1st grade: Degradation of extracellular matrix (ECM) protein byMT1-MMP

Summary: ECM degradation by MT1-MMP is the first step of cancer invasion. MT1-MMP is a metalloproteinase inserted in the plasma membrane of malignant cancer cells. MT1-MMP is transported from inside of the cytoplasm to the plasma membrane by vesicle trafficking, where it interacts with ECM, tissue inhibitor of metalloprotease-2 (TIMP-2) and matrix metalloproteinase-2 (MMP-2) forming complexes with TIMP-2 and MMP-2 (Fig.1).

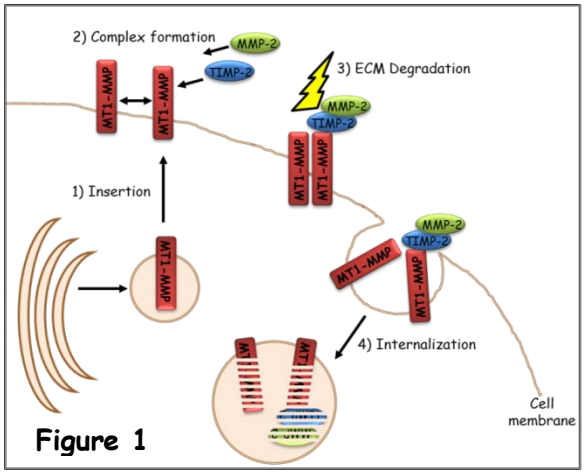

Figure 1

Cartoon and A-Cell model: MT1-MMP-related events shown in Summary are composed of following four steps: insertion to the plasma membrane, complex formation with TIMP-2 and MMP-2, ECM degradation, and internalization. These four steps are summarized below:

1) Insertion and internalization

Both insertion and internalization proceed with vesicles. In the mesoscopic view, these processes are thought to be a discrete process. Here we construct continuous model as an averaged view of many discrete process, and expressed as 1st order reactions in A-Cell (Fig.2). Free MT1-MMP (M14 in the model) was assumed to internalize. If you interested in a discrete model, see the following article (Watanabe, A., et al., PLoS Biol.Comp., 2013).

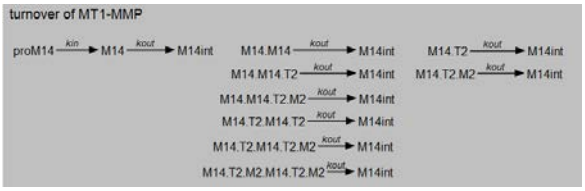

Figure 2

2) Complex formation

All possible complexes formed by MT1-MMP (MMP14), TIMP-2, and MMP-2 are shown in Fig.3 together with pathways to form the complex. This figure helps us to count up all interactions without missing. Fig.4 is an A-Cell model, which is a direct consequence of Fig.3. A complex MMP14:MMP14:TIMP2:proMMP2, where proMMP2 is inactive form of MMP-2, is thought to activate proMMP2 by shedding its inhibitory domain by MMp14 free from TIMP2, which is expressed by reactions shown in Fig.5.

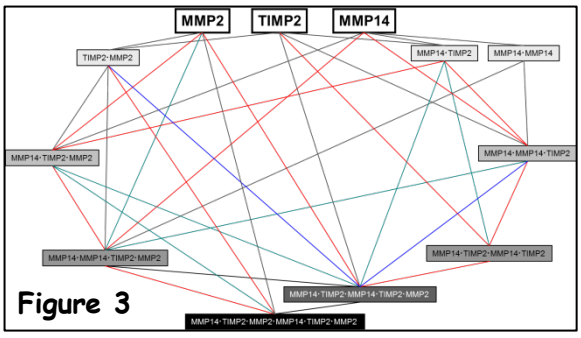

Figure 3

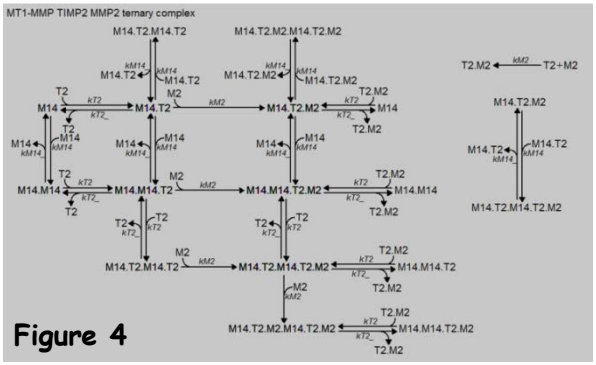

Figure 4

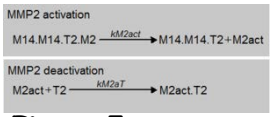

Figure 5

3) ECM degradation

Complexes engaged in the degradation of ECM are M14, M14:M14, M14:M14:T2, and M14:M14:T2:M2. A-Cell model of ECM degradation by these four complexes is shown in Fig.6. Since MT1-MMP act as a catalytic enzyme to ECM proteins, ECM degradations are expressed as Michaelis-Menten enzymatic reactions. fn in Fig.6 is fibronectin, which was used as an ECM protein in the model. Since there are two

sites of ECM degradation in

M14:M14, the rate of ECM degradation by this complex could be twice to that of other complexes with one site. In this model, however, the reaction is simplified by using the same rate constants. ECM degradation by MMP-2 is neglected for simplicity here. A complete model including these can be found elsewhere (Hoshino, D., et al., PLoS Biol.Comp., 2013; Watanabe, A., et al., PLoS Biol.Comp., 2013)

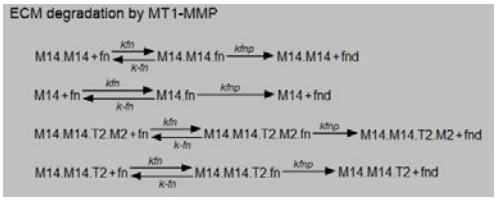

Figure 6

Simulation result is shown in Figure 7 with following simulation conditions: simulation time = 0-150 s; calculation step = 1 μs; output step = 0.1 s. fn is degraded within 150 s. This simulation was run by generating simulation program automatically by A-Cell.

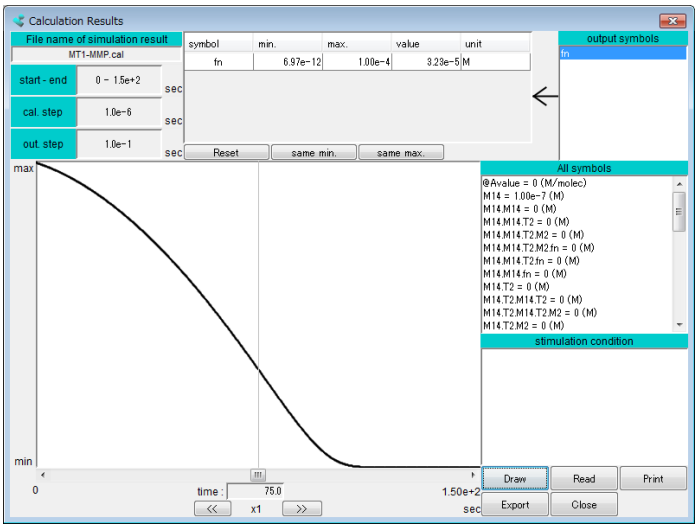

Figure 7