CellPress

Addicted to secrete – novel concepts and targets in cancer therapy

Nicolas Dejeans[1,2], Serge Manié[3,4], Claudio Hetz[5,6,7], Frédéric Bard[8,9], Ted Hupp[10], Patrizia Agostinis[11], Afshin Samali[12], and Eric Chevet[1,2,3]

[1] Inserm U1053, F-33000 Bordeaux, France
[2] University Bordeaux-Segalen, F-33000 Bordeaux, France
[3] University of Lyon, 69000 Lyon, France
[4] UMR CNRS 5286, INSERM 1052, Cancer Research Center of Lyon, 69000 Lyon, France
[5] Biomedical Neuroscience Institute, ICBM, Faculty of Medicine, University of Chile, Santiago, Chile
[6] Neurounion Biomedical Foundation, Santiago, Chile
[7] Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, MA, USA
[8] Laboratory Regulation of Membrane Traffic, Institute of Molecular and Cell Biology, Singapore, Singapore
[9] Department of Biochemistry, National University of Singapore, Singapore, Singapore
[10] Cell Signaling Unit, p53 Signal Transduction Laboratories, Edinburgh Cancer Research Centre, University of Edinburgh, Crewe Road South, Edinburgh EH4 2XR, UK
[11] Department of Cellular and Molecular Medicine, University of Leuven (KU Leuven), Leuven, Belgium
[12] Apoptosis Research Centre, School of Natural Sciences, NUI Galway, Galway, Ireland

The unfolded protein response (UPR) mediates the adaptation of the secretory pathway (SP) to fluctuations in cellular protein demand or to environmental variations. Recently, drug screenings have confirmed the therapeutic potential of targeting the UPR in cancer models. However, the UPR may not be the only druggable target of the SP. Moreover, recent studies have revealed other contributions of the SP to cancer development. This article does not intend to describe the well-established implication of UPR signaling pathways in cancer cell life and cell decision, but rather aims at defining the concept of 'tumor cell secretory addiction', from molecular, cellular, and therapeutic perspectives. Furthermore, the implication of UPR modulations in this context will be discussed.

Overview of the secretory pathway in cancer

Approximately one-third of the polypeptides synthesized by a cell enter the endoplasmic reticulum (ER), the first compartment of the secretory pathway (SP) (see Glossary). From there, the polypeptides undergo different maturation steps including folding, glycosylation, and disulfide bond formation, thereby enabling the properly folded proteins to exit the ER and reach their final destination. These multistep and active processes are tightly regulated and controlled to maintain ER protein homeostasis (or ER proteostasis) [1,2]. Any physical, chemical, or biological conditions that disturb this efficient ER proteostasis network are rapidly sensed as part of the cell stress response. The main signaling pathway governing these molecular mechanisms is collectively known as the

Corresponding authors: Dejeans, N. (nicolas.dejeans@gmail.com); Chevet, E. (eric.chevet@inserm.fr).
Keywords: unfolded protein response; secretory pathway; cancer therapy.

