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Review

Regulation of mucin expression: Mechanistic aspects and implications for cancer and inflammatory diseases

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Abstract

Mucins are large multifunctional glycoproteins whose primary functions are to protect and lubricate the surfaces of epithelial tissues lining ducts and lumens within the human body. Several lines of evidence also support the involvement of mucins in more complex biological processes such as epithelial cell renewal and differentiation, cell signaling, and cell adhesion. Recent studies have uncovered the role of select mucins in the pathogenesis of cancer, underscoring the importance of a detailed knowledge about mucin biology. Under normal physiological conditions, the production of mucins is optimally maintained by a host of elaborate and coordinated regulatory mechanisms, thereby affording a well-defined pattern of tissue-, time-, and developmental state-specific distribution. However, mucin homeostasis may be disrupted by the action of environmental and/or intrinsic factors that affect cellular integrity. This results in an altered cell behavior that often culminates into a variety of pathological conditions. Deregulated mucin production has indeed been associated with numerous types of cancers and inflammatory disorders. It is, therefore, crucial to comprehend the underlying basis of molecular mechanisms controlling mucin production in order to design and implement adequate therapeutic strategies for combating these diseases. Herein, we discuss some physiologically relevant regulatory aspects of mucin production, with a particular emphasis on aberrations that pertain to pathological situations. Our views of the achievements, the conceptual and technical limitations, as well as the future challenges associated with studies of mucin regulation are exposed.

Keywords: Mucin; MUC; Regulation; Cancer; Inflammation

Contents

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1. Introduction

Historically, the term "mucin" (MUC for human and Muc for other species) was coined in reference to members of a family of large glycoproteins representing the major structural components of the mucus [102,138,239,272]. Thus far, a total of 19 human mucins have been identified and more are likely awaiting discovery. These include MUC1, -2, -3A, -3B, -4, -5AC, -5B, -6, -7, -8, -9, -11, -12, -13, -15, -16, -17, -19, and -20 [60,131,138,239]. Due to the unique characteristics and multifunctional properties of mucins [40,102,138,239,297], there has been a renewed interest in learning more about their intricate biology. This is evidenced by the plethora of relevant literature that has accumulated over the past decade.

Under normal physiological conditions, mucins exhibit a well-defined profile of tissue-, time-, and developmental state-specific expression. This tightly regulated homeostatic expression, however, is often compromised by a variety of insults that affect cellular integrity, thereby leading to pathological conditions. Deregulated mucin expression has been viewed as one of the most prominent characteristics of numerous types of cancers and inflammatory diseases [85,102,138,237]. Moreover, recent studies have provided compelling evidence supporting the role of mucins in the pathogenesis of various malignancies [207,315,389]. It is, therefore, critically important to understand the mechanisms regulating the production (synthesis and/or secretion) of mucins in order to uncover the molecular basis of their altered expression, and accordingly, to formulate appropriate strategies that will rectify the associated aberrations. In this respect, the present report will summarize the past findings and discuss recent advances related to the regulation of mucin synthesis, with special emphasis on its mechanistic aspects and implications in cancer and inflammatory diseases. Although our main focus will be on the regulatory mechanisms observed in tumor cells, several cases related to inflammation have also been addressed in light of the links between chronic inflammatory disorders and cancer [136]. The regulation of mucin secretion is beyond the scope of this review and will not be covered. Moreover, rather than providing an exhaustive account of the myriad of findings, specific cases have been selected to highlight key aspects of the progress made on the subjects covered. A number of conceptual and technical issues inherent in the many studies that have led to important discoveries are also exposed. Details about other important aspects of mucins have been described elsewhere [102,138,151,239] and will not be discussed at great length to avoid redundancy. Nonetheless, basic facts bearing a direct relationship to the matter at hand are provided. Furthermore, although this report is primarily concerned with human mucins, relevant information about other species has been included to illustrate specific points wherever appropriate.

2. Structure and classification of mucins

The basic structure of a mucin molecule reveals a protein backbone, termed "apomucin", decorated with a large number of O-linked oligosaccharides and a few N-glycan chains. Additional post-translational modifications, including sialylation or sulfation, are also commonly observed on mature mucin glycoproteins. A hallmark of mucins is the presence of specific tandemly repeated motifs (referred to as the "tandem repeats [TRs]") centrally positioned within the protein backbones [102,109,239]. Due to the fluctuating sizes of their TR regions, mucins frequently exhibit a polymorphism of the "variable number of tandem repeat" (VNTR) type, both within and between individuals [102,239]. Of note, TRs are particularly rich in Ser and Thr residues, which represent potential sites for extensive O-glycosylation [73,328]. The sugar moieties