

A Novel Signaling Pathway That Governs Cell Adhesion

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ABSTRACT

MMPs (Matrix Metalloproteinases) are a family of extracellular proteases. They can mediate tissue remodeling. Their main function is to cleave substrates including extracellular matrix and signaling molecules. However, the molecular mechanisms of their function in tissue remodeling still need to be identified. Although the vertebrate MMP family is large and functionally redundant, the fruitfly *Drosophila melanogaster* has only two MMPs. NijA, a transmembrane protein, was identified as a two-hybrid binding partner for Mmp1, and co-immunoprecipitations confirmed that the two proteins physically interact in vivo.

I have recently shown that when *NijA* is expressed in S2 cells, they lose adhesion to surfaces, and that this affect is cell-nonautonomous. *Mmp1* activity is required for the *NijA*-mediated loss of adhesion, as when *Mmp1* activity is inhibited, the cells remain adherent. The *NijA* secreted ectodomain is sufficient to induce loss of adhesion at levels comparable to the whole molecule. The ectodomain no longer needs *Mmp1* activity after it has been released. Thus the Mmp1 protease is responsible for shedding the N-terminal ectodomain of NijA protein from cells, and the ectodomain acts nonautonomously on cells to cause them to lose adhesion. We have data suggesting that the ectodomain of NijA signals through another molecule of NijA to modulate cell adhesion. NijA is also sufficient for receiving the signal to lose adhesion. For the cellular requirements of interpreting the NijA signal, endocytosis is involved in the signaling pathway. Integrin level is decreased in the *NijA* expressing cells. S2 cells expressing *NijA* also show a marked reduction in phagocytosis of *E.coli* compared to cells not expressing *NijA*.

In sum, we have identified a new signaling pathway governing adhesion and phagocytosis. We have determined how the signal gets activated, and have begun to unravel how it is interpreted by receiving cells. It will be interesting to learn how this signal regulates cell adhesion and phagocytosis *in vivo*.