1471-4914/$ – see front matter
 http://dx.doi.org/10.1016/j.molmed.2013.12.003

Glossary

Aneuploidy: condition in which a cell has an incorrect number of chromosomes.
Autophagy: an intracellular degradative process that delivers cytoplasmic materials to the lysosome for degradation.
Endoplasmic reticulum (ER): the first component of the cell SP; it encompasses an extensive network of membrane tubules, vesicles, and flattened cisternae within the cytoplasm. The main function of the ER is to serve as a platform for lipids, or carbohydrate metabolism, secretory protein folding, and maturation and control of cell calcium homeostasis.
Glycosylation: post-translational modification process in which carbohydrates (glycans, saccharides, or sugars) are covalently attached to proteins, lipids, or other organic molecules.
Golgi apparatus: membranous organelle and component of the cell SP that receives the output (proteins and lipids) from the ER and allocates them to their final destinations. It also acts as a reaction chamber for specific protein glycosylations, phosphorylations, and cleavages.
Immunogenic cell death: a cell death subroutine that, in contrast to the physiological caspase-mediated-tolerogenic apoptosis, stimulates cancer cell immunogenicity along with a protective anticancer immune response *in vivo*.
Oncogenesis: all the events which will lead to the transformation of normal cells to cancerous cells.
Proteostasis: refers to a proper balance among synthesis, maturation, and degradation of cellular proteins.
Proteotoxic compounds: compounds that alter proteostasis.
Secretome: the collection of all molecules secreted by a cell, including trophic factors and immunomodulatory cytokines.
Secretory pathway (SP): the complex network of eukaryotic cell organelles that mediates the folding, maturation, and trafficking of transmembrane and secreted proteins. It is also responsible for biogenesis and proper intracellular distribution of a wide range of complex carbohydrates and lipids.
Tumor cell secretory addiction: describes the need for cancer cells to possess a particularly efficient SP. This need can be the result of (i) an increase in secretory protein demand (due to aneuploidy or oncogene expression); (ii) a metabolic crisis associated with cancer cell high metabolism and energy depletion; or (iii) high levels of proteotoxic stresses mediated by basal oxidative stress or chemotherapy. Furthermore, this need creates a dependency of cancer cells for the SP and makes the SP an interesting therapeutic target.
Unfolded protein response: an evolutionarily conserved cellular response that mediates the adaptation of the SP to fluctuations in the cellular protein demand or to environmental variations. It encompasses a set of distinct signaling pathways that aim at reducing global protein load to the ER and increasing the levels of chaperones and the degradation of misfolded proteins.

