Regina Fluhrer

Current Position: Galetti Professor of Bioengineering and Adjunct Professor Medicine at the University of California, San Diego

Education: Ph.D. in Biochemistry (2003) from the Ludwig-Maximilians-University of Munich in Germany

Non-scientific Interests: Hiking, skiing, numismatics

For my Ph.D. studies, I joined the laboratory of Christian Haass in 2000 where Jochen Walter and I worked intensively on BACE-1 (β-site APP cleaving enzyme) and BACE-2. BACE-1 is one of the key players involved in the generation of the Amyloid-β-peptide (Aβ), a major factor in the development of Alzheimer disease. During that time I became increasingly interested in the presenilin (PS) molecules. PSs form the active site containing subunit of the γ-secretase complex, the second enzyme involved in Aβ production. These polytopic transmembrane proteins founded a new class of intramembrane proteases, the G*X*GD-aspartyl proteases. A few years later, signal peptide peptidase (SPP) and its homologues, the SPP-like (SPPL) proteases, were described. Although the active site motive of SPP/SPPL-proteases and PSs is highly conserved, the members of this new family of G*X*GD-aspartyl proteases, in contrast to γ-secretase, do not form high molecular weight complexes. To learn more about the general function and the proteolytic mechanism of G*X*GD aspartyl proteases, my mentor and colleague, Christian Haass, and I began investigating the SPP/SPPL-proteases in more detail.

Christian Haass

Current Position: Professor of Biochemistry at the Ludwig-Maximilians-University München and chair of the department

Education: Ph.D. in Molecular Biology (1989) from University of Heidelberg; postdoc (1990-93) at Harvard Medical School

Non-scientific Interests: Ornithology, collecting modern art (German Informel)

Intramembrane proteolysis is of central importance for the generation of Alzheimer disease Amyloid β-peptide. I originally became interested in Alzheimer disease during my Ph.D. at the Center for Molecular Biology in Heidelberg, where Konrad Beyreuther had his laboratory next door. He had just cloned the Amyloid Precursor Protein at this time and demonstrated that Amyloid β-Peptide must be generated by proteolytic processing. With Konrad's recommendation, I went to the laboratory of Dennis Selkoe where I began studying the generation of amyloid β-peptide by proteolytic processing. After investigating the *in vivo* generation of Amyloid β-peptide in Boston, I became very much interested in the secretases, the proteases mediating the N- and C-terminal cleavage required to liberate amyloid ß-peptide. Together with Harald Steiner, I described a novel G*X*GD active site signature motif for the catalytic component of the γ-secretase complex and immediately realized that the identical active site motive is also used by completely unrelated bacterial aspartyl proteases. Moreover, shortly after the first description of this novel signature motive, signal peptide peptidase was identified and shown to contain the same active site G*X*GD motive. Data bank searches then revealed a number of additional signal peptide peptidase-like proteases of unknown function. Since these proteases are much simpler than the four component γ-secretase complex, Regina Fluhrer and I began investigating these proteases. Indeed, we found a number of surprising similarities of signal peptide peptidases, their homologues, and γ-secretase, and we learned much about the cellular and molecular mechanisms of intramembrane proteolysis as well as its function in signal transduction.

Read Drs. Fluhrer and Haass' article entitled: Intramembrane Proteolysis by Signal Peptide Peptidases: A Comparative Discussion of G*X*GD-type Aspartyl Proteases … http://www.jbc.org/cgi/content/full/284/21/13975