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# Regulation of extracellular matrix remodeling and cell fate determination by matrix metalloproteinase stromelysin-3 during thyroid hormone-dependent post-embryonic development

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**Abstract**

Interactions between cells and extracellular matrix (ECM), in particular the basement membrane (BM), are fundamentally important for the regulation of a wide variety of physiological and pathological processes. Matrix metalloproteinases (MMP) play critical roles in ECM remodeling and/or regulation of cell–ECM interactions because of their ability to cleave protein components of the ECM. Of particular interest among MMP is stromelysin-3 (ST3), which was first isolated from a human breast cancer and also shown to be correlated with apoptosis during development and invasion of tumor cells in mammals. We have been using intestinal remodeling during thyroid hormone (TH)-dependent amphibian metamorphosis as a model to study the role of ST3 during post-embryonic tissue remodeling and organ development in vertebrates. This process involves complete degeneration of the tadpole or larval epithelium through apoptosis and de novo development of the adult epithelium. Here, we will first summarize expression studies by us and others showing a tight spatial and temporal correlation of the expression of ST3 mRNA and protein with larval cell death and adult tissue development. We will then review in vitro and in vivo data supporting a critical role of ST3 in TH-induced larval epithelial cell death and ECM remodeling. We will further discuss the potential mechanisms of ST3 function during metamorphosis and its broader implications.
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*Keywords:* Thyroid hormone receptor; Extracellular matrix; Matrix metalloproteinase; *Xenopus laevis*; Metamorphosis; Apoptosis

*Abbreviations:* ECM, extracellular matrix; LR, laminin receptor; MMP, matrix metalloproteinase; ST3, stromelysin-3; TH, thyroid hormone; TR, thyroid hormone receptor.

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## 1. Introduction

The extracellular matrix (ECM) is a complex structure composed of many proteins and other macromolecules (Hay, 1991; Timpl & Brown, 1996). The ECM serves as a structural support media for the cells that it surrounds and is essential for maintaining the 3-dimensional structure of the tissue or organ. The ECM can also affect cell function by interacting directly with cells through cell surface ECM receptors, especially the integrins (Damsky & Werb, 1992; Schmidt et al., 1993; Brown & Yamada, 1995) or by modulating the availability and levels of many signaling molecules, such as growth factors that are stored in the ECM (Vukicevic et al., 1992; Werb et al., 1996). Since most cells in multicellular organisms, such as vertebrates, are surrounded by ECM, alterations in the ECM can influence cell fate and behavior by affecting cell–cell and cell–ECM interactions (Hay, 1991; Ruoslahti & Reed, 1994). The critical roles of ECM are reflected by the fact that ECM degradation and remodeling always accompany tissue remodeling, organogenesis, and pathogenesis throughout the animal kingdom.

ECM remodeling and degradation is largely due to the proteolytic action of matrix metalloproteinases (MMP). MMP are extracellular or membrane-bound enzymes (Alexander & Werb, 1991; Birkedal-Hansen et al., 1993; Barrett et al., 1998; Nagase, 1998; Parks & Mecham, 1998; Pei, 1999; McCawley & Matrisian, 2001). This large family of proteolytic enzymes can be divided into 5 subfamilies, collagenases, gelatinases, stromelysins, membrane-type MMP, and others. MMP consist multiple domains, including from the N- to C-terminus the pre- and pro-peptides, a catalytic domain, a hinge region, and, in most MMP, the hemopexin-like domain. In addition, gelatinase A (MMP2) and B (MMP9) also contain the fibronectin-like domain within the catalytic domain, and membrane-type MMP have a transmembrane or membrane attachment domain in the C terminus (Fig. 1). MMP are synthesized as pre-enzymes, and the pre-peptide is cleaved upon secretion into the ECM as pro-enzymes with a few exceptions, such as stromelysin-3 (ST3) and membrane-type MMP. The pro-enzymes are enzymatically inactive and are activated extracellularly through proteolytic removal of the propeptide (Nagase et al., 1992; Birkedal-Hansen et al., 1993; Kleiner & Stetler-Stevenson, 1993; Barrett et al., 1998; Nagase, 1998; Murphy et al., 1999). ST3 and membrane-type MMP are activated intracellularly through a furin-dependent process and are, thus, secreted or attached to the plasma membrane as the mature enzymes, respectively (Fig. 1; Pei & Weiss, 1995; Sato & Seiki, 1996; McCawley & Matrisian, 2001). The mature or activated MMP have different but often overlapping substrate specificities (Barrett et al., 1998; Uria & Werb, 1998; McCawley & Matrisian, 2001; Overall, 2002). Collectively, they are capable of cleaving all protein components of the ECM. In addition, MMP are capable of degrading non-ECM extracellular or membrane-bound proteins, such as pro-MMP, pro-growth factors, proteinase inhibitors, and cell surface proteins, etc. (Barrett et al., 1998; Uria & Werb, 1998; McCawley & Matrisian, 2001; Overall, 2002). Thus, MMP may influence cell behavior and tissue development through both ECM remodeling and other mechanisms.

