Seminars in Cell & Developmental Biology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

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

Correlation between mucin biology and tumor heterogeneity in lung cancer

Menglin Xu, Diane C. Wang, Xiangdong Wang (Dr)*, Yong Zhang (MD, PhD)*

Zhongshan Hospital Institute of Clinical Science, Fudan University, Shanghai Institute of Clinical Bioinformatics, Biomedical Research Center, Shanghai, China

ARTICLE INFO

Article history:
Received 22 August 2016
Accepted 24 August 2016
Available online xxx

Keywords:
MUC
Tumor heterogeneity
Lung cancer
Diagnosis
Therapy

ABSTRACT

Mucins (MUC) are a family consisting of large O-glycoproteins whose primary functions are to protect and lubricate cell epithelial surfaces and contribute to intra- and inter-cellular signal pathways, cell proliferation, growth and apotosis. With the development of new technologies, MUCs begin to be identified as an effective marker in evaluating the tumor heterogeneity in lung cancer. MUCs' diverse expressions in subtypes of lung cancer indicate the inter-tumor heterogeneity. MUCs' mutation may also contribute to the development of intra-heterogeneity and evolution of lung cancer. Understanding MUCs' association with lung cancer heterogeneity and its molecular regulatory mechanism will benefit the development of diagnosis, therapy choice, and prognosis prediction of lung cancer.

Contents

1. Introduction

Mucins (MUC) are a family consisting of large O-glycoproteins composed of a long peptidic chain linked with hundreds of oligosaccharide chains. MUCs can, according to their structures, be divided into membrane-bound MUCs and the gel-forming/secreted MUCs. The membrane-bound MUCs belong to a group of type I membrane-anchored proteins, of which the prototype is composed of an extracellular O-glycosylated PTS domain, a TM domain and a cytoplasmic tail, and two EGF-like and one SEA domains in most [1,2]. The structure is thought to play, at least partly, an important role in cell-cell or cell-matrix interactions and cell signaling, and regulate epithelial cells (Fig. 1A). The specific expressions of membrane-bound MUCs in different types of epithelial cancers make MUC both potent biomarkers and therapeutic targets, especially for cancer vaccine. MUC1, MUC3A/3B, MUC4, MUC12, MUC13, MUC15, MUC16, MUC17, MUC20, MUC21, and MUC22 belong to the abovementioned category [1,3,4]. The secreted MUCs, e.g. MUC2, MUC5AC, MUC5B, MUC6, MUC7, MUC9, and MUC19, form a three-dimensional network via oligomerization domains, participate in mucus formation, and protect epithelia against inflammation, bacteria, virus, or pollutants [4,5]. Some MUCs are initially expressed on the cell surface and subsequently shed into the extracellular fluids and serum following proteolytic cleavage, even though they still belong to the membrane-bound MUCs, e.g. MUC16 [6].

Lung cancer is a heterogeneity disease with complicated signaling pathways modification caused by relevant genetic alterations. MUCs are associated with various cellular signal pathways in lung cancer affecting cell proliferation, growth and apotosis [7] (Fig. 1B). The distinct alteration of the tumorigenicity and metastasis ability in various lung cancer cells has been proved to be

* Corresponding authors.
E-mail addresses: xdwang@fuccb.com (X. Wang), zhang.yong@zs-hospital.sh.cn (Y. Zhang).

