# 14. MOLECULAR SIGNALING IN THYROID CANCER

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## INTRODUCTION

Molecular signaling – or signal transduction – is central to our understanding of the core biological processes in any type of cancer. Defining the responses of cancerous cells to environmental and endogenous signals, and comparing them to those exhibited by their counterpart normal parental cells can provide valuable insight into the intimate mechanisms underlying malignancy formation, progression, invasion and spread to distant sites (metastasis). Further, detailed knowledge of cancer cell signaling allows us to envisage molecular strategies, upon which novel anticancer therapies will be founded. Ideally, within the context of a particular cancer, our understanding of where and how signal transduction pathways become deranged should enable us to design therapies targeted to the "diseased" elements of the relevant pathway(s). Moreover, the delineation of the evolution of such molecular derangements at each step along the oncogenic transformation process could provide us with the opportunity to intervene at early or intermediate stages of cancer development, i.e., prior to the emergence of irreversible genomic instability, which usually accompanies the transition of a microscopic (or *in situ*) malignancy to the phenotypes of invasive macroscopic carcinoma and metastatic disease (1). In many cases, alterations in molecular signaling in cancer cells are etiologically linked to the oncogenic process. Undoubtedly, the oncogenic potential of a molecule along a signaling pathway can be released through multiple genetic mechanisms (e.g., point mutation or over-/underexpression), ultimately leading to tumor formation. However, it is also true that a number of (qualitative or quantitative) changes

in signaling pathway molecular elements could merely represent an epiphenomenon of the oncogenic process, and, hence, the potential significance of the existing descriptive data on such changes needs to be scrutinized carefully and with due circumspection.

All the above notions are highly relevant to thyroid cancer (TC). Indeed, during the past decade, a rapidly evolving body of knowledge has been accumulated on signaling pathways in TC, and their significance in its pathogenesis and progression. An excellent example of the complexity and interconnectedness of such pathways is the thyrotropin (TSH)-dependent signaling system. Although most of the elements of molecular signaling in TC cells are shared with those existing in normal thyrocytes, some are certainly unique to TC cells, such as protein products of fusion genes (*RET/PTC* and *Pax-8/PPARγ*, as presented in the Chapters 4 & 7 respectively. Additionally, other shared elements that are expressed in both normal and malignant thyroid tissues may be altered in specific ways (e.g., overexpressed or mutated) in malignant thyrocytes, a sound example being protein products of mutationally activated *ras* or *b-raf* genes, expanded upon in Chapter 7. Of note, as the thyroid follicular cell is an endocrine cell, it possesses a wide variety of "identity-specific" signaling systems, which are pertinent to the multitude of its endocrine functions and are correlated with its status of differentiation. Specific alterations in these endocrine function-related systems can accompany malignant transformation (e.g., loss of thyroglobulin [Tg] or sodium-iodide symporter [NIS] expression), and usually coexist with derangements in signaling pathways unrelated to the endocrine character of the cell, as commented upon in the contributions in Chapters 13 & 17.

In this chapter, we make an effort to present the currently accumulated knowledge in this important field by appropriately categorizing the various pathways studied to-date, and summarizing the molecular (known or suspected) derangements along these pathways. We will focus our contribution on carcinomas arising from the follicular epithelial cells (thyrocytes), i.e. papillary, follicular and anaplastic TC's (PTC's, FTC's and ATC's, respectively). Further, we will restrict our review to membrane receptor-associated signaling systems. Intracellular (including nuclear) receptor signaling is also an integral part of cell regulation, as recently highlighted by the role of the Pax-8/PPARγ oncoprotein in FTC's (see Chapter 4) and the presence of functional estrogen and thyroid hormone receptors in PTC's and FTC's (refer to Chapter 9), but we will not comment on this subject as it is exhaustively dealt with by other contributors.

In broad terms, signaling essentially begins with the signal molecule/ligand-sensing receptors, and is based on modulation of the activity of "downstream" pathways (or cascades) that are dependent upon the activation of the aforementioned receptors. In order to place some degree of conceptual order in an unwieldy body of data, we have attempted to categorize signaling in TC cells that occurs via activation of plasma membrane receptors and their downstram effector systems, i.e., (i) G-protein coupled receptors (GPCR's) and associated proteins and (ii) enzyme-coupled receptors and downstream pathway elements. Of note, although ion channels and various symporters (e.g., NIS) are expressed in TC, to-date, the only definitive demonstration of