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Review

The role of matrix metalloproteinases in muscle and adipose tissue development and meat quality: A review

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ABSTRACT

Matrix metalloproteinases (MMPs) are a group of enzymes that degrade extracellular matrix components but are also important signaling molecules that regulate many biological processes including muscle, adipose and connective tissue development. Most recently it has been discovered that MMPs act as intracellular signaling molecules inducing gene expression and altering related proteins in the nucleus. Several single nucleotide polymorphisms of MMPs and their inhibitors are known to exist and most of the research on MMPs to date has focused on their activity in relation to human health and disease. Nevertheless there is a growing body of evidence identifying important roles of MMPs as regulators of myogenesis, fibrogenesis and adipogenesis. The aim of this review is to highlight the currently known functions of the MMPs that have a direct bearing on the deposition of meat components and their relationship with meat quality. Some central pathways by which these enzymes can affect the tenderness, the amount and type of fatty acids are highlighted.

Contents

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1. Introduction

The metzincin superfamily of metallo-endopeptidases includes serralysins, astacins, paplaysins, adamlysins (which comprise ADAMs and ADAMTs) and matrixins, also known as matrix metalloproteinases, or MMPs (Vandenbrouke & Libert, 2014). Metzincins are all zinc-dependent proteases whose activity is regulated in vivo by endogenous tissue inhibitors of metalloproteinases (TIMPs). In addition to general activities as proteases of extracellular proteins, several groups of metzincins are known to be important regulators of cell signaling at the cell-matrix interface. Extensive and comprehensive reviews exist on the structure and function of the general metalloproteinase clan and their role in normal tissue functions and disease, some of which are referenced in Table 1, together with previous reviews on the structure, composition, expression, activation, regulation and physiological/pathological roles of MMPs.

Historically, (e.g. Woessner, 1991) it was thought that MMPs principally act as enzymes that degrade structural components of the extracellular matrix (ECM), but newer evidence shows that MMPs are also involved in a wide range of extra- and intra-cellular signaling pathways. MMPs play a central role as regulator of the tissue microenvironment under physiological conditions during development and tissue remodeling or conditions contributing to tissue destruction (Shiomi, Lamaitre, Darmiento, & Okada, 2010).

In this review we will focus specifically on the functions of the matrix metalloproteinases which have obvious or potential relations with meat quality. The major themes in this regard are (i) those roles associated with myogenesis and growth of muscle tissue (ii) the role of MMPs in the competing processes of fibrogenesis and adipogenesis, and (iii) the degradation and turnover of the extracellular matrix components in skeletal muscle and how this could be manipulated to improve meat tenderness. Lastly, we will discuss variations in the activity of the MMP system between different muscles in the carcass, or variations caused by SNPs in the genes coding for MMPs as contributors to variations in meat quality.

Table 1
Selected reviews on MMPs, ADAMs and ADAMTS which provide detailed accounts of metalloproteinase structure, regulation, inhibition and review various aspects of known functions. This list is by no means exhaustive.

