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Organelles in Focus

Implications of the Golgi apparatus in prostate cancer

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ABSTRACT

The classical view of the Golgi apparatus is of a small membranous organelle involved in protein transport and secretion. Recent descriptions of the molecular network connecting the Golgi to other organelles demonstrate the essential roles of the Golgi in cellular activities as a stress sensor, apoptosis trigger, lipid/protein modifier, mitotic checkpoint, and a mediator of malignant transformation. Thus, the Golgi function should have a fundamental impact on cancer cell survival. Prostate cancer is initially responsive to androgenic hormones; however, it almost invariably progresses to a castration-refractory or hormone-insensitive state. Nevertheless, androgen signaling remains active at this stage and is important as a therapeutic target. Certain Golgi-associated molecules have recently been demonstrated to be regulated by androgen action, and the Golgi is emerging as a new therapeutic target in prostate cancer. The key Golgi-associated molecules essential for prostate cancer development and the potential therapeutic options targeting the Golgi apparatus are discussed.

1. Introduction

The Golgi apparatus is a central organelle that is involved in secretion and endocytosis. Recent studies demonstrate a crucial role for the Golgi in cell death signaling, including apoptosis and autophagy, supporting the idea of an organelle cell death network including the endoplasmic reticulum (ER), mitochondria, plasma membrane, and nucleus (Wlodkowic et al., 2009). Numerous pro-apoptotic factors and mitosis-related molecules are localized to the Golgi membrane, and various cell death-inducing stimuli cause the fragmentation of the Golgi, in turn inducing apoptosis and/or autophagy. Therefore, the Golgi apparatus is becoming increasingly important as an anti-cancer target.

Prostate cancer is the second most diagnosed cancer in males, and it is characterized by androgen-dependent growth. Specifically, the androgen receptor (AR) plays a critical role in the growth and survival of prostate cancer. Therefore, androgen deprivation or AR-targeted therapies, which induce prostate cancer apoptosis, are basic approaches for prostate cancer treatment. However, these strategies will inevitably fail to cure or control the disease because it eventually progresses to hormone-refractory prostate cancer (HRPC). Although the mechanisms of escaping androgen dependence in prostate cancer are not fully defined, a large body of evidence demonstrates that AR signaling remains active in HRPC despite the low-androgen environment. Therefore, the investigation of the AR signaling pathway in prostate cancer progression and the development of new drugs that target AR signaling for prostate cancer treatment are of paramount importance. Comprehensive gene expression analyses provide evidence that the expression of some Golgi-associated proteins are regulated by AR signaling and are useful biomarkers for diagnosis or prognosis of prostate cancer. Furthermore, Golgi-targeting drugs have been shown to be effective in both androgen-sensitive and androgen-independent prostate cancer. In this review, we focus on the therapeutic implications of the Golgi apparatus specifically in prostate cancer.

2. Organelle function

The functions of the Golgi apparatus are well established and include vesicular trafficking and protein and lipid biosynthesis. Newly synthesized proteins and lipids from the ER are subjected to further processing into their final functional forms in the Golgi. Specifically, immature proteins are modified by *N*- and *O*-linked glycosylation and oligosaccharide chain processing in the Golgi. Recent evidence indicates that the Golgi can act as a platform for cellular signaling molecules between the Golgi and other organelles, including the ER, nucleus, and plasma membrane. Through this organelle network, the Golgi is involved in multiple biological functions, including cell signaling, stress sensing/effecting, cell death/survival, mitosis checkpoints, cell motility, and lipid homeostasis (Wilson et al., 2011; Munro, 2011).

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Table 1
Golgi dysfunctions related to prostate cancer pathogenesis.

Biology	Aberrations	Effects	Other tumor type	References
Cell death and survival	Death receptors	Apoptosis, immune evasion, inflammation	Most tumors	Guseva et al. (2004)
	Ganglioside GD3	Apoptosis, stress sensor, invasion and metastasis, angiogenesis, immunosuppression	Glioma, melanoma, sarcoma, colorectal, pancreas, leukemias	Fabbri et al. (2011)
	EBAG9	Apoptosis, immune homeostasis	Breast, liver, pancreas	Takahashi et al. (2003)
Cell signaling	PKD1 and PKD3	Proliferation, survival, motility, epithelial–mesenchymal transition	Breast, gastro-intestine, pancreas	Mak et al. (2008) Chen et al. (2008)
	Src	Transformation, invasion, anti-apoptosis	Breast, colon, lung, pancreas, etc.	Tatarov et al. (2009)
Protein and lipid modification	*O*-Glycans	Invasion and metastasis	Colon, pancreas, breast, ovary, stomach	Brockhausen (2006)
	Sialylation	Metastasis	Breast and ovary	Yang et al. (2011)
	Fucosylation	Adhesion, cell signaling, cancer specific glycan	Pancreas, liver, breast, ovary, lung	Kyselova et al. (2007)
	N-Glycans	Invasion and metastasis, transformation, anti-apoptosis	Breast, lung, melanoma, sarcoma, etc.	Kyselova et al. (2007)
Golgi pH	Acidification	Multidrug resistance, loss of cell polarity, impaired glycosylation	Breast	Rivinoja et al. (2011)
	Alkaline	Increased T-antigen	Breast, colorectal	Glinsky et al. (2001)
Tumor biomarker	GOLPH2/GOLM1/GP73	Unknown	Liver	Kristiansen et al. (2008)

