INTRODUCTION

At the time of conception, the human organism is a single cell zygote. During the course of development into an adult, this cell expands into a complex mass of approximately 100 trillion cells, with an enormous variety of shapes, sizes, and functions. Normal tissue growth and development require prolific cell division, exquisitely regulated cell differentiation, and appropriately timed cell death or apoptosis. Neoplastic transformation of tissue generally occurs when abnormal regulatory mechanisms promote excessive cell division, impaired cell differentiation, and/or failure of apoptosis. In most tumor types, this aberrant control originates at the genetic level.

Intensive study of these regulatory mechanisms has led to significant progress in our ability to diagnose, predict biological behavior, and understand the basic molecular pathophysiology of thyroid neoplasms. The upcoming sections explore the major advances in the study of thyroid oncogenes and tumor suppressor genes. As this discussion relies on the knowledge of some basic concepts, the essential elements of the cell cycle and gene function are first briefly reviewed.

THE CELL CYCLE

The life cycle of a cell can be viewed as consisting of two alternating stages: interphase and mitosis (Fig. 1). Interphase—the longer stage—is composed of three subphases or phases: gap 1 (G1), DNA synthesis (S), and gap 2 (G2). During the G1 stage, cells use DNA as a template to transcribe mRNA then to translate mRNA, into proteins. In the S phase, DNA is replicated, which doubles the cellular DNA content. During the G2 phase, DNA repair corrects any mutations that occurred during the S phase as the cell makes final preparations for entry into mitosis (1).

Mitosis is a much shorter stage when cell division occurs, comprised of four sequential phases. In prophase, sister chromatids pair by attaching at their centromeres; the nuclear membrane disappears and cytoplasmic spindle fibers begin to form. During metaphase, the chromosomes condense and line up along the equator of the cell attached to the spindles. The anaphase is characterized by the separation of sister chromatids and migration of individual chromatids along the spindles to opposite ends of the cell. In telophase, two new nuclear membranes form and cytoplasmic division (cytokinesis) occurs. The end result is two daughter cells, each with a complete set of 23 chromosome pairs (1).

Meiosis is a more complicated type of cell division that takes place only in germ cells. This process consists of two consecutive cell divisions; however, the second division is not preceded by DNA replication. In contrast to mitosis, meiosis produces four daughter cells, each with only 23 single chromosomes (1).

GENES

The basic blueprints of life are contained within our genes. A gene is a segment of DNA that carries the information necessary for a cell to produce a specific protein. There are approximately 50,000–100,000 genes in every human cell. To be successful, a gene must perform essential functions, such as expression, replication, and repair.

Gene expression (Fig. 2) takes place predominantly during the G1 period of interphase. Genes have two general regions—termed the regulatory and structural (coding) regions. Nuclear proteins (known as transcription factors) bind to the regulatory regions and govern the rate at which the structural region is transcribed into mRNA. mRNA molecules then travel to the cytoplasm where they are translated into the proteins characteristic of that particular cell phenotype. These proteins carry out the functional activities of the cell (1).

Gene replication (Fig. 3) occurs during the S phase. At this time, enzymes known as helicases unwind the DNA double helix, leaving two single strands of unpaired DNA. Using these as templates, DNA polymerases then promote

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the assembly of free nucleotide bases into two new complementary chains that bind to each of these single strands, which leads to the formation of two new identical DNA double helices (1).

Gene repair, occurring during G2, utilizes a complex set of enzymes collectively referred to as the DNA repair system. Contained within each cell, the human genome consists of approximately three billion nucleotide pairs that are replicated with each cell division. It is estimated that spontaneous mutations occur at a rate of about two per million base pairs during each S phase; thus, as many as 6000 mutations may appear each time a cell divides. The proteins of the DNA repair system rapidly and efficiently scan along the chromosomes to detect and repair most or all of these mutations before the cell proceeds into mitosis (1).

ONCOGENES AND TUMOR SUPPRESSOR GENES

Throughout their lifespan, somatic cells can be thought of as progressing through three overlapping transitional stages (Fig. 4). Stem cells initially proliferate by undergoing repetitive cell division, causing a rapid expansion of immature tissue mass. Subsequently, these cells differentiate into mature cells that deliver the functions characteristic of their particular phenotype. Later, they grow senescent and undergo programmed cell death or apoptosis. Tumor development (or neoplasia) results from stimuli that augment cellular proliferation or impair cell differentiation and/or apoptosis. A diverse set of signaling and effector proteins is involved in the precise regulation of this enormously complex series of events. Mutations in the genes encoding these proteins have been found to underlie the majority of human malignancies (2).

Genes that encode the proteins promoting normal cell proliferation are called proto-oncogenes. Proto-oncogenes sometimes develop activating or gain-of-function mutations that result in the production of proteins that are qualitatively...