour suppression with ageing is rather unwarranted. Moreover, such an argument is further weakened by recent experimental evidence discussed hereunder, indicating that the relationship between p53 function and whole-organism ageing might be a laboratory artefact.

2. What selective pressures participate in p53 evolution?

It is well established that the main molecular signal that induces the stabilisation of p53 is the presence of either single or double-stranded DNA breaks (Nelson and Kastan, 1994; Huang et al., 1996). Thus, any chemical or physical insult able to induce enough DNA breaks might be an inducer of p53 stabilisation. Most experiments showing stabilisation of p53 protein have been carried out in vitro, by exposing cells to ionising radiation, UV-light or inducers of ROS that may damage DNA. Indeed, ionising radiation is relatively a poor inducer of p53 when compared with UVC (100–280 nm) that is actually not present in the biosphere since such wavelengths are basically filtered by the Earth's atmosphere (Diffey, 1991; Lu and Lane, 1993).

Only UVB (280–320 nm) and UVA (320–400 nm) are significant components of radiation reaching the biosphere. A significant fraction of UVB is absorbed by the ozone layer of the atmosphere, thus UVA constitutes 95% of the solar UV reaching the surface of the Earth (Besaratinia et al., 2005). Only photons at wavelengths shorter than 320 nm can directly damage nucleic acids (Setlow, 1974; Diffey, 1991). However, UVA has been shown to induce oxidative DNA damage via photosensitization reactions that may be detected at UVA doses that are non-cytotoxic ($\leq$36 J/cm^2). Nevertheless, per joule basis UVB is up to 50,000 times more genotoxic than UVA (Besaratinia et al., 2005). Exposure of normal skin fibroblasts to a mix of UVB and UVA corresponding to 1.5 the 24 h minimal erythema dose induces detectable levels of p53 protein that peak at 48 h (Hall et al., 1993). Moreover, p53 immunoreactivity can be detected in chronically sun-exposed skin of white Caucasians living in subtropical regions (van der Pols et al., 2006). Under natural conditions the observable effects of UV-radiation are limited to the skin and the eyes (erythema, sunburn, cataracts) because the low penetrating properties of UV-radiation (less than 1 mm into naked skin) preclude its action upon internal tissues (Diffey, 1991). Most mammals have their skins covered by fur that protects the skin from incoming UV-radiation. Therefore, under natural conditions the exposure of most mammalian tissues to UV-radiation is rather limited or non-existent indeed. Thus, solar radiation is unlikely to be a selective pressure that may favour the presence of *p53* within the mammalian genome. If *p53* evolved so as to protect metazoan genomes from the effects heavy irradiation it must have evolved when the Earth biosphere was exposed to high radiating energies. However, there is no evidence that the Earth biosphere has been subjected to heavy irradiation at least in the last 50 million years, and so *p53* would not be subjected to positive selection and should drift and mutate randomly in absence of selection but this is not the case.

Over-expression of the *myc* oncogene induces DNA breaks both in vitro and in vivo and this leads to stabilisation and activation of p53 (Vafa et al., 2002; Pusapati et al., 2006). However, such an over-expression of *myc* is an unlikely phenomenon occurring in rare cells undergoing hyper-activating mutational events in the *myc* locus. Selective pressures must be acting rather continuously and for extended periods of time upon the organisms so as to achieve the selection and fixation of new gene functions. Thus, oncogene-induced DNA damage is unlikely to be a selective pressure for fixing *p53* within the mammalian genome.