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Laboratory-Clinic Interface

Emerging potential of natural products for targeting mucins for therapy against inflammation and cancer ☆

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ABSTRACT

Deregulated mucin expression is a hallmark of several inflammatory and malignant pathologies. Emerging evidence suggests that, apart from biomarkers, these deregulated mucins are functional contributors to the pathogenesis in inflammation and cancer. Both overexpression and downregulation of mucins in various organ systems is associated with pathobiology of inflammation and cancer. Restoration of mucin homeostasis has become an important goal for therapy and management of such disorders has fueled the quest for selective mucomodulators. With improved understanding of mucin regulation and mechanistic insights into their pathobiological roles, there is optimism to find selective non-toxic agents capable of modulating mucin expression and function. Recently, natural compounds derived from dietary sources have drawn attention due to their anti-inflammatory and anti-oxidant properties and low toxicity. Considerable efforts have been directed towards evaluating dietary natural products as chemopreventive and therapeutic agents; identification, characterization and synthesis of their active compounds; and improving their delivery and bioavailability. We describe the current understanding of mucin regulation, rationale for targeting mucins with natural products and discuss some natural products that modulate mucin expression and functions. We further discuss the approaches and parameters that should guide future research to identify and evaluate selective natural mucomodulators for therapy.

Introduction

Mucins are high molecular weight glycoproteins, primarily expressed by epithelial cells on apical surfaces for lubricating and protecting the epithelia of ducts and body lumens against harmful exogenous and endogenous agents like bacteria, drugs, toxins, digestive enzymes and acids [1–3]. In addition, they are also involved in nutrient and cofactor adsorption in the gut, gaseous exchange in the lungs, transparency at the ocular surface and chemical sensing [3]. Under physiological conditions, mucins mediate diverse biological functions like cell–cell adhesion, renewal and differentiation of the epithelium, inflammation and immune responses. Somewhat paradoxically, for what evolved as a protective mechanism for epithelial cells under normal physiological conditions, aberrant and deregulated expression of mucins in epithelial malignancies contributes to tumorigenesis and metastasis. These mucins either by physical interactions or by regulating signaling cascades, promote malignant transformation, cancer cell growth, cell invasiveness, metastasis, decreased immune

Abbreviations: ECM, extracellular matrix; TGF-α, transforming growth factor-α; EGFR, epidermal growth factor receptor; STAT, signal transducer and activation of transcription; VEGF, vascular endothelial growth factor; TME, tumor microenvironment; IKKβ, inhibitor of nuclear factor-κB kinase-β; PG, prostaglandin; HIF-1α, hypoxia inducible factor-1α; HRE, HIF responsive elements; PEA3, polyomavirus enhancer activator-3; CREB, cyclic adenosine monophosphate responsive element binding protein; PKA, protein kinase A; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; ACF, aberrant crypt foci; MDF, mucin depleted foci; HNF1-α, hepatocyte nuclear factors-α; RA, all-trans-retinoic acid; EGCG, epigallocatechin gallate.

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surveillance and drug resistance [4–6]. Further, due to aberrant glycosylation in malignancies, mucins mediate cancer cell interactions with leukocytes, endothelial cells and platelets present in the tumor microenvironment during metastasis [3]. Owing to these above mentioned attributes, mucins have emerged as attractive targets for therapy and diagnosis [7].

Based on their structure, mucins are classified into transmembrane/membrane-bound (MUC1, MUC3A, MUC3B, MUC4, MUC12, MUC16 and MUC17) and secreted/gel-forming mucins (MUC2, MUC5AC, MUC5B, MUC6 and MUC19) [8]. The bulk of membrane bound mucins is extracellular and comprised of several unique domains that modulate various biological properties by selective interactions with various ligands, cell-surface proteins and the components of extracellular matrix [8]. The C-terminal cytoplasmic tails of mucins contain several phosphorylation sites and are believed to be involved in signal transduction by serving as docking sites for scaffolding proteins. Secreted mucins on the other hand lack hydrophobic transmembrane domain and on secretion form mucus layer on the apical surfaces of healthy epithelial cells particularly in the aerodigestive and genitourinary system that are exposed to the external environmental stresses.

The promise of mucins as therapeutic targets can be appreciated by the ongoing clinical studies and has been described by us in previously published articles [7,9]. Most mucin-targeted therapies have relied on the overexpression of mucins for eradication of cancer cells. These include immunotherapy to target epitopes presented by aberrantly expressed mucins on cancer cells, radioimmunotherapy to deliver cytotoxic radionuclides, or targeted therapy using anti-mucin antibodies or aptamers for delivering drugs toxins and nanoparticles specifically to mucin overexpressing cancer cells [2,3]. Most of the current mucin-based therapeutic approaches have focused on MUC1, MUC2, MUC4, MUC5AC and MUC16, and target single mucin at a time [7,9]. Since mucins are emerging as functional contributors to the pathobiology of inflammation and cancer and multiple mucins are expressed by tumor cells, therapeutic approaches based on comprehensive understanding of coordinated mucin regulation during inflammation and cancer can have significant impact. Therefore, it seems logical to use agents that can target multiple mucins simultaneously for more pronounced anti-cancer effects. In this context, development of novel small molecule inhibitors and natural product based formulations may result in simultaneous modulation of various mucins and mucin mediated diverse signaling pathways.

