Nevus Size and Number Are Associated with Telomere Length and Represent Potential Markers of a Decreased Senescence *In vivo*

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Abstract

Nevus counts represent one of the strongest risk factors for melanoma. They appear in childhood and adolescence and involute from middle age onwards. Recent evidence has shown that nevus cells undergo oncogene-induced senescence involving the p16/retinoblastoma pathway. However, telomere length also influences senescence in proliferative somatic cells and varies between individuals. This study explores whether telomere length measured in white cells is associated with nevus count and size in 1,897 Caucasian women ages 18 to 79 years. Total body nevus counts were positively correlated with white cell telomere length (mean, 7.09 kbp; range, 5.09-9.37) after adjustment for age (P = 0.0001). Age-adjusted telomere length was also associated with nevus count for nevi above 5 mm in diameter (P = 0.04). Subjects in the top category for nevus count had an average age-adjusted telomere length 150 bp longer than those in the lowest category. The positive correlation between white cell telomere length and nevi number and size may reflect an increased replicative potential (reduced senescence) in individuals with longer telomeres, which may not be melanocyte specific. Understanding mechanisms influencing the induction and involution of nevi will not only help in understanding the pathophysiology of melanoma but should also shed light on the complex relationship between aging and cancer. (Cancer Epidemiol Biomarkers Prev 2007;16(7):1499–502)

Introduction

Nevus numbers vary greatly in any Caucasian populations and undergo a significant reduction from middle age onwards (1, 2). Mean total body nevus count in the United Kingdom is 30 and remains the most powerful predictive marker of risk for melanoma (3-5). Nevus number is known to be significantly influenced by genetic factors, with twin studies showing that 60% of the variation in nevus number is explained by additive genetic factors (6-8). Furthermore, in families with a genetic susceptibility to melanoma, affected individuals often have large numbers of common and atypical nevi (9, 10). In these melanoma-prone families, nevi continue to appear in large numbers in adulthood and have a delayed involution with large numbers of nevi still present in older age groups (10, 11).

The melanoma suppressor gene *CDKN2A* is now known to encode the two cell cycle inhibitors p16 (INK4a) and ARF (alternative reading frame), with the related p15 (INK4b; ref. 12). Germ-line and somatic CDKN2A mutations and deletions have been linked respectively to familial and sporadic melanoma, and p16 carriers often show large numbers of nevi (10, 13). p16 inhibits cell proliferation by binding to cyclin-dependent kinases (cyclin-dependent kinases 4 and 6), preventing phosphorylation of the retinoblastoma protein. p16 is also known to be important in cell senescence in all cell types (14). Another well known effector pathway for human replicative cell senescence is attributed to telomere shortening and a DNA damage response through other growth inhibitors, such as p53 and p21 (15, 16).

Telomeres are specialized DNA-protein complexes that cap the end of eukaryotic chromosomes and are essential for maintaining genome stability and integrity. The human telomeric complex is composed of TTAGGG repeated DNA sequences with the enzyme telomerase where present and several associated proteins controlling telomere length and capping. Shortening of telomeres occurs naturally with successive divisions in somatic cells, whereas in the germ-line and most cancer cells, high telomerase activity allows cells to maintain long telomeres and avoid senescence (17-19). Twin and family studies have shown that telomere length in white cells is partly heritable, although environmental factors, such as inflammation, smoking, and obesity, are also important (20-22). Shorter white cell telomere length has also been linked to chronic diseases of aging, such as atherosclerosis, osteoarthritis, and diabetes (18, 23-26). Telomere attrition causes cell senescence via the p53 pathway, although p16 is also likely to be involved as senescent cells overexpress p16 (14, 15, 17). We speculate that telomere shortening may play a key role, as well as the p16 pathway, in limiting nevus growth and may be involved in the disappearance of nevi with age. The aim of this study was to explore this hypothesis by correlating leukocyte telomere length with total body nevus counts and nevus size in a large population-based sample of adults.

Materials and Methods

Caucasian female subjects (2,786) were recruited with collection of phenotypic skin data from the UK Adult Twin Registry (Twins UK) at St. Thomas Hospital (London, United Kingdom) between January 1997 and December 2003 (27). As well as

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