The prostate is a secretory organ that functions predominantly in the maintenance of sperm and is critical to fertility. The prostatic fluid includes high levels of Golgi-associated proteins, including prostatic acid phosphatase (PAP) and prostatic-specific antigen (PSA). PSA cleaves the gel-forming proteins, semenogelin I and II, and contributes to semen liquefaction and initiation of sperm motility; therefore, the Golgi is a key organelle in the maintenance of prostatic function.

3. Cell physiology

The Golgi apparatus is localized in the perinuclear region and has a characteristic structure, comprising stacks of flattened cisternal membranes. Golgi stacks are connected to form a ribbon, which is important for the polarized secretion of the Golgi-derived carriers to the plasma membrane. The Golgi consists of three functional regions: the *cis*-, *medial*-, and *trans*-Golgi. The *cis*- and *trans*-Golgi networks (TGN) are implicated in protein import and export, respectively. In general, the physiology of the Golgi includes the following three major roles. First, the Golgi is required for the direction of ER-derived proteins toward their appropriate destinations. The ER generates proteins in COPII (coatomer protein II)-coated vesicles that subsequently fuse with the *cis*-Golgi. After the processing in the Golgi stack, secreted and cell surface proteins are sorted at the TGN into carriers for transportation to the cell membrane. Second, the Golgi modifies ER-derived proteins by glycosylation, sulfation, phosphorylation, and proteolysis for protein maturation. The Golgi stacks influence the extent of this process. Diverse glycosylation patterns are mainly determined by the activity of various glycosyltransferases. Third, the Golgi is also involved in the modification and sorting of lipids. The Golgi converts the ceramide produced in the ER into sphingolipids, which are major components of the lipid bilayer. Thus, the Golgi maintains the fatty acid composition of cell membranes. Recent advances in cell physiology and structural studies of the Golgi are described in detail in other reviews (Lowe, 2011; Wilson et al., 2011; Munro, 2011).

4. Organelle pathology

4.1. Role of the Golgi apparatus in prostate cancer development

As described above, because the Golgi is a fundamental organelle that is involved in cell survival and/or death, Golgi function has been investigated in cancer biology, including in prostate cancer (Table 1). Aberrant glycosylation is well characterized as a common feature of malignant transformation and tumor progression. Glycosylation-dependent cancer pathogenesis is defined by certain phenotypes, including proliferation, angiogenesis, migration, apoptosis, and invasion (Hakomori, 2002). In prostate cancer, abnormal glycosylation has been reported; however, its biological significance is not well understood. Thomsen–Friedenreich antigen is expressed on the surface of prostate cancer cells and may be involved in cancer cell adhesion to endothelial cells or immune attack evasion (Glinsky et al., 2001). Oncogenic MUC1 is highly glycosylated in a variety of cancers; however, the tumor-promoting effect of MUC1 in prostate cancer remains enigmatic (Premaratne et al., 2011). A traffic signal from ER phosphorylates and activates the Golgi pool of Src family kinases (Pulvirenti et al., 2008), which are involved in prostate cancer initiation and development.

Androgen-responsive molecules in the Golgi are considered to be important for both prostate cancer development and treatment; therefore, some of these molecules are described below.

4.1.1. ARFGAP3

The ADP ribosylation factor (ARF) family of GTPases, a subfamily of the Ras superfamily, is involved in the recruitment of various coat protein complexes to the Golgi membrane. ARF attachment to the Golgi is regulated by guanine nucleotide exchange factors (GEFs) and Golgi-associated GTPase-activating proteins (GAPs). ARFGAPs contain the common ARFGAP catalytic domain and convert ARF-GTP into ARF-GDP, thereby inducing the dissociation of coated vesicles from the Golgi. ARFGAP3 has been identified as an androgen-responsive gene that promotes the proliferation of androgen-dependent LNCaP prostate cancer cells, whereas the