Due to their structural diversity, natural products derived from medicinal plants and microorganisms provide "privileged scaffolds" [10] and have thus been significant contributors to drug development. Some of the earliest natural product-based drugs including actinomycin, anthracycline, taxol, campthothecin and *vinca* alkaloids were developed and approved between 1964 and 1997. Then followed a decade of lull from 1997 to 2007, when

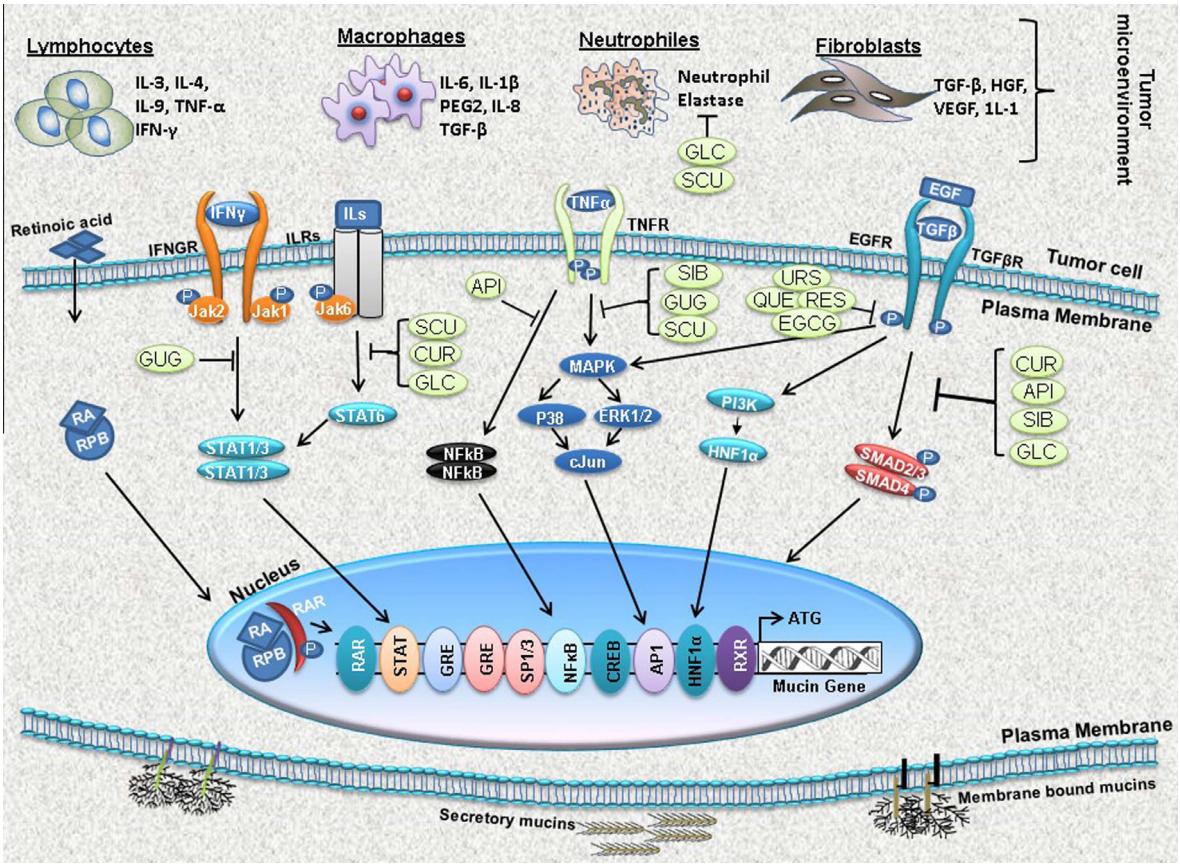

Fig. 1. Schematic representation of natural compounds that target signaling pathways regulating expression of mucins. Cytokines, interleukins and the growth factors secreted by the tumor cells or other cells of tumor microenvironment (lymphocytes, macrophages, neutrophils and fibroblasts) activate various signaling cascades like PI3K-AKT, Jak/STAT, MAPK/ERK/P38 and SMAD pathways involved in mucin regulation. Several dietary natural product derivatives modulate these signaling pathways at various steps to regulate mucin expression. Abbreviations: NFκB, nuclear factor kappa B; P, phosphate; PI3K, phosphatidylinositol-3-kinase; STAT3, signal transducer and activator of transcription 3; TNF, tumor necrosis factor; IL, interleukin; IFN, interferon; TGF, transforming growth factor; MEK, mitogen-activated protein kinase (MAPK) extracellular signal regulated kinase; ERK, extracellular signal regulated kinase; STAT, signal transducers and activators of transcription; Sp, specificity protein; HRE, hypoxia response element; ER, estrogen receptor; AP, activator protein; CUR, curcumin; GUG, guggulsterone; API, apigenin; GLC, glycyrrhizin; THY, thymoquinone; SIL, silibinin; SCU, scutellarin; GRA, graviola, QUE, quercetin; URS, ursolic acid; RES, resveratrol; EGCG, epigallocatechin gallate.