Colloquia in Cellular Signaling

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Wednesday 14.09.2016 10:00 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: Modification of proteins by ubiquitin (Ub) ("ubiquitination") plays a prominent role in the regulation of many eukaryotic processes including cell cycle control, DNA repair processes, response to hypoxia, and differentiation. In recent years, components of the Ub-conjugation system have emerged as potential targets in the treatment of human disease because their deregulation has been associated with the development of distinct disorders or because they control pathways that, for instance, are of fundamental importance for the proliferative potential of cancer cells. A prime example is represented by the E3 Ub ligase E6AP, which is encoded by the *UBE3A* gene on chromosome 15q11-13 and has been linked to three distinct clinical pictures: Hijacking of E6AP by the E6 oncoprotein of distinct human papillomaviruses (HPV) contributes to the development of cervical cancer, while loss of E6AP expression or function is the cause of the Angelman syndrome, a neurodevelopmental disorder, and increased expression of E6AP has been involved in autism spectrum disorders. In this presentation, the role of E6AP in disease and its potential to serve as target for therapeutic strategies will be discussed.

Ubiquitination 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 length) 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 Ub field has been the lack of sufficient amounts of homogeneously ubiquitinated proteins (i.e. modified at a defined Lys residue) for detailed biochemical analysis. To generate homogeneously ubiquitinated proteins, we are making use of the "unnatural amino acid technology". Recent progress in this direction will be discussed.