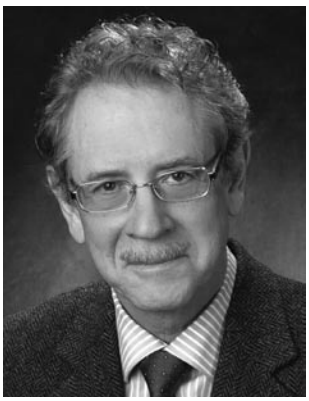


1968	PhD, University of Frankfurt/Main
1968-1977	Postdoc at Biotest-Serum Institute, Frankfurt/M; Policlinic and Biochemistry II, Heidelberg
1977	Habilitation, *venia legendi* in Biochemistry
since 1980	Professor of Biochemistry; Group Leader until retirement (October, 1st, 2005)
1981-1986	Dean of Preclinical Faculty
1991	Visiting Professor Yale University
1996-2005	Spokesman Division "Biology and Medicine of Reproduction" of the German Endocrine Society

Wolfgang Merz

Molecular Endocrinology of Early Pregnancy

Goal

To understand how hCG (human chorionic gonadotropin), the most important proteohormone of human first-trimester placenta, folds and assembles during biosynthesis.

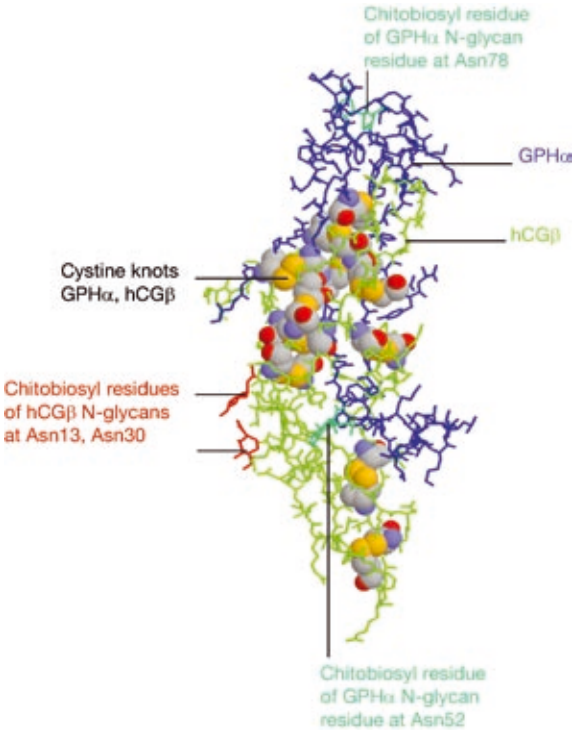
Background

The implantation of the human embryo into the uterus requires a highly sophisticated environment of steroid and proteohormones, growth factors and a definite cellular ambience. For initiation and maintenance of human pregnancy hCG is a mandatory factor. This fetal protein is produced by the blastocyste before implantation and by the placenta. It is a member of the glycoprotein hormone family, (LH, FSH, TSH, hCG) and is composed of a common α-subunit (GPH-α) and α hormone-specific β-subunit (hCGβ). Structural integrity of both subunits is maintained by a cluster of disulfide bridges typical for proteins of the growth-factor cystine-knot protein family. Correct folding, disulfide bridge formation, attachment of N-glycans, and subunit assembly is necessary for acquirement of the biological functions of hCG and is warranted by the quality control of the endoplasmic reticulum (ER). Using a panel of 15 extensively characterized monoclonal antibodies (mAbs), monitoring folding in definite microdomains, we investigate the chronology of these processes, their interdependencies and the generation of molecular variants of hCG and free subunits.

Research Highlights

Subunit assembly seems to take place immediately after translation between N-glycosylated, almost completely folded GPHα and immature hCGβ (1, 4). Folding of hCGβ starts around the cystine knot region together with the formation of immunologic epitopes on loops L2 and L3 (1). The formation kinetics even of the strongly overlapping epitopes β2 and β4 located on loops L2 and L3 could be resolved by the corresponding mAbs indicating the power of the technique used. Maturation of the hCGβ part of hCG αβ-heterodimers occurs within 40 min. In that time, while being associated with GPHα, hCGβ passes through at least 8 intermediates due to the progression of disulfide bridge formation. Some of these intermediates represent complexes with chaperones (calnexin, calreticulin, BiP) (4).

During folding of the intact hCGβ, a hCGβ core-fragment ($hCG\beta_{cf}$) epitope is formed transiently (1). This epitope is increased in Down's syndrome pregnancies serving as a diagnostic marker for early detection (Triple-test). It was so far described only on a proteolytic fragment reportedly generated in the mother's kidney. This does not



make sense because hCGβ of a Down's fetus is structurally not different from hCGβ of normal pregnancy. Our findings suggest a more reasonable explanation which could imply in Down's syndrome pregnancy the release of intact immature hCGβ expressing a $hCG\beta_{cf}$ epitope either due to a leakiness of the quality control or an increased destruction of placenta cells.

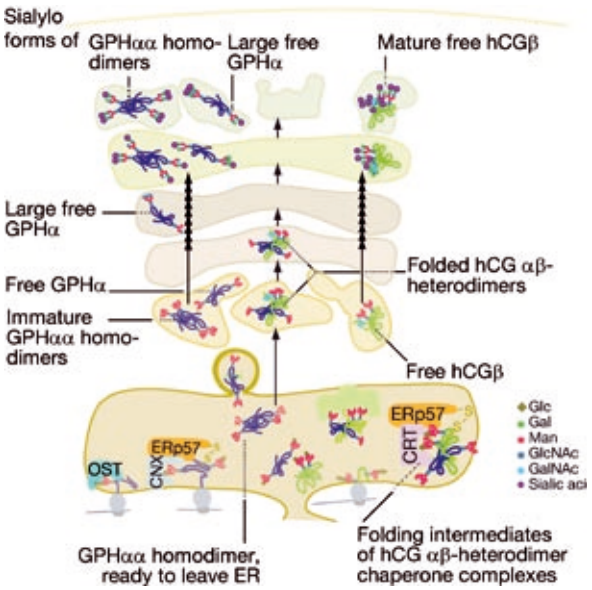


Fig.2: Snapshot of hCG and subunit variant maturation in JEG-3 cells approximately 10 min before the start of secretion. CNX, calnexin; CRT, calreticulin; ERp57, glycoprotein-specific protein disulfide isomerase; OST, oligosaccharyltransferase.

Besides forming hCG αβ-heterodimers excessive GPHα dimerizes to yield GPHαα homodimers or undergoes further glycosylation, generating free large GPHα (3). GPHαα homodimers were also observed in the seminal plasma of healthy fertile men (2). Free hCGβ, free large GPHα and GPHαα are processed and sialylated within 40 min whereas the hCG αβ-heterodimers have not yet reached the medial Golgi most probably due to prolonged interaction with the calnexin/calreticulin/ERp57 cycle in the ER (4, see Figure 2). Our investigations show that in the case of hCG subunit assembly decreases the hCGβ folding, in contrast to immunoglobulin synthesis were the assembly of subunits drives folding.

Selected Publications 2004 - 2007

(1) J. Roig, J-M. Krause, P. Berger, W.E. Merz (2007).Time-dependent folding of immunological epitopes of the human chorionic gonadotropin β-subunit. Mol. Cell. Endocrinol. 260-262, 12-22.

(2) P. Berger, M. Gruschwitz, G. Spoettl, S. Dirnhofer, S. Madersbacher, R. Gerth, W.E. Merz, E. Plas, N. Sampson (2007). Human chorionic gonadotropin (hCG) in the male reproductive tract. Mol. Cell. Endocrinol. 260-262, 190-196.

(3) J-M. Krause, P. Berger, J. Roig, V. Singh, W. E. Merz (2007). Rapid maturation of glycoprotein hormone free α-subunit (GPHα) and GPHαα homodimers. Mol. Endocrinol., 21, 2551-2564.

(4) W. E. Merz, J-M. Krause, J. Roig, V. Singh, P. Berger (2007). Non-assembled human chorionic gonadotropin subunits and αα-homodimers use fast-track processing in the secretory pathway in contrast to αβ-heterodimers. Endocrinology, 148, 5831-5841.

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