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Molecular profiles in foregut oncology

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Oncology is and will continue to evolve resulting from a better understanding of the biology and intrinsic genetic profile of each cancer. Tumor biomarkers and targeted therapies are the new face of precision medicine, so it is essential for all physicians caring for cancer patients to understand and assist patients in understanding the role and importance of such markers and strategies to target them. This review was initiated in an attempt to identify, characterize, and discuss literature supporting clinically relevant molecular markers and interventions. The efficacy of targeting specific markers will be examined with data from clinical trials focusing on treatments for esophageal, gastric, liver, gallbladder, biliary tract, and pancreatic cancers.

Keywords Cancer, neoplasm, liver, digestive system, tumor marker

Introduction

Cancer, characterized by an aberrant overgrowth of cells, is a substantial disease making it the second leading cause of death behind heart disease (1). Before the term cancer was established, it was referenced during the pyramid age in Egypt as bulging breast tumors. These records were documented in *The Edwin Smith Surgical Papyrus* dating back to 3000 BC (2). Hippocrates described non-ulcer and ulcer forming tumors with the terms *carcinos* and *carcinoma*, which is a Greek description for being crab-like. The Roman physician Celsus later translated the Greek term into *cancer* which is Latin for crab. Another Greek physician Galen used the word *oncos*, Greek for swelling, to describe tumors. A new era of treating diseases with chemicals began in the early 1900s when German chemist Paul Ehrlich coined the term chemotherapy (3). The first four decades of the 20th century were devoted to developing cancer models and thereafter research was dedicated to finding effective chemotherapies. In 1943 nitrogen mustard rolled out as the first cancer treatment, antifolates came in 1948, thiopurines in 1951, 5-Fluorouracil in 1957, methotrexate in 1958, adjuvant chemotherapy in 1968–1975, imatinib or Gleevac in 1996, the first monoclonal antibody in 1997, tyrosine kinase inhibitors in 2005, and ultimately target specific screening began in 2007 (3). The 1940s also included the advent of tumor markers, which are cancer cell specific. Advances in cancer genetics allowed tumor markers to be used as diagnostic and monitoring tools, and more recently predictors of treatment efficacy.

Oncology continues to evolve as a result of ongoing scientific inquiry, technical innovation, and evidence based combination treatments which led to precision healthcare. Personalized chemotherapeutic regimens are based on individual variations in genes, presence or absence of tumor markers, tumor immunostains, and more accurate diagnosis by modern imaging modalities. For example, monoclonal antibodies directed against a wide range of oncoprotein biomarkers allow specific and targeted therapy based on tumor type and molecular characteristics.

It is essential for all physicians caring for cancer patients to understand the role and importance of molecular tumor markers as the biology of each cancer is becoming well known. These physicians should also assist patients in understanding the critical role of the specific markers. The goals of this review are to identify, characterize, and discuss literature supporting clinically relevant molecular markers and interventions as a means to assist physicians in forming a treatment plan targeting specific aberrations. This review presents the relevant biological tumor markers, pathogenesis, immunohistochemical and histological definition, and current targeted therapies for esophageal, gastric, liver, gallbladder, biliary tract, and pancreatic neoplasms.

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Biological tumor markers

ADAM-17

ADAM enzymes are zinc dependent cell surface proteins which cleave various other proteins (4). The cleaved proteins can then have autocrine, juxtacrine, paracrine, or endocrine downstream effects. ADAM-17 is a tumor necrosis factor (TNF)-α converting enzyme (TACE), which cleaves and converts TNF-α into a soluble form.

ABCG8

Adenosine triphosphate-binding cassette transporter (ABCG8) is among a class of ATP binding cassette transporters which regulate molecular movement across the cell membrane. The mechanism of ABCG8 is to pump plant sterols and cholesterol out of the intestinal epithelium and back into the lumen of the gastrointestinal tract. ABCG8 is indicated in gallstone formation because gallstones are primarily composed of cholesterol (5).

AXL

AXL is a receptor tyrosine kinase (RTK) with oncogenic potential and transforming activity. The AXL extracellular domain consists of two immunoglobulin-like domains. Upregulation of AXL and binding to its ligand, growth arrest-specific 6 (GAS6), has been associated with cell survival, proliferation, and migration (6).

BCL-2

BCL-2 is an anti-apoptotic protein found on the outer membrane of mitochondria. It prevents activation of pro-apoptotic proteins BAX and BAK, also found on the mitochondria membrane. Apoptosis is induced by BAX and BAK aggregating to form a pore that releases intermembrane proteins and triggers the caspase cascade (7).

COX

Cyclooxygenases (COX-1 and COX-2) are involved in the formation of prostaglandins from arachidonic acid. COX-1 is constitutively expressed while COX-2 is induced, but both can be inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs). COX-2 is strongly associated with inflammation, while the constitutive aspect of COX-1 provides prostaglandins to the stomach and intestine for the maintenance of mucosal epithelium integrity (8).

EGFR

The gene expressing epidermal growth factor receptor (EGFR) is one of the most common to be affected in human cancers. EGFR binds to ligands such as EGF and transforming growth factor (TGF)-α (9). EGFR has an extracellular ligand-binding region, a single membrane-spanning region, and a cytoplasmic region containing a tyrosine kinase domain. Ligand binding causes receptor homo- and hetero-dimerization leading to stimulation of the tyrosine kinase and subsequent intracellular signal transduction. Alterations in these signaling pathways can ultimately lead to carcinogenesis.

ERCC1

Excision repair cross complementary 1 (ERCC1) is a DNA repair enzyme which has ATP-dependent DNA helicase activity. ERCC1 is involved in transcription coupled nucleotide excision repair and defects in this gene are associated with multiple syndromes (10).

hENT1

Human equilibrative nucleoside transporter 1 (*hENT1*) gene encodes a transmembrane glycoprotein located in the cellular and mitochondrial membranes. hENT1 functions by mediating the cellular uptake of nucleosides required for cells lacking de novo nucleoside synthesis pathways also mediating the uptake of cytotoxic nucleosides used in cancer treatment (11–13).

HER2

Human epidermal growth factor receptor 2 (HER2) is involved in cell growth and differentiation. HER2 belongs to the epidermal growth factor receptor family because it has intrinsic tyrosine kinase activity, but does not bind directly to ligands (14,15). It forms a heterodimer by tightly binding other ligand bound EGFR family members.

IGF-1

Insulin-like growth factor-1 (IGF-1) and its tyrosine kinase receptor transduce cellular signals for mobility, adhesiveness, vascularization, proliferation, apoptosis, migration and differentiation (16). IGF-1 is known to have paracrine and autocrine activity dependent upon nutritional status and insulin plays a role in its synthesis, secretion and activity.

KRAS

KRAS is a member of the family of *RAS* proto-oncogenes which encodes a GTPase. Mutant KRAS is known to activate downstream signal transduction pathways that stimulate tumorigenesis and resistance to therapies. Such pathways and intermediates include the phosphatidylinositol 3-kinase pathway, mitogen-activated protein kinase (MAPK) MEK, and mammalian target of rapamycin (mTOR) (17).

Mesothelin

Mesothelin is found on human mesothelial cell membranes, and plays a role in cell adhesion, recognition, cell survival, migration, invasion, and tumor progression. It is the C-terminal cleavage product of a precursor protein initially identified in a human pancreatic cancer cell line (18). The N-terminal cleavage product, megakaryocyte proliferation factor, is not currently a reliable serum tumor marker for pancreatic adenocarcinoma.