transplanted shortly after labeling (i.e., shortly after recombination) that the reconstituting stem cells have a different recombination frequency than the actual stem cells (Nakagawa et al., 2007). This establishes that the cell population with the higher recombination frequency is transient, indicating that transit-amplifying progenitor cells are potential stem cells in this system (Figure 1). Furthermore, by studying mice over long time periods, Nakagawa and colleagues provide evidence that actual stem cells are lost and replaced over time (Nakagawa et al., 2007), although it is unclear whether they are replaced by potential stem cells or through symmetric divisions of actual stem cells.

An important and fortuitous feature in the system exploited by Nakagawa and colleagues is a different recombination frequency between the stem cells and progenitor cells. If the frequency were the same in both compartments, there would be no reduction in the number of recombined potential stem cells over time, as they would be replenished at the same recombination frequency from actual stem cells. The much larger absolute number of progenitor cells than actual stem cells cannot explain their results. The reason for the different recombination efficiency in these cellular compartments is unknown but could, for example, be due to different levels of expression of the transgene, different epigenetic states, or chromatin structure.

The results of Nakagawa et al. (2007) indicate that stem cell function is not strictly cell autonomous and that there is a potential for some cells to gain stemness. Strictly speaking, a lineage relationship between the actual and potential stem cells has not been established in their study, but the most plausible model is that the potential stem cells are the immediate descendants of the actual stem cells.

Stem cells are notoriously difficult to identify in tissues, which has hampered the study and use of these cells. Transplantation assays have been invaluable for the identification of stem cells in several tissues (Weissman, 2000). The results of Nakagawa et al. (2007), however, underscore the difficulty of drawing definitive conclusions regarding the identity of actual stem cells from transplantation or regeneration experiments alone. Strategies for genetic labeling similar to those used by Nakagawa and colleagues can be developed for other stem cell lineages. This may reveal whether potential stem cells are a general feature of many tissues and may aid in the identification of the actual stem cell population.

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The Sunny Side of p53

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DOI 10.1016/j.cell.2007.02.027

Skin, the largest organ of our body, is often plagued by cancer because of exposure to ultraviolet radiation from the sun. A report by Cui et al. (2007) in this issue of *Cell* explains how the tumor suppressor p53 protects the skin by stimulating the suntan response.

The p53 tumor suppressor gene is one of the most frequent targets for genetic alterations in cancer. Direct mutational inactivation of p53 is observed in close to half of all human tumors. This has spurred extensive research on p53, its biochemistry, and the mechanisms whereby it suppresses cancer (Levine et al., 2006). It is now appreciated that a key role of p53 as a tumor suppressor is to prevent the emergence of cells with permanently defective genomes, which are likely to spawn cancer. To a large extent, the functions of p53 rely on its ability to act as a sequence-specific transcriptional regulator. Moreover, p53 is strategically positioned to respond to a wide array of conditions that may endanger genome integrity.

How does p53 prevent the emergence of cells with defective genomes? Initially, p53 was viewed primarily as an executioner, capable of identifying cells with severe genomic damage and eliminating them from the replicative pool,

through either induction of apoptotic cell death or irreversible cell-cycle exit, commonly termed cellular senescence. However, it gradually became appreciated that p53 also plays an important role as a protector, in an attempt to save cells from reaching a stage where they acquire severe DNA damage that mandates their execution. Notably, p53 can enhance various types of DNA repair. Recently, the protective role of p53 was highlighted by the discovery of its ability to turn on genes encoding proteins that maintain an antioxidant intracellular environment, thereby preventing the induction of genotoxic damage by reactive oxygen species (Sablina et al., 2005). Cui et al. (2007) now report a new surprising genoprotective function of p53: regulation of the suntan response.

Exposure to ultraviolet (UV) radiation represents a continuous threat to the skin. In particular, UV-induced DNA damage strongly promotes skin cancer. A major line of defense against such threat is the production of melanin, which is synthesized in skin melanocytes and is then transported into adjacent keratinocytes. There, melanin serves to absorb the UV radiation, as well as neutralize free radicals generated by UV. When this defense mechanism is inefficient, as occurs in fair-skinned people, cancer-promoting genotoxic damage is more likely to emerge. Exposure of the skin to UV triggers melanin production (Figure 1); this is orchestrated by α-MSH (melanocyte-stimulating hormone), which can be produced locally by skin melanocytes and particularly by keratinocytes (Millington, 2006). α-MSH is produced by proteolysis from a multicomponent precursor polypeptide, encoded by the *pro-opiomelanocortin* (*POMC*) gene. As shown by Cui et al. (2007), this tanning response is controlled by p53. Exposure of dermal keratinocytes to UV results in p53 activation. As a transcription factor, p53 binds directly to the *POMC* gene promoter in such keratinocytes and induces *POMC* transcription and α-MSH production (Figure 1). Consequently, mice lacking p53 fail to mount a tanning response