http://dx.doi.org/10.1016/j.semcdb.2016.08.027
1084-9521/

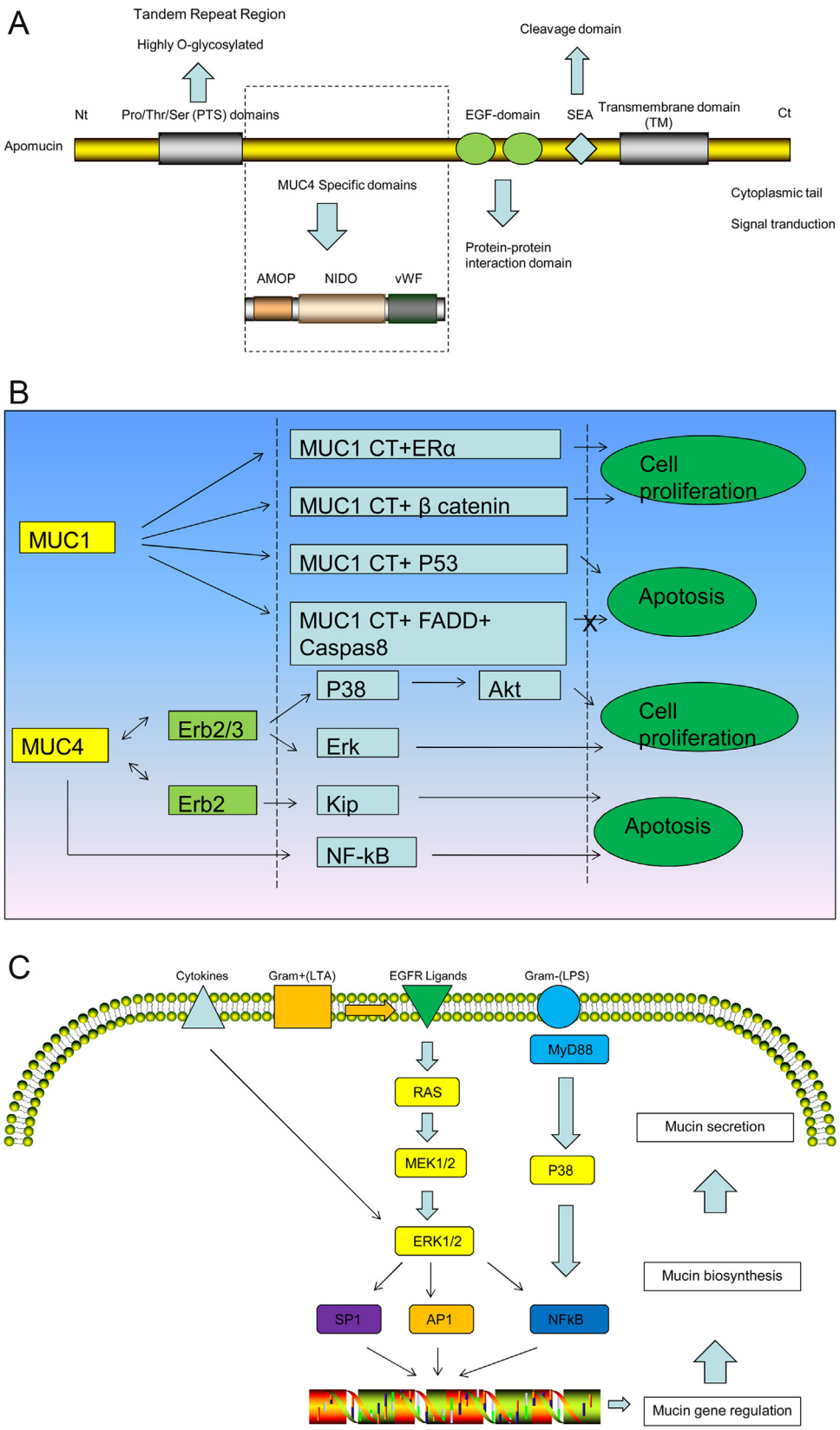

Fig. 1. The structure and involved pathways of membrane-bound mucin protein.
Fig. 1A MAembrane-bound mucin prototype. Membrane-bound mucins are modular proteins sharing conserved domains such as epidermal growth factor-like (EGF), Sea urchin sperm protein Enterokinase and Agrin (SEA) or Pro/Thr/Ser (PTS) domains or MUC4-specific domains (AMOP, NIDO and vWF-D). Fig. 1B: Divergent mechanisms of MUC1 and MUC4 for enhanced cancer cell proliferation and illustration of different mechanisms of MUC1 and MUC4 for the repression of apoptosis. Fig. 1C: Schematic of signal transduction pathways that regulate mucin gene transcription. Cytokines, LTA and LPS regulation mucin expression and work through common RAS and P38 pathways in epithelial cell.

Please cite this article in press as: M. Xu, et al., Correlation between mucin biology and tumor heterogeneity in lung cancer, Semin Cell Dev Biol (2016), http://dx.doi.org/10.1016/j.semcdb.2016.08.027