THE CYTOSKELETON: AN INTERMEDIATE IN THE EXPRESSION OF THE
TRANSFORMED PHENOTYPE IN MALIGNANT CELLS

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INTRODUCTION

Transformation of cells in vitro by viral or chemical agents is accompanied by a variety of physiological, morphological, and growth-related changes, including altered lectin-binding characteristics and changes in surface proteins (Burger 1973; Pollack and Burger, 1969). In many forms of neoplasia, striking changes occur in cell morphology, including the transition from flattened anisotropic forms that grow as monolayers to rounded pleomorphic forms that pile up as multilayered foci in culture (Temin and Rubin, 1958; Stoker and Abel, 1962). Changes in growth properties include loss of density-dependent control of growth (Todaro et al., 1964), loss of contact-inhibited mobility (Gail and Boone, 1971), and acquisition of anchorage-independent growth (Stoker and MacPherson, 1961; Freedman and Shin, 1974; Benedict et al., 1975; Evans and DiPaolo, 1975; Risser and Pollack 1974). Transformed cells grow well in media containing reduced serum content and are often characterized by reduced cyclic AMP levels (Smith et. al., 1971; Holly and Kiernan, 1968; Anderson et al., 1973; Sheppard, 1972; Mohanhan et al., 1973). Although it is known that various properties in this list are dissociable and are not linked as a group to malignant transformation, taken collectively these findings attest to the molecular complexity of cell transformation. Since most carcinogenic agents are also thought to be mutagens which interact with nuclear DNA producing point mutations and chromosome rearrangements how are these mutations manifested in the broad spectrum of phenotypic changes which accompany transformation?

This article will review evidence indicating that the cytoskeleton is a direct intermediate in the expression of the transformed
phenotype. A brief review of the components of the cytoskeleton will be given along with a documentation of the changes in cytoskeletal organization which accompany cell transformation in vitro. Recent evidence which suggests that some cytoskeletal proteins are substrates for viral transforming proteins will also be reviewed.

Components of the Cytoskeleton

Through advances in electron microscopy and immunocytochemistry as well as through biochemical studies much has been learned about the fibrous components of cytoplasm. The cytoskeleton is a term given to a complex system of anastomosing intertwining filaments and tubules which extend throughout the cytoplasm of eukaryotic cells. There have been many excellent reviews on the cytoskeleton (Goldman et al., 1976; Watson and Albrecht-Buehler, 1982; Wilson, 1982) and I will only present an overview of the components in the space that follows. The cytoskeleton can be divided into two functional entities: Structural components which include microtubules, microfilaments and intermediate filaments, and regulatory components consisting of various enzymes, binding proteins and cofactors which modulate cytoskeletal activity. The cytoplasmic ground substance or microtrabeculae (Wolosewick and Porter, 1979) also forms a highly structured lattice in the cytoplasm and contributes to the skeletal material of cytoplasm. In this review however, we will confine our comments to microtubules, microfilaments and intermediate filaments.

The cytoskeleton is involved in many diverse functions including force production, force transduction, cell movement, cell shape, phagocytosis, secretion, axonal transport, and cell surface receptor modulation. More subtle functions including hormone action, gene transcription, DNA synthesis and growth control have been implicated in recent studies. The cytoskeleton's central function in this wide range of cellular activities would suggest its involvement in neoplastic transformation.

Microtubules

Like other developments in the field of cell biology, advances in knowledge of the cytoskeleton was largely made possible by a series of technical achievements dating back over two decades. Although a fibrous network was detected in silver-stained neurons by Cajal in the 19th Century, we generally credit early electron microscopists with the discovery of microtubules and microfilaments. The vast improvements in fixation afforded by glutaraldehyde (Sabatini et al., 1963) led to the widespread recognition of microtubules in most eukaryotic cells. Prior to the glutaraldehyde era, discrete "filaments" were recognized in the mitotic spindles of amoebae (Roth and Daniels, 1962) and even earlier fibrous elements were faintly seen to form a 9+2 pattern in dismembered and sectioned cilia (Manton and Clark, 1952; Fawcett and Porter, 1954).