5 Zusammenfassung

Beim Versuch der Identifizierung von an der Vasopressin-vermittelten Wasserrückresorption im Sammelrohr der Niere beteiligten *protein kinase A anchoring proteins* (AKAPs) wurde beim *Screening* einer Rattennieren-cDNA-Bibliothek der Partialklon 2.1 (1747 bp, *GenBank accession number AF387102*) isoliert. Bei diesem Klon handelt es sich um das Rattenorthologe (rHt31 1-576) des humanen AKAP hHt31 (Carr et al. 1992a). Die Identität zwischen rHt31 (582 Aminosäuren) und hHt31 auf die gesamte Proteinlänge bezogen, beträgt 67,7 %. Die der klassischen Bindungsdomäne für die regulatorischen Untereinheiten der PKA (RII) von hHt31 entsprechende RII-Bindungsdomäne befindet sich im Bereich der Aminosäuren 65-78 von rHt31. Eine zweite Bindungsdomäne befindet sich im Bereich der Aminosäuren rHt31 470-576. Diese ist für die RII-Untereinheiten scheinbar weniger affin, die Bindung der RI-Untereinheiten wurde noch nicht untersucht.

Durch eine Kombination von RACE-Experimenten und Datenbankanalysen konnte die bisher nur teilweise bekannte cDNA-Sequenz von hHt31 ermittelt werden. Die vollständige hHt31-cDNA (1-8442 bp) beinhaltet auch die cDNA-Sequenzen des humanen *breast cancer nuclear receptor binding auxillary protein* (hBrx, Rubino et al. 1998) und des *guanine nucleotide exchange factors* (GEF) Proto-Lbc (Sterpetti et al. 1999). Bei diesen Proteinen handelt es sich daher um kürzere Spleißvarianten von hHt31. Alle drei Proteine werden von einem Gen auf Chromosom 15, welches aus 36 Exons besteht, kodiert.

Mit einer rHt31-spezifischen Sonde konnten im Herzen und im Skelettmuskel sowie durch Edemir (1999) in der inneren Medulla der Niere mRNA-Transkripte von ca. 9 und größer 9,5 kb detektiert werden, was darauf hindeutet, das auch das Rattenorthologe eine ähnlich große cDNA aufweist.

Mit einem Antikörper, der sowohl rHt31/hHt31 als auch hBrx erkennt, wurde in den Brustkrebszellinien ZR-75-1 und MCF-7 sowohl in den löslichen als auch in den partikulären und nukleären Zellfraktionen ein immunreaktives Protein im hochmolekularen Bereich (ca. 300-400 kDa) detektiert, bei dem es sich wahrscheinlich um hHt31 handelt. In verschiedenen Geweben und Zellinien wurden außerdem immunreaktive Proteine unterschiedlicher Größe detektiert. Dies deutet auf die Existenz weiterer Spleißvarianten hin. Die Existenz einer aufgrund der Sequenz postulierten RII-Bindungsdomäne in hBrx konnte für die Deletionsmutante hBrx 84-378 experimentell

nicht sicher nachgewiesen werden. Allerdings hat ein ca. 170 kDa-Protein in der partikulären Fraktion der ZR-75-1-Zellen, bei dem es sich wahrscheinlich um hBrx handelt, im RII-*overlay* die RII-Untereinheiten gebunden. Sowohl hHt31 als auch bei Nachweis einer RI RII-Bindungsdomäne die kürzere Spleißvariante hBrx können zu den multifunktionellen Adaptorproteinen gezählt werden, welche über verschiedene Effektoren eine Vielzahl transmembranäre und intrazelluläre Signaltransduktionsprozesse regulieren.

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