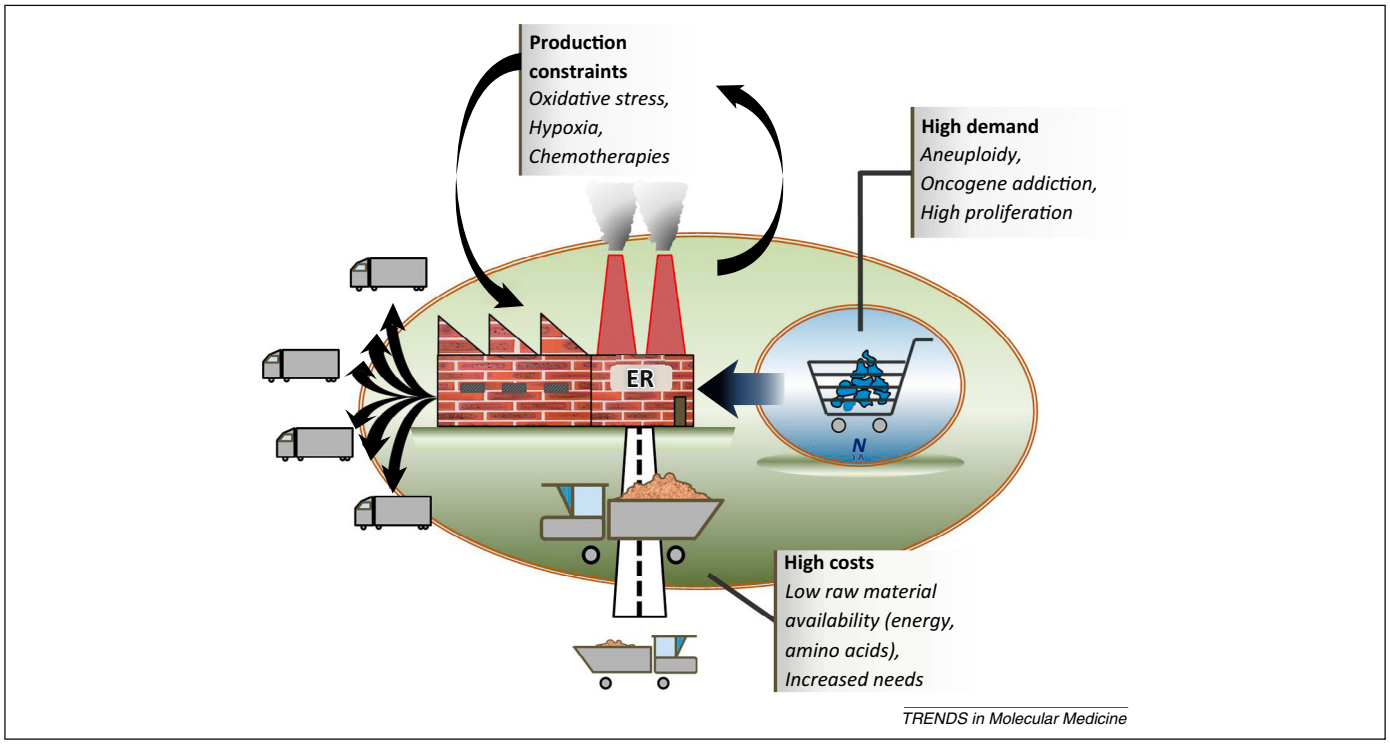

Figure 1. Secretory protein demand, cost, and price in cancer: the secretory crisis. The secretory pathway can be considered as a whole as one of the 'factories' of the cell. In this view, production of secreted proteins is dependent on the demand, dictated by the nucleus, the availability of raw materials (e.g., energy, amino acids), and production constraints. Critical factors destabilizing this system in cancer cells are indicated. Abbreviations: N, nucleus; ER, endoplasmic reticulum.

unfolded protein response (UPR) and is initiated by three ER transmembrane proteins in mammals, namely, activating transcription factor 6 (ATF6), protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), and inositol-requiring enzyme 1 (IRE1) [3]. Thus, the UPR aims at restoring ER homeostasis under stressful conditions, and if this fails then cell death is engaged.

By nature, features of cancer cells, such as aneuploidy, increase in metabolic demand, and high proliferation rates, require particularly robust ER and secretory machineries. This increased demand for the secretory functions in tumors is likely to trigger an alteration of ER homeostasis and consequently result in 'basal' or constitutive UPR induction (Figure 1). Moreover, in certain cancer types, SP-associated functions have been identified as fundamental players in oncogenesis. As such, the UPR plays prooncogenic or antioncogenic roles depending on the tumor context. It can be tumor suppressive in early stages of cancer development, as reported in melanoma or Ras-driven lung cancer [4,5], whereas it can be tumor promoting in established cancer, such as in multiple myeloma (MM) [6] and other cancers [7,8]. Moreover, beyond the general increase in the demand that challenges the SP, the secretion of prooncogenic factors, such as growth factors and their associated receptors, might also confer specific dependency of the cancer cells towards the SP. This is well illustrated by the interaction of tumor cells with their environment [9]. Indeed, tumor–stroma interactions are controlled by cytokines, extracellular matrix (ECM) proteins, matrix metalloproteases (MMPs), integrins, and other contact proteins, all trafficked to their final destination through the SP. Modulation of the SP by endogenous or exogenous stress factors could therefore result in cell ECM destabilization and an increase in cancer dissemination and invasion. Finally, the relation between the SP and oncogenesis is illustrated by the increasing number of reports describing a role for plasma membrane exposure of major ER-resident proteins in tumor immunogenicity [10,11]. All these factors have prompted us to reconsider the contribution of the tumor cell secretory machinery in cancer development and progression.

The economics of secretory protein production: cost, demand, and price to pay in cancer cells

Aneuploidy is a hallmark of cancer cells that contributes to tumorigenesis by providing gain of oncogenes or loss of tumor suppressor genes [12]. Adding to that, an increase in the number of chromosomes was found to induce hypersensitivity to conditions interfering with protein synthesis and protein folding in yeast [13], and in human cancer cells [14]. This suggests that aneuploidy-mediated translation increase is an Achilles' heel of cancer cells because it alters proteostasis. Along these lines, an increase in ploidy was recently found to be associated with ER stress in cancer [7]. Consequently, interfering with proteostasis represents an appealing strategy to target cancer cells specifically (Figure 2). Moreover, the aneuploidy-induced SP challenge is also associated with immunogenicity, due to aberrant cell surface exposure of calreticulin (CRT).

However, the dependence of cancer cells to the SP is not restricted to aneuploidy and a variety of cancer-associated molecular processes are responsive to alterations in the secretory machinery. These include, but are not limited to, high proliferation, elevated metabolism, and oncogene-mediated increases in protein demands. Indeed, Huber *et al.* found that cell transformation results in an increase