COLLOQUIA IN CELLULAR SIGNALLING

Venue: Medical University Vienna, Center for Physiology and Pharmacology,
Institute of Pharmacology, Waehringerstrasse 13a, 1090 Vienna, "**Leseraum**".
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Friday **12.04.2013 12.15 s.t.** **Martin Scheffner** **(host: H. Sitte)**

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"The ubiquitin ligase E6AP and its role in human disease"

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Abstract:
The E3 ubiquitin ligase E6AP is a prime example for the notion that deregulation of modification of proteins by ubiquitin ("ubiquitination") plays an important role in the development of human disease. Firstly, E6AP was originally identified as a protein that is utilized by the E6 oncoprotein of cancer-associated human papillomaviruses (HPVs) to target the tumor suppressor p53 for ubiquitin-dependent degradation. Thus, it is commonly assumed that unscheduled activation of E6AP contributes to HPV-induced cervical carcinogenesis. Secondly, E6AP is encoded by the *UBE3A* gene, which has been etiologically linked to the development of the Angelman syndrome (AS), a genetic neurodevelopmental disorder. In fact, there is considerable evidence to suggest that loss of the E3 activity of E6AP is sufficient to cause AS. Finally, deregulation of E6AP expression has been associated with autism spectrum disorders, and studies with transgenic mice suggest that amplification of the *Ube3a* gene resulting in increased E6AP levels contributes to autistic phenotypes.
In addition to its role as E3 ligase, E6AP was reported to affect nuclear hormone receptor-mediated transcription by E3-independent mechanisms. However, the pathophysiological relevance of this property remains enigmatic. In this seminar, data will be discussed to indicate that the ability of E6AP to affect estrogen receptor-mediated transcription contributes to the development of AS and, possibly, autism spectrum disorders.

Modification of proteins with ubiquitin (Ub) has proteolytic and non-proteolytic functions, raising a question on the mechanism(s) involved in determining the eventual fate(s) of ubiquitinated proteins. In a simplified view, ubiquitination results in two general species of proteins, mono-ubiquitinated (i.e. modified by single Ub moieties) and poly-ubiquitinated (i.e. modified by Ub chains of various lengths) proteins. Thus, an obvious possibility is that the type of ubiquitination determines the fate of a modified protein by altering its biochemical properties in a distinct manner. While this hypothesis is likely to be correct, it is similarly likely that in addition to the "Ub signal", distinct amino acids or properties of the modified protein are involved in determining its fate. A general obstacle in the ubiquitin field has been the lack of sufficient amounts of homogeneously ubiquitinated proteins (i.e. modified at a defined Lys residue) for detailed biochemical analyses. To generate homogeneously mono-ubiquitinated proteins, we are making use of the "unnatural amino acid technology" combined with "click chemistry". If time allows, recent progresses in this direction will be discussed.