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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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