Chapter 10

Tropomyosin as a Regulator of Cancer Cell Transformation

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Abstract

Tropomyosins (Tms) are among the most studied structural proteins of the actin cytoskeleton that are implicated in neoplastic-specific alterations in actin filament organization. Decreased expression of specific nonmuscle Tm isoforms is commonly associated with the transformed phenotype. These changes in Tm expression appear to contribute to the rearrangement of microfilament bundles and morphological alterations, increased cell motility and oncogenic signaling properties of transformed cells. Below we review aspects of Tm biology as it specifically relates to transformation and cancer including its expression in culture models of transformed cells and human tumors, mechanisms that regulate Tm expression and the role of Tm in oncogenic signaling.

Introduction

Over thirty years ago cell biologists made the seminal observation that transformed cells exhibit loss of actin filament bundles, also called stress fibers.[1-5] Since then subsequent studies have shown that alterations in the actin-based cytoskeleton are an established characteristic of transformed cells. It is now known that oncogenic signaling pathways directly target the actin cytoskeleton including the expression of actin-binding proteins, as well as pathways that regulate cytoskeleton dynamics. Oncogene-mediated disruption of stress fibers and associated adhesive structures are responsible for enhanced motility and invasiveness of tumor cells. In addition to changes in cell morphology and motility, transformation is also associated with abnormal growth control of cells in culture including the ability to grow in low serum, grow on soft agar and to escape apoptosis. The first clue suggesting that the actin cytoskeleton directly participates in growth control came from early studies showing that changes in microfilament structure were correlated with anchorage-independent growth and cellular tumorigenicity.[6] There is a well-developed body of knowledge that suggests changes in the cytoskeleton are causally associated with activation of oncogenic signaling pathways because ectopic expression of specific actin filament stabilizing proteins in transformed cells not only restores microfilament bundles and focal adhesions, but revereses the ability of transformed cells to grow in low serum, grow on soft agar, escape apoptosis and form tumors in mice. These observations raise the intriguing hypothesis that the actin cytoskeleton plays a direct role in oncogenic signaling. However, the mechanism(s) by which oncogene-mediated changes in the actin cytoskeleton contribute to aberrant signaling events and thereby provide a tumor cell with a selective growth advantage, remain to be discovered. Once we understand how the actin cytoskeleton

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functions in oncogenic signaling, it will be possible to develop new therapeutic strategies that target signaling pathways dependent on the cytoskeleton.

As described above, transformed cells have characteristic changes in the expression of actin filament associated proteins. Tropomyosins (Tms) are among the most studied structural proteins of the actin cytoskeleton that are implicated in alterations of actin filament organization in transformed cells. Decreased expression of nonmuscle tropomyosins is commonly associated with the transformed phenotype. The changes in Tm expression appear to correlate well with the rearrangement of microfilament bundles and morphological alterations observed in transformed cells. The decrease in Tm synthesis has been reported to occur in cells transformed by a variety of agents including chemical carcinogens, UV radiation, DNA and RNA tumor viruses and various oncogenes. In addition, the changes in Tm expression following transformation occur in cells of all species examined including chicken, rodents (mouse and rat) and human, indicating that alterations of Tm expression is a common feature of the transformed phenotype and that Tm gene expression may represent a target for oncogene action. Below we review aspects of Tm biology as it specifically relates to transformation and cancer including its expression in transformed cells and human tumors, mechanisms that regulate Tm expression and the role of Tm in oncogenic signaling.

Tm Expression in Transformed Cells and Human Tumors

Tms are a family of actin-filament binding proteins that bind to actin filaments and stabilize actin filaments. They are expressed from a multigene family comprised of four genes via alternative promoters and alternative RNA splicing, giving rise to approximately 40 different isoforms (See chapters 2 and 16). Nonmuscle cells express both HMW (high molecular weight. 284 amino acids) and LMW low molecular weight (LMW, 248 amino acids) Tms, termed HMW Tm1, Tm2, Tm3 and Tm6 and LMW isoforms LMW Tm-4, TM-5(NM1), Tm-5a and Tm-5b (see Chapter 2). In untransformed cells Tm-1, Tm-2 and Tm-3 are the major HMW Tms and Tm-4 is the major LMW Tm. Although nonmuscle cells express multiple forms of both HMW and LMW Tms, the expression of only HMW TM isoforms are decreased during oncogenic transformation. Since the first observations by Hal Weintraub's lab in the early 1980s, alterations in Tm expression have been reported in a variety of transformed cell lines.[7-15] Perturbations in Tm synthesis have been reported to occur in cells transformed by a variety of agents including chemical carcinogens, UV radiation, DNA and RNA tumor viruses and various oncogenes including Ras, raf, Src, fes, fms, mos, myc, c-Jun, raf and erbB2 (reviewed in Stehn et al[16]). In addition, the changes in Tm expression following transformation occur in cells of all species examined including chicken, rodents (mouse and rat) and human, indicating that modulations in Tm expression is a common feature of the transformed phenotype and that Tm gene expression may represent a target for oncogene action. Decreased expression of HMW Tms is associated with the disruption of stress fibers in transformed cells. As described below, HMW Tms protect actin filaments from severing proteins better than LMW Tms, consistent with their absence leading to a loss of stress fibers following transformation.

The importance of Tms in human cancer is highlighted by several studies indicating that changes in Tm expression are found in a variety of human tumors. Studies of breast tumors demonstrate that HMW Tms are decreased in malignant breast lesions when compared to benign or normal tissue.[17-19] Down regulation of HMW Tm1, Tm2 and Tm3 were found in transitional cell carcinoma of the urinary bladder.[20] Studies of tumors associated with the central nervous system revealed that low-grade astrocytic tumors express HMW Tms, while highly malignant CNS tumors did not, suggesting a correlation between HMW Tm expression and tumor grade.[21] Studies of astrocytomas show an increase in HMW Tms in neoplastic astrocytes, as compared to normal astrocytes.[22] Interestingly, studies by Lin and colleagues identified a novel LMW Tm isoform preferentially associated with colon cancer.[23] It is possible that differences are due to cell-type specific differences in the patterns of Tm expression observed in malignancies associated with different tissues. These studies using human tumor tissues demonstrate that alterations in the expression of Tms observed in transformed cells are likely not simply the result of in vitro culture conditions. Clearly more