Biochimie 124 (2016) 34–52

Contents lists available at ScienceDirect

Biochimie

journal homepage: www.elsevier.com/locate/biochi

Review

Tripping on TRIB3 at the junction of health, metabolic dysfunction and cancer

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ARTICLE INFO

Article history:
Received 10 July 2015
Accepted 4 February 2016
Available online 6 February 2016

Keywords:
TRIB3
Metabolic syndrome
Cancer
ER-stress
PI3K/AKT/mTOR
Autophagy

ABSTRACT

Metabolic diseases like obesity, atherosclerosis and diabetes are frequently associated with increased risk of aggressive cancers. Although metabolic dysfunctions in normal cells are manifested due to defective signaling networks that control cellular homeostasis, malignant cells utilize these signaling networks for their increased survival, growth and metastasis. Despite decades of research, a common mechanistic link between these chronic pathologies is still not well delineated. Evidences show that the unfolded protein response (UPR) and the endoplasmic reticulum stress (ERS) pathways are often dysregulated in both metabolic diseases and cancer. The UPR also triggers coordinated signaling with both PI3K/AKT/mTOR and Autophagy pathways in order to promote stress-adaptive mechanisms. Whereas, uncontrolled UPR and the resultant ERS escalates cells towards metabolic dysfunctions and ultimately cell death. In this review, we will discuss findings that implicate a crucial role for the multifunctional ERS-induced protein, TRIB3. The 'pseudokinase' function of TRIB3 facilitates the inactivation of multiple transcription factors and signaling proteins. The MEK1 binding domain of TRIB3 enables it to deactivate multiple MAP-kinases. In addition, the COP1 motif of TRIB3 assists ubiquitination and proteasomal degradation of numerous TRIB3 associated proteins. The most well studied action of TRIB3 has been on the PI3K/AKT/mTOR pathway, where TRIB3-mediated inhibition of AKT phosphorylation decreases insulin signaling and cell survival. Conversely, cancer cells can either upregulate the AKT survival pathway by suppressing TRIB3 expression or alter TRIB3 localization to degrade differentiation inducing nuclear transcription factors such as C/EBPα and PPARγ. The gain-of-function Q84R polymorphism in TRIB3 is associated with increased risk of diabetes and atherosclerosis. TRIB3 acts as a crucial 'stress adjusting switch' that links homeostasis, metabolic disease and cancer; and is being actively investigated as a disease biomarker and therapeutic target.

Contents

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http://dx.doi.org/10.1016/j.biochi.2016.02.005

1. A long sought-after connection between metabolic dysfunction and cancer

1.1. Metabolic diseases increase cancer-associated morbidity and mortality

Chronic metabolic diseases like obesity, type-2 diabetes, atherosclerosis, and cardiovascular disease (CVD) are becoming increasingly prevalent worldwide [1–4]. Both hyperinsulinemia and hyperglycemia contribute to the progression of obesity and diabetes, and insulin resistance, manifested due to decreased insulin receptor signaling, is the primary risk factor for these metabolic disorders [5,6]. Interestingly, metabolic diseases are also frequently associated with poorer cancer outcomes [7,8]. In the past few decades, a number of studies have documented a clear link between the metabolic syndromes and higher morbidity and mortality due to different malignancies [9–11]. However, the crucial mechanism(s) involved in linking these chronic pathologic manifestations is not properly understood. As early as 1995, Steenland et al., showed that men with diabetes present with a 39% higher risk of developing colorectal and prostate cancer [12]. Calle et al. (2003) published finding from the multicenter Cancer Prevention Study (CPS) which followed more than one million adults during 1982–1996, and clearly demonstrated that obese men and women had a 40–80% increased threat of dying from cancers [13,14]. The danger of having aggressive pancreatic, breast and colorectal cancers are reported to be amplified in patients with high body mass index (BMI) and several meta-analyses in patients with diabetes also showed significantly higher cancer mortality, as compared with nondiabetic individuals [15,16]. Indeed, the clinically approved glyburide, metformin has provided better clinical outcome in diabetic patients with advanced cancers [17]. Hence, a thorough understanding of the long sought-after relationship between metabolic diseases and cancers will not only provide early biomarkers for disease progression, but will also elucidate novel therapeutic targets to decrease cancer-associated complications. Furthermore, since tremendous increases in metabolic syndrome are being reported in younger adults [4], which makes them more susceptible to malignancies later in life, studies on the common etiologies in metabolic diseases and cancer are garnering a lot of attention [7,17–22].

Deleterious consequences of chronic inflammation and oxidative stress are known to increase tumor progression and metastasis, and also facilitate tumor resistance to both chemotherapy and radiotherapy [7,20,23–28]. Studies have documented that the visceral adipose tissue secreted inflammatory cytokines can promote insulin resistance in vascular cells [29–32]. Metabolic complications of insulin resistance make individuals more susceptible to chronic oxidative stress, neoplastic transformation and aggressive tumor growth. A number of studies have also demonstrated that second messenger signaling via the insulin and insulin like growth factor (IGF) receptors play a crucial role in numerous other chronic diseases such as autoimmunity, arthritis, alzheimer's disease and aging [33–36]. Thus, it is becoming apparent that the chronic effects of inflammation in disrupting stress-adaptive pathways in both normal and malignant cells may influence progression of these chronic diseases.

1.2. Inflammation: a common etiology in chronic diseases

Obesity induced adipokines, inflammatory cytokines, leptin, proteolytic enzymes, and endogenous sex steroids, are known to suppress the anti-inflammatory actions of insulin. The resultant activation of vascular endothelium and decreased vasodilation of smooth muscle cells increases blood pressure and causes hypertension [32,37,38]. Increased adhesion of leukocytes and platelets and the ensuing atherosclerotic thrombus formation further fosters inflammatory stress and insulin resistance of the vasculature. Adipose tissue infiltrated macrophages and foam cells can also produce a state of chronic oxidative stress and inflammation, which further promote the chronic metabolic dysfunctions [39,40]. Interestingly, the deleterious effects of insulin resistance, inflammation and oxidative stress have also been implicated in both oncogenic transformation of normal cell [41,42] and in increased proliferation and metastasis of tumor cells, as shown by us [43] and others [20,28,44]. Furthermore, since insulin resistance increases both estrogen and testosterone levels by decreasing SHBG (sex hormone binding globulin) [45] metabolic diseases can also augment the growth of endocrine tumors like breast and prostate cancers [7,23,43]. Therefore, insulin resistance is postulated to be a common link and comorbidity in both metabolic diseases and cancer. Indeed, insulin-induced glucose uptake is dysregulated in