European Journal of Cancer 101 (2018) 165–180

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Influence of eukaryotic translation initiation factor 6 on non–small cell lung cancer development and progression

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Received 3 April 2018; received in revised form 22 June 2018; accepted 2 July 2018

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https://doi.org/10.1016/j.ejca.2018.07.001
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KEYWORDS
Non–small cell lung cancer;
Adenocarcinoma;
Squamous cell carcinoma;
Eukaryotic translation initiation factor 6

Abstract Non–small cell lung cancer (NSCLC) is the leading cause of cancer-related death worldwide. Dysregulation of protein synthesis plays a major role in carcinogenesis, a process regulated at multiple levels, including translation of mRNA into proteins. Ribosome assembly requires correct association of ribosome subunits, which is ensured by eukaryotic translation initiation factors (eIFs). eIFs have become targets in cancer therapy studies, and promising data on eIF6 in various cancer entities have been reported. Therefore, we hypothesised that eIF6 represents a crossroad for pulmonary carcinogenesis. High levels of *eIF6* are associated with shorter patient overall survival in adenocarcinoma (ADC), but not in squamous cell carcinoma (SQC) of the lung. We demonstrate significantly higher protein expression of eIF6 in ADC and SQC than in healthy lung tissue based on immunohistochemical data from tissue microarrays (TMAs) and on fresh frozen lung tissue. Depletion of eIF6 in ADC and SQC lung cancer cell lines inhibited cell proliferation and induced apoptosis. Knockdown of *eIF6* led to pre-rRNA processing and ribosomal 60S maturation defects. Our data indicate that eIF6 is upregulated in NSCLC, suggesting an important contribution of eIF6 to the development and progression of NSCLC and a potential for new treatment strategies against NSCLC.
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1. Introduction

Non–small cell lung cancer (NSCLC), accounting for more than 85% of newly diagnosed lung cancer, is the leading cause of cancer-related death worldwide [1,2]. Despite a large arsenal of treatment options, the future perspective for patients suffering from NSCLC is dismal, with a combined 5-year overall survival (OS) rate of ~15–18% [1,2].

This study investigates the role of eukaryotic translation initiation factor 6 (eIF6) in the two major subtypes of NSCLC, adenocarcinoma (ADC) with ~50% and squamous cell carcinoma (SQC) with ~40% occurrence [3,4]. ADCs occur primarily in the distal airways, whereas SQCs arise mainly in the proximal airways [3], indicating that the two entities differ morphologically and on the molecular level.

One of the major activities of a eukaryotic cell is ribosomal biosynthesis to ensure continuous protein translation. Thus, dysregulation of translation initiation has received considerable attention, and a number of studies revealed aberrant eukaryotic translation initiation factors (eIFs) expression in various cancer entities [5–13].

eIFs facilitate the formation of a translation-competent 80S ribosome, a rate-limiting step during carcinogenesis [14,15]. Translation initiation can be divided briefly into four steps: (1) formation of 43S pre-initiation complex by recruiting the ternary complex eIF2-GTP-tRNAi(met) to the small 40S ribosomal subunit, (2) assembly of the 48S initiation complex by 5′ cap recognition by eIF4F joining the 43S complex, (3) scanning of the mRNA starting from the 5′UTR region to the start codon and (4) formation of the mature 80S ribosome by joining the 60S subunit, which is accomplished by eIF5B and eIF6 [15,16]. The mammalian ribosome consists of a 60S (large) and a 40S (small) subunit. Its biogenesis starts in the nucleus where the precursor ribosomal RNAs (rRNA) 5S and 35S as well as ribosomal proteins and assembly factors (including eIF6) bind to either the pre-40S or pre-60S ribosomal subunit [17,18]. During the assembly process, the two subunits are transported into the cytoplasm, where eIF6 dissociates to facilitate binding of the 40S and 60S subunits [19,20]. The 40S subunit contains the 18S rRNA, whereas the 60S subunit comprises three rRNAs, 25S, 5.8S and 5S [17,21,22].

Recent studies suggest that eIF6, a 27-kDa protein, has a dual function [9,19]. It was first described as an anti-association factor that prevents assembly of the 40S and 60S ribosomal subunit [23,24]. On the other hand, eIF6 is necessary for ribosome biogenesis in the nucleus [25]. Previous studies report that eIF6 is an important factor in tumorigenesis, cell cycle progression and invasiveness of cancer cells [19,26,27]. In addition, the important cellular role of eIF6 was emphasised by a study in which mice with a total depletion of *eIF6* had a lethal phenotype [28]. Dysregulation of eIF6 was shown in various cancer entities, such as colorectal carcinoma (CRC) [13], malignant pleural mesothelioma (MPM) [9] and breast cancer [29]. In CRC and MPM, eIF6 was overexpressed compared to non-neoplastic tissue, suggesting a key contribution to carcinogenesis and highlighting eIF6 as a potential new biomarker [9,13]. In this study, we correlated eIF6 expression with patients' survival in pulmonary ADC and SQC and investigated how eIF6 expression affects tumorigenic properties of representative cell lines of these two NSCLC entities.

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