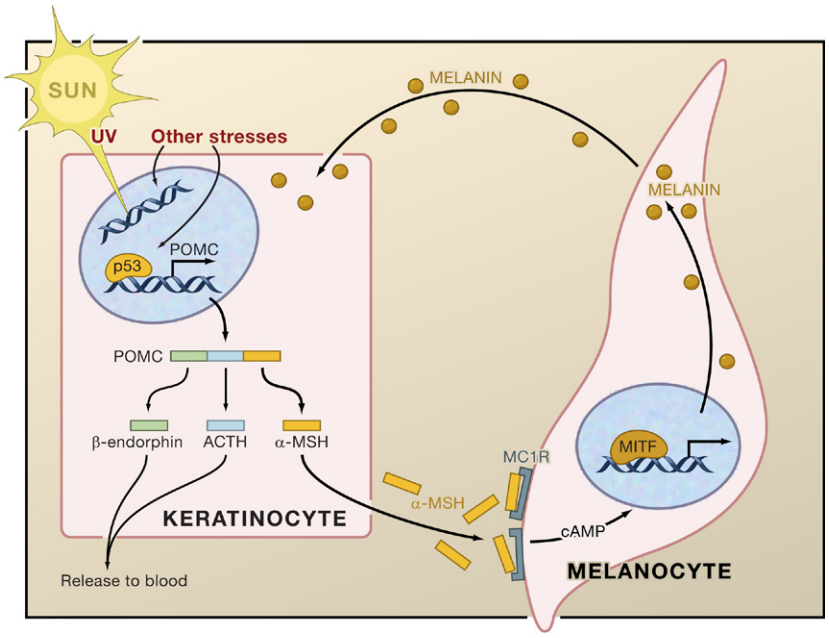

Figure 1. The Role of p53 in Skin Pigmentation
In response to UV-induced genotoxic stress, p53 becomes activated in skin keratinocytes and stimulates transcription from the *pro-opiomelanocortin* (*POMC*) gene promoter. The POMC precursor polypeptide is then processed into several bioactive products including α-MSH, which, through a paracrine effect on epidermal melanocytes (mediated by the α-MSH receptor MC1R and the melanocytic transcription factor MITF), leads to melanin production and redistribution among skin cells. The release of ACTH (adrenocorticotropic hormone) and the opioid peptide β-endorphin into the blood may relieve inflammation and contribute to sun-seeking behavior.

to UV, which may account for their increased propensity to develop UV-induced skin cancer. Hence, p53 exerts a crucial maintenance function in normal skin, protecting the genomes of dermal keratinocytes and melanocytes against genotoxic damage and the risk of subsequent malignant transformation. Loss of this protective effect of p53 is probably responsible for the well-documented association between p53 mutations and skin cancer (Brash, 2006).

Intriguingly, in some but not all basal cell carcinomas (the most frequent type of human skin cancer, derived from transformed keratinocytes), the tumors become pigmented due to the colonization of melanocytes. Cui et al. (2007) found that this occurs only in tumors that retain wild-type p53 but not those harboring p53 mutations. Such unscheduled pigmentation may reflect the recently discovered constitutive activation of the DNA-damage response machinery (including p53 activation) during oncogenesis, which provides an inducible barrier to prevent tumor progression, through induction of cancer cell death or senescence (Bartkova et al., 2005; Gorgoulis et al., 2005). Cancer progression requires that this barrier be broken, and in skin tumors this often occurs through p53 mutations. The data of Cui et al. (2007) suggest that in subsets of basal cell carcinomas with wild-type p53, the constitutive activation of the p53-POMC mechanism leads to constitutive α-MSH production in the tumor, perhaps serving as a chemoattractant for colonizing melanocytes.

The beneficial effect of p53 in the skin may extend even beyond the genoprotective effect of α-MSH. Adrenocorticotropic hormone (ACTH) and the opioid peptide β-endorphin, additional products of POMC processing, possibly help relieve irritation and local inflammation in UV-exposed skin. This adds to the already documented anti-inflammatory effects of p53 (Komarova et al., 2005), and may contribute to sun-seeking behavior. The latter effect, mediated by β-endorphin, might facilitate vitamin D metabolism, for example. Thus,

through regulation of POMC, a process much more pronounced in keratinocytes than in other cell types, p53 ensures our well being in many different and complementary ways.

As UV is probably the most prominent naturally occurring environmental carcinogen, it is quite conceivable that this newly described role of p53 has been an important driving force in the selective pressure to maintain p53 function during evolution. In this regard, it is noteworthy that a common p53 gene polymorphism, affecting amino acid position 72 of p53, exhibits a striking geographical bias, with the allele encoding proline at position 72 becoming much more prevalent as one approaches the equator (Beckman et al., 1994). It is tempting to speculate that the 72Pro isoform of p53 is a more competent inducer of POMC transcription, thus driving strong evolutionary selection in its favor in heavily sun-exposed areas.

Another intriguing aspect of the discovery of the p53-POMC pathway relates to the current efforts to stimulate p53 function by small molecules (Vassilev, 2007). One may imagine designing skin lotions that moderately activate p53 in our keratinocytes—enough to trigger the suntan response safely—without causing DNA damage and hence avoiding the health risks otherwise inherent in UV exposure. It is conceivable that the p53-regulated pigmentation mechanism will become particularly handy in the coming decades of escalating environmental pollution and global warming.

ACKNOWLEDGMENTS

The authors are supported by the Danish Cancer Society, the Danish National Research Foundation, the Flight Attendant Medical Research Institute, and grants from the MSM (no. 6198959216), the EC (LSHC-CT-2004-503576 and LSHC-CT-2004-502983), and the National Cancer Institute (R37 CA40099).

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N-WASP Generates a Buzz at Membranes on the Move

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DOI 10.1016/j.cell.2007.02.028

The fast-growing ends of actin filaments push against membranes to create cell-surface protrusions and to propel the movement of membrane vesicles. Co et al. (2007) now show that the neural Wiskott-Aldrich syndrome protein (N-WASP) mediates dynamic attachment between membranes and the growing ends of actin filaments to sustain membrane movement.

Actin polymerization drives protrusions at the cell surface and the propulsion of membrane vesicles (Pollard and Borisy, 2003). In these processes, actin subunits are added to the barbed end of a filament—the same end that pushes against the membrane. Yet, if the barbed end abuts the membrane, how are actin subunits added to it? It has been proposed that thermal motion of the filament might create a gap between the membrane and the barbed end that allows the binding of an actin monomer (Mogilner and Oster, 1996). Restoring the position of the filament would then provide the power to push the membrane. This model also pre-