Reference	Title	Principal topics covered
Matrisian (1992)	The matrix-degrading metalloproteinases	MMP structure, specificity, regulation by TIMPs, normal extracellular roles, MMP as mediators of growth factors and cytokines.
Nagase et al. (2006)	Structure and function of the matrix metallo-proteinases and TIMPs	Structure of the MMPs, mechanism of activation, inhibitions by TIMPs, MMP activity in cardiovascular disease.
Verma and Hansch (2007)	Matrix metalloproteinases (MMPs): Chemical–biological function and (Q)SARs	Structure and substrate selectivity of MMPs, chemistry of artificial inhibitors, structure–activity relationships, clinical trials of MMP inhibitors.
Alameddine (2012)	Matrix metalloproteinases and skeletal muscle: A brief review	MMP roles in muscle development, muscle repair, myopathies and response to exercise/disuse atrophy.
Chen and Li (2009)	Role of matrix metalloproteinases in skeletal muscle	Role of MMPs in normal muscle development and injury repair.
Murphy (2010)	Fell-muir lecture: Metalloproteinases: From demolition squad to master regulators	Overview of MMPs and ADAMs function roles in ECM degradation and ectodomain shedding, involvement in disease and therapeutic approaches.
White (2003)	ADAMs: modulators of cell–cell and cell–matrix interactions	ADAMs as disintegrin, sheddases, roles in normal biology and pathology.
Huovila et al. (2005)	Shedding light on ADAM metalloproteinases	ADAMs as sheddases genetic manipulations of activities, signaling pathways downstream of sheddase activity.
Khokha et al. (2013)	Metalloproteinases and their natural inhibitions in inflammation and immunity	Structure and activity of MMPs, ADAMs and TIMPs, expression and regulation, roles in inflammation and immunity.
Shiomi et al. (2010)	Matrix metalloproteinases, a disintegrin and metalloproteinases, and a disintegrin and metalloproteinases with thrombospondin motifs in non-neoplastic disease.	Structure and characteristics of metalloproteinases and TIMPs, involvement in disease of the circulatory, respiratory and nervous systems, liver, kidneys, joints and muscular disease.
Kelwick et al. (2015)	The ADAMTS (A disintegrin and Metalloproteinases with thrombospondin motifs) family.	ADAMTS genes and evolution, structure localization and activity, gene knockout and polymorphism effects, roles in development and disease.
Kessenbrock et al. (2010)	Matrix metalloproteinases regulators of the tumor microenvironment.	MMP characteristics, regulation, in vivo functions, role in apoptosis and specifically involvement in many aspects of cancer cell migrations and tumor progression.

2. Structural and biological characteristics of MMPs

2.1. General structure and properties of MMPs

The principal structural features of MMPs, as well as ADAMs and ADAMTS, are summarized in Fig. 1 (From Khokha, Murthy, & Weiss, 2013). Matrisian (1992); Nagase, Visse, and Murphy (2006), and Verma and Hansch (2007) in their publications describe in more detail the basic structure of the MMPs and their differences according to their grouping.

Currently, 24 different types of MMP have been identified as expressed proteases among vertebrates (Ajay Kumar, Mamta, Alok, Kamlesh, Shanthy et al., 2010). At least 11 MMPs and 3 of the 4 known TIMPs have been shown to be expressed in bovine skeletal muscle (Balcerzak, Querengesser, Dixon, & Baracos, 2001).

A typical MMP has in its structure four functional domains; a signal peptide plus a pro-domain with a conserved cysteine switch motif, the catalytic domain, the hemopexin domain and a linker peptide of variable length (Nagase et al., 2006). Very roughly speaking, the pro-domain is involved in activation of the enzyme, variations in the catalytic relate to differences in the preferred substrates of the enzymes, and variations in the last two domains relate to variations in localization of the enzymes. Based on their structural characteristics, MMPs thus are classified into secreted-type MMPs or membrane-anchored types (MT-MMPs), of which there are only six (Shiomi et al., 2010). The MT-MMPs are inserted in the plasma membrane by a transmembrane segment or a glycosylphosphatidylinositol (GPI) anchoring sequence (Manello & Medda, 2012). Both MT-MMPs and MMPs are divided into subgroups according to substrate specificity (Shiomi et al., 2010). Thus, MMPs are grouped into collagenases, gelatinases, stromelysins, membrane type (MT) and others.

2.2. Expression, secretion and regulation of MMPs

The regulation of MMP activity can be at several different levels and involves the gene expression, activation of zymogens and inhibition of the enzymes by endogenous inhibitors (Manello & Medda, 2012). Hence, regulation of MMP activation and activity is a multi-faceted process that has many inputs and cross-connections to multiple signally pathways. Fig. 2 describes these events in relation to the normal extracellular activation of MMPs. The vast majority of current knowledge