Human chorionic gonadotropin (hCG) is a very unique rule breaker to the basic guidelines of biochemistry and physiology, it is one name and a large group of 5 or 6 completely independent or separate molecules. Each has a common α-subunit and β-subunit amino acid sequence and is separated by difference in O-glycosylation, differences in N-glycosylation, differences in sulfation and differences in mutations and merism (Table 1). It is with these differences that the forms of hCG somehow fold differently, bind different receptors and have partially-independent or completely independent roles.

Recently, a simplified renaming was recommended, hCG-1, hCG-2, hCG-3, hCG-4, hCG-4β and hCG-5. These names are used in parenthesis after the lengthy names commonly used and used in this report (Submitted 2016, “The hCG Family of Independent Molecules Needs Urgent Renaming.” Obstet Gynecol).

Briefly, there is the original hormone hCG (hCG-1) produced by placenta syncytiotrophoblast cells during pregnancy, molecular weight 36,525 (Table 1). The hormone acts on an luteinizing hormone (LH)/hCG joint hormone receptor and controls establishment of hemochorial placentation a fetal nutrition system during pregnancy [1, 2]. The hormone also control suppression of contractions during pregnancy [3, 4], suppression of maternal macrophage phagocytosis during pregnancy [5, 6], and promotion of maternal corpus luteum progesterone production during early pregnancy [7].

Secondly, there is hyperglycosylated hCG (hCG-2) a molecule produce by placental cytrophoblast cells, molecular weight 39,149 (Table 1). This is an autocrine that antagonizes a transforming growth factor-β2 (TGF-β2) receptor [8-10]. Hyperglycosylated hCG controls implantation of the fertilized blastocyst in pregnancy [11, 12]. It also promotes placenta growth during the course of pregnancy [13-15].

Thirdly, there is pituitary sulfated hCG (hCG-3) a molecule produced by pituitary gonadotrope cells, molecular weight 35,943 (Table 1). This is the hormone that promotes pituitary luteotropic activity acting on a LH/hCG receptor [16, 17]. Research suggest that this molecule and not LH is the primary pituitary luteotropic agent [16]. Pituitary sulfated hCG (hCG-3) promotes synthesis of androstenedione, and follicular growth during the follicular phase of the menstrual cycle. It promotes meiosis, stigma formation and enzymatic ovulation during the ovulatory phase of the cycle. It promotes corpus luteum formation and production of progesterone during the luteal phase of the cycle.

Fourthly, trophoblastic cancer cells produce a super glycosylated form of hCG, molecular weight 40,461 (Table 1). This is an autocrine that antagonizes a TGF-β2 receptor on trophoblastic cancer cells promoting cell growth, blocking apoptosis and promoting cell production of collagenases and metalloproteases the cell invasion enzymes [13, 18,19]. Non-trophoblastic cancers produce a superglycosylated hCG free β-subunit. This function the same way antagonizing a TGF-β2 receptor promoting growth, blocking apoptosis and promoting collagenase and metalloproteases production [8, 20-22].

Finally, the fetus produces a form of hCG during pregnancy, fetal hCG (hCG-5). The physical properties and the molecular weight of this molecule are unknown (Table 1). The fetal hCG (hCG-5) is produced by the fetal kidney and liver and functions to promote fetal organ growth and development independent
of the maternal hormone hCG (hCG-1) and hyperglycosylated hCG (hCG-2) [23-25].

This is the hCG family. Six molecules all sharing a common beta-subunit and beta-subunit amino acid sequence yet having independent functions as an autocrine or hormone. Here we examine these molecule and their role in human physiology one by one.

The Hormone hCG (hCG-1)

It is difficult to say who was the first discoverer of the hormone that for 100+ years has been called human chorionic gonadotropin (hCG). Looking at it from today’s standpoint, chorionic comes from the Latin chorda or afterbirth or placenta (hCG also produced by pituitary), gonadotropin or releases steroids from the gonads (does many more things), are statements that are far from completely correct. hCG has many more major functions. The only remaining word “human” is the only factual word in the name today.

In 1912 Bernard Aschner in Vienna showed that water-soluble extracts of human placenta stimulated the genital tract of guinea pigs [29]. In 1913, Otto Fellner in Germany used saline extracts of human placenta to induce ovulation in rabbits [30]. All of these works showed that there was a clear hormonal link between the placenta and the ovary. Around this time, the name human chorionic gonadotropin (hCG) was conceived. In 1927, Ascheim and Zondek showed that repeated injection of human placental tissue stimulated ovulation in rabbits [31]. All of these works showed that there was a clear hormonal link between the placenta and the ovary.