We have been using frog metamorphosis as a model to study MMP function in vivo. Frog development takes place in 2 phases. Its embryogenesis produces a free living, aquatic, and often herbivorous tadpole. After a growth period, the tadpole undergoes metamorphosis that changes essentially every organ of the animal to produce, in vast majority of the cases, a terrestrial carnivorous frog in a process that is entirely dependent upon thyroid hormone (TH; Shi, 1999). Molecular analysis has revealed that a number of MMP genes are induced by TH either directly or indirectly during metamorphosis. They include *Rana catesbeiana* collagenase 1 (MMP1; Oofusa et al., 1994), *Xenopus laevis* stromelysin-3 (ST3 or MMP11), gelatinase A (MMP2), gelatinase B (MMP9), collagenases 3 (MMP 13) and 4 (MMP18), membrane-type 1-MMP1 (MMP14) (Shi & Brown, 1993; Wang & Brown, 1993; Patterton et al., 1995; Stolow et al.,

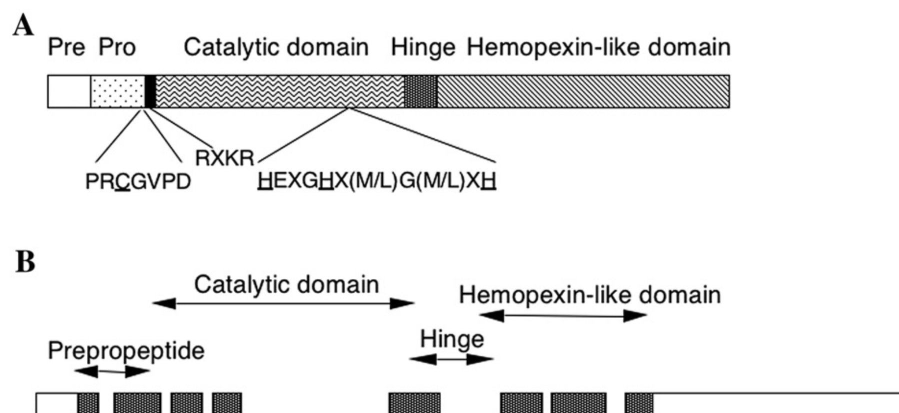


Fig. 1. Structure of ST3. (**A**) ST3 protein. Like most MMP, ST3 contains 4 domains. These are the pre- and pro-peptides and catalytic and hemopexin-like domains from N to C terminus, respectively. A conserved peptide sequence is present in the propeptide where a C residue (underlined) is involved in coordination with the catalytic Zn atom in the inactive proenzyme. In the catalytic domain, a conserved region contains 3 H residues (underlined) that coordinate with the catalytic Zn atom. Like membrane-type MMP, ST3 contains an RXKR sequence for furin-dependent intracellular activation. (**B**) ST3 gene. The hinge region and the hemopexin-like domain of ST3 are encoded by only 4 exons instead of 6 exons as in other MMP (Anglard et al., 1995; Li et al., 1998; Wei & Shi, 2005). The individual exons are shown as bars. The dotted bars indicate the coding region and the open bars represent the 5′ and 3′ UTRs. The individual domains of the coding region are indicated on the top.

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