Table 1. Multiple semi-independent variants of hCG. Molecular weights (MW) consider the final analyses of Elliott et al. (26), (27) and the recent corrections of Cole (28).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>hCG</th>
<th>Hyperglycosylated hCG</th>
<th>Sulfated hCG</th>
<th>Superglycosylated cancer hCG</th>
<th>Superglycosylated cancer free beta-subunit</th>
<th>Mutated Fetal hCG free beta-subunit</th>
</tr>
</thead>
<tbody>
<tr>
<td>New name</td>
<td>hCG-1</td>
<td>hCG-2</td>
<td>hCG-3</td>
<td>hCG-4</td>
<td>hCG-4fβ</td>
<td>hCG-5</td>
</tr>
<tr>
<td>Source cells</td>
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<td>Cytotrophoblast</td>
<td>Pituitary</td>
<td>Trophoblastic malignancies</td>
<td>Non-trophoblastic malignancies</td>
<td>Fetal kidney &amp; liver</td>
</tr>
<tr>
<td>Mode of action</td>
<td>Endocrine</td>
<td>Autocrine</td>
<td>Endocrine</td>
<td>Autocrine</td>
<td>Autocrine</td>
<td>Non-Endocrine</td>
</tr>
<tr>
<td>Total MW</td>
<td>36,525</td>
<td>39,149</td>
<td>35,943</td>
<td>40,461</td>
<td>26,271</td>
<td>Variable</td>
</tr>
<tr>
<td>Site of action</td>
<td>LH/hCG receptor</td>
<td>TGFβ antagonism</td>
<td>LH/hCG receptor</td>
<td>TGFβ antagonism</td>
<td>TGFβ antagonism</td>
<td>Fetal organ</td>
</tr>
<tr>
<td>Amino acids α-</td>
<td>92</td>
<td>92</td>
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<td>Amino acids β</td>
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<tr>
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<td>25,813</td>
<td>25,813</td>
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<td>Variable</td>
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<td>Type 2</td>
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<td>Type 2</td>
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<tr>
<td>Type N-linked</td>
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<td>Biantennary</td>
<td>Biantennary + SO₄</td>
<td>Triantennary β</td>
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<td>10,130</td>
<td>14,648</td>
<td>10,728</td>
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<td>34%</td>
<td>28%</td>
<td>36%</td>
<td>41%</td>
<td>Not determined</td>
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</tbody>
</table>

Cite this article: Laurence A. The hCG Family of Independent Molecules. J J Physiology. 2016, 2(1): 014.
Looking at the placental hormone today it is part of the glycoprotein hormone family (hCG, LH, follicle stimulating hormone (FSH) and thyroid stimulating hormone (TSH)) a group of dimeric hormones with a common beta-subunit, and a specific ß-subunit. LH and hCG (hCG-1) both bind a joint LH/hCG hormone receptor which functions through production of cyclic AMP.

hCG (hCG-1) has a 92 amino acid common ß-subunit and a 145 amino acid ß-subunit [26,34] (Figure 2). hCG evolved from a deletion mutation in LH ß-subunit with early simian primates 37 million years. LH evolved from the fish dimeric betaß hormone gonadotropin ancestral hormone-II (GAH-II), which evolved from duplication of the early fish monomeric autocrine ancestral beta-subunit which evolved from the autocrine TGF-ß2. hCG structurally has a common cystine knot structure with TGF-ß2 [35,36].

Figure 1. The role of the hormone hCG (hCG-1) in building hemochorial placentation.
hCG is a highly glycosylated molecule with two N-linked oligosaccharides on the beta-subunit at beta52 and beta78, a monoantennary 8 sugar residue (Structure NM, Figure 3) and a biantennary 11 sugar residue structure (Structure NN, Figure 3) [26,27]. It also has two N-linked biantennary structures on the β-subunit at β13 and β30 (Structures NN and NNF, Figure 3), and 4 O-linked oligosaccharides trisaccharides and tetrasaccharides at β121, β127, β132 and β138 on the β-subunit (Structures Type 1A and 1B, Figure 3) [26-28]. Overall sugars account for 29% of molecular weight on hCG (hCG-1) (Table 1).

hCG is a very acidic hormone, isoelectric point (pI) 3.5 with a very long circulating ½-life of 36 hours [1,37]. hCG is approximately 345-fold more biological potent that LH the hormone that hCG evolved from [16].

The placental hormone hCG (hCG-1) has multiple functions in pregnancy. Its primary function is to generate and maintain hemochorial placenta formation in pregnancy, or the mechanism whereby nutrients and food are provided to the fetus (Figure 1) [1,2]. In the generation of hemochorial placenta, hyperglycosylated hCG (hCG-2) promotes growth of the villous cytotrophoblast structure [1,2], and the hormone hCG (hCG-1) promotes fusion of cytotrophoblast cells to make the syncytiotrophoblast skin [38]. hCG (hCG-1) also promotes extension of the uterine spiral arteries to reach the hemochorial placenta structure, and the generation of the umbilical vascular system to link the villous trophoblastic structure to the fetus (Figure 1) [39,40].

hCG (hCG-1) has multiple other function in pregnancy including suppression of contractions during pregnancy [3,4], suppression of maternal macrophage phagocytosis and its rejection of foreign placental and fetal tissues [5,6], and promotion of maternal ovarian corpus luteum progesterone production 3 weeks to 7 weeks of gestation [7].

The Autocrine Hyperglycosylated hCG (hCG-2)

A second form of hCG is also produced by placental cytotrophoblast cells. This is the autocrine hyperglycosylated hCG (hCG-2). This molecule was discovered by Laurence Cole PhD, the author of this review in 1987 [41]. I first noticed that hyperglycosylated hCG (hCG-2) was produced by choriocarcinoma cases and was seemingly unique to these cases. We today know choriocarcinoma hCG as superglycosylated cancer hCG (hCG-4) [28]. As found it seemed uniquely unlike the hormone hCG (hCG-1) promoting choriocarcinoma cancer invasiveness.

It was not just larger that hCG (hCG-1) on gel filtration chromatography columns, but more acidic than hCG on DEAE ion exchange chromatography columns and seemingly involved in choriocarcinoma invasion, it very much appeared like a separate molecule to the hormone hCG (hCG-1).

I chose to name this unique molecule invasive trophoblast antigen (ITA). I wrote multiple article using this name [42]. Four years later I received a very official letter from the World Health Organization (WHO). As stated, I claim in my papers that this molecule called ITA has the same amino acid sequence as hCG and different carbohydrate side chains to hCG, therefore under their rules, it must have a name that includes the word hCG. In 2000 I rename ITA hyperglycosylated hCG.

Today we know that hyperglycosylated hCG (hCG-2) bind a completely separate receptor to the hormone hCG (hCG-1), it is an autocrine and not a hormone, and has completely separate functions to hCG (hCG-1). I very much wish that I had kept the independent name ITA. Today, when I teach medical students that a total hCG test detects both hCG the hormone and hyperglycosylated hCG an unrelated autocrine that has nothing to do with the hormone hCG. Medical student ask, why if it is a separate molecule to hormone hCG does it include the confusing name hCG? All I can respond is “WHO rules state that it had to be named hCG because it shares 66% of its structure with hCG.” Student respond that this is cause of confusion to the and confusion to users of hCG tests. As stated hCG tests should only detect the hormone hCG and not an unrelated molecule.

Three independent groups have now shown that hyperglycosylated hCG is an autocrine and binds and antagonizes a TGF-ß2 receptor [8-10], rather than the LH/hCG hormone receptor. In binding this receptor it promotes cell growth, blocks cell apoptosis and promotes cell invasive enzyme, collagenase and metalloproteinase production [13-15,18,19].

Multiple authors have set out to examine the crystal structure of hCG [43-45]. All found that a crystal could only be made after hCG was completely deglycosylated, all sugars removed, and after C-terminal peptide of β-subunit was removed. X-ray crystallography was performed on just 50% of an hCG molecule, a root molecule that could neither be considered as the hormone, as hyperglycosylated hCG or as any of the other hCG forms [43-45].

Stephen Butler PhD thermodynamically computer modelled the complete structure of hCG and hyperglycosylated hCG based around the x-ray crystallography model (unpublished data). As found, the three dimensional structure of hyperglycosylated hCG is different to the hormone hCG (hCG-1) exposing the common cystine knot structure with TGF-ß2, its ancestral molecule, causing autocrine TGF-ß2 receptor binding. Figure 4 shows Stephen Butler’s proposed three dimensional models of hCG (hCG-1) and hyperglycosylated hCG (hCG-2). Note the differences in the folding of the β-subunit C-terminal peptide structures at β127-ß135.

Cite this article: Laurence A. The hCG Family of Independent Molecules. J J Physiology. 2016, 2(1): 014.
Hyperglycosylated hCG (hCG-2) was first found in choriocarcinoma cases where it can comprise 100% of the total hCG produced (superglycosylated cancer hCG). Working with my hyperglycosylated hCG preparation C5 [26], a specific monoclonal antibody was generated to hyperglycosylated hCG, antibody B152 [42]. Using this assay hyperglycosylated hCG was shown to be the predominant molecule produced in early pregnancy [11,12]. Studies use this antibody to show that hyperglycosylated hCG is critical in early pregnancy to control pregnancy implantation [11,12]. It was found that miscarriages of pregnancy and biochemical pregnancies were a consequence of deficient hyperglycosylated hCG at pregnancy implantation.

Figure 2. The amino acid sequence of hCG subunits

**Alpha-subunit**

1  Ala - Pro - Asp - Val - Gln - Asp - Cys - Pro - Glu - 10  
   Cys - Thr - Leu - Gln - Glu - Asp - Pro - Phe - Phe - Ser - 20  
   Gln - Pro - Gly - Ala - Pro - Ile - Leu - Gln - Cys - Met - 30  
   Gly - Cys - Phe - Ser - Arg - Ala - Tyr - Pro - Thr - 40  
   Pro - Leu - Arg - Ser - Lys - Lys - Thr - Met - Leu - Val - 50  
   Gln - Lys - Asn - Val - Thr - Ser - Glu - Ser - Thr - Cys - 60  
   Cys - Val - Ala - Lys - Ser - Tyr - Asn - Arg - Val - Thr - 70  
   Val - Met - Gly - Gly - Phe - Lys - Val - Glu - Asn - His - 80  
   Thr - Ala - Cys - His - Cys - Ser - Thr - Cys - Tyr - Tyr - 90  
   His - Lys - Ser.

**Beta-subunit**

1  Ser - Lys - Glu - Pro - Leu - Arg - Pro - Arg - Cys - 10  
   Arg - Pro - Ile - Asn - Ala - Thr - Leu - Ala - Val - Glu - 20  
   Lys - Glu - Cys - Pro - Val - Cys - Ile - Thr - Val - 30  
   Asn - Thr - Thr - Ile - Cys - Ala - Gly - Tyr - Cys - Pro - 40  
   Thr - Met - Thr - Arg - Val - Leu - Gln - Gly - Val - Leu - 50  
   Pro - Ala - Leu - Pro - Gln - Val - Cys - Asn - Tyr - 60  
   Arg - Asp - Val - Arg - Phe - Glu - Ser - Ile - Arg - Leu - 70  
   Pro - Gly - Cys - Pro - Arg - Gly - Val - Asn - Pro - Val - 80  
   Val - Ser - Tyr - Ala - Val - Ala - Leu - Ser - Cys - Glu - 90  
   Cys - Ala - Leu - Cys - Arg - Arg - Ser - Thr - Thr - Asp - 100  
   Cys - Gly - Gly - Pro - Lys - Asp - His - Pro - Leu - Thr - 110  
   Cys - Asp - Asp - Pro - Arg - Phe - Glu - Asp - Ser - Ser - 120  
   Ser - Ser - Lys - Ala - Pro - Pro - Pro - Ser - Leu - Pro - 130  
   Ser - Pro - Ser - Arg - Leu - Pro - Gly - Pro - Ser - Asp - 140  
   Thr - Pro - Ile - Leu - Pro - Gln

Figure 3. The N-linked and O-linked sugar structures attached to hCG forms.

<table>
<thead>
<tr>
<th>N-linked oligosaccharides</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NM</td>
<td>MAN α1,3 MAN 5.1,4 GlGNAc 5.1,4 GlGNAc-N-Asn</td>
</tr>
<tr>
<td>NN</td>
<td>MAN 5.1,4 GlGNAc 5.1,4 GlGNAc-N-Asn</td>
</tr>
<tr>
<td>NNF</td>
<td>MAN 5.1,4 GlGNAc 5.1,4 GlGNAc-N-Asn</td>
</tr>
<tr>
<td>NNM</td>
<td>MAN 5.1,4 GlGNAc 5.1,4 GlGNAc-N-Asn</td>
</tr>
<tr>
<td>NNF</td>
<td>MAN 5.1,4 GlGNAc 5.1,4 GlGNAc-N-Asn</td>
</tr>
<tr>
<td>N-SO4</td>
<td>MAN 5.1,4 GlGNAc 5.1,4 GlGNAc-N-Asn</td>
</tr>
<tr>
<td>SO4-SO4</td>
<td>MAN 5.1,4 GlGNAc 5.1,4 GlGNAc-N-Asn</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>O-linked oligosaccharides</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type IA</td>
<td>MAN 5.1,4 GlGNAc 5.1,4 GlGNAc-O-Ser</td>
</tr>
<tr>
<td>Type 1B</td>
<td>MAN 5.1,4 GlGNAc 5.1,4 GlGNAc-O-Ser</td>
</tr>
<tr>
<td>Type 1SO4</td>
<td>MAN 5.1,4 GlGNAc 5.1,4 GlGNAc-O-Ser</td>
</tr>
<tr>
<td>Type 2A</td>
<td>MAN 5.1,4 GlGNAc 5.1,4 GlGNAc-O-Ser</td>
</tr>
<tr>
<td>Type 2B</td>
<td>MAN 5.1,4 GlGNAc 5.1,4 GlGNAc-O-Ser</td>
</tr>
</tbody>
</table>

Hyperglycosylated hCG (hCG-2) has the same amino acid sequence as the hormone hCG (Figure 2). It also has N-linked sugar structure similar to the hormone hCG (hCG-1), with monoantennary and biantennary structure on the beta and β-subunits (structures NM, NN and NNF in Figure 3) [26-28]. The 4 O-linked sugar structure are what differentiate hCG (hCG-1) and hyperglycosylated hCG (hCG-1). Hyperglycosylated hCG has four Type 2A and Type 2B (Figure 3) structures, and not Type 1 structures like the hormone hCG [26-28]. As shown by Stephen Butler (Figure 4), it is the folding of this region of the molecule that differentiates the two independent molecules.
Studies published by myself and others show that hyperglycosylated hCG acts in cytotrophoblast cell growth and invasion [13-15,18,19]. Hyperglycosylated hCG controls growth and invasion in implantation of pregnancy (Figure 5) [11,12]. Hyperglycosylated hCG also control growth of cytotrophoblast cells of the placenta during the course of pregnancy [1,2]. Cytotrophoblast cells fuse to form syncytiotrophoblast cells during the pregnancy, the other type of placental cell. As such, hyperglycosylated hCG effective controls placental growth during pregnancy [1,2,14,15,47].

Figure 4. Three dimensional structure of hCG (hCG-1) and hyperglycosylated hCG (hCG-2) as modelled by Stephen Butler. The black line are β-subunit, and the grey lines are beta-subunit.

Figure 5 illustrates the process whereby hyperglycosylated hCG (hCG-2) controls invasion and growth in pregnancy implantation. As illustrated, hyperglycosylated hCG is an autocrine, first secreted and then feeding back to a TGF-β2 receptor on cytotrophoblast cells. On antagonizing the TGF-β2 receptor in promotes cell growth, it blocks cell apoptosis, and promotes cell invasion by promoting production of collagenases and metalloproteinases.

Figure 5. The role of hyperglycosylated hCG (hCG-2) in blastocyst implantation.

1. Blastocyst attaches to uterine epithelium through syncytiotrophoblast microvilli linking to glycocalyx.

2. Cytotrophoblast cells invade through uterine epithelium through uterine stroma and into myometrium tissue. They produce hyperglycosylated hCG which feedback to a TGFβ receptor promoting growth and invasive collagenase and metalloproteinase secretion.

Pituitary Sulfated hCG (hCG-3)

hCG was first generated in lower simian primates by a deletion mutation in the LH β-subunit gene. As such, it is no surprise that pituitary gonadotrope cells, the cell that make LH, started
making a much more potent molecule pituitary hCG (hCG-3). hCG did not remain just produced by pituitary gonadotrope cells, it is produced by root placental cytotrophoblast cell as hyperglycosylated hCG (hCG-2), and by fused cytotrophoblast cells or syncytiotrophoblast cells as the hormone hCG (hCG-1).

Multiple articles describe pituitary gonadotrope cell production of a sulfated variant of hCG [17,48-57]. As shown, pituitary hCG (hCG-3) is unusual in having sulfated sugar side chains. It is regulated like FSH and LH by hypothalamic gonadotropin releasing hormone pulses, and is secreted itself in pulses [17,48-57]. Relatively low concentration of pituitary hCG (hCG-3) are produced in men and women, 0.01 – 30 mIU/ml [16].

Pituitary sulfated hCG (hCG-3) has 4 N-linked sugar side chains and 4 O-linked sugar side chains like the hormone hCG (hCG-1). Approximately 30% of O-linked and N-linked sugar antennae terminate in N-acetylgalactosamine (GalNAc) -sulfate, rather than galactose (Gal)-N-acetylneuraminic acid (NeuAc) [17].

As shown in Figure 3, structures N-SO4 and SO4-SO4 are N-linked to hCG, and structures Type1SO4 is O-linked to hCG beta- and ß-subunit [17].

Recently, I showed that considering biological activity, that pituitary hCG (hCG-3) predominates in total biological activity over LH in terms of luteotropic activity. This indicates that pituitary hCG (hCG-3) thrives over LH in terms of promoting ovulation, promoting steroidogenesis and possible in terms of promoting corpus luteum formation [16]. Pituitary hCG evolved form lower simian LH, and appears to take over the luteotropic job of LH, most notably in humans.

In terms of biological activity pituitary hCG (hCG-3) is a hormone that binds the LH/hCG receptor. It controls follicular ovulation, ovarian and testicular steroidogenesis and promotes male spermatogenesis and female corpus luteum formation. Figure 6 illustrates pituitary hCG (hCG-3) and LH driving the multiple stages of ovulation, promoting dominant follicle growth, promoting meiosis, promoting thinning and stigma formation, and finally using proteolytic enzymes to drive ovulation.

Figure 6. Actions of pituitary hCG (hCG-3) and LH during ovulation.
**Superglycosylated Trophoblastic Cancer hCG (hCG-4)**

Trophoblastic cancers are small group of malignancies including placental choriocarcinoma, testicular germ cell malignancies, testicular seminomas, testicular embryonal carcinoma, testicular yolk sac carcinoma, testicular choriocarcinoma and testicular teratoma. Ovarian germ cell malignancies include ovarian teratoma, ovarian dysgerminoma, ovarian yolk sac tumor, ovarian embryonal carcinoma and ovarian choriocarcinoma [58].

Choriocarcinoma is a malignancy of placental tissue, testicular, ovarian and other germ cells malignancies are a disease in which cancer cells form in the germ cells, the egg and sperm cells of the ovary and testis. These malignancies take on placental cytotrophoblast and syncytiotrophoblast tissue histology and produce a form of hCG [58], a superglycosylated cancer hCG (hCG-4).

Superglycosylated cancer hCG is a variant of hCG with triantennary N-linked sugar side chains and Type 2 O-linked sugar structures. Like hyperglycosylated hCG with Type 2 sugar side chains this fold differently to hormone hCG and is an autocrine antagonizing a TGF-ß2 receptor driving cancer growth, blocking apoptosis, and driving cancer invasion enzymes collagenase and metalloproteinases [8,10,13,18,19].

**Figure 7.** Superglycosylated cancer hCG and its free ß-subunit, action on cancer cells.

Superglycosylated cancer hCG (hCG-4) is the largest form of hCG molecular weight 40,461 (Table 1). The triantennary N-linked sugar structures include structures NNM, NNN and NNNF (Figure 3) (26-28). The Type 2 O-linked sugar structures include Type 2A and Type 2B (Figure 3) [26-28]. Superglycosylated cancer hCG (hCG-4) is the most acidic human molecule (Pi = 3.2) and the most glycosylated glycoprotein, 41% sugar by molecular weight.

Figure 7 illustrates a trophoblastic malignancy invasion and how superglycosylated cancer hCG is an autocrine driving cancer tissue growth, blocking apoptosis and using collagenase and metalloproteinases to force invasion.

**Superglycosylated Cancer hCG Free ß-subunit (hCG-4ß)**

All other non-trophoblastic human cancers (hundreds so cannot be listed) function similar to trophoblastic malignancies. In many respects it seem like all human cancers steal the hyperglycosylated hCG TGF-ß2 implantation growth and invasion protocol and use it to drive human malignancies. While pregnancy implantation is a controlled use of this pathway, with regular hCG modulated implantation invasion, the cancer processes uses this stolen mechanism to in an uncontrolled out-of-control manner.

It appears that a key part of carcinogenesis and malignant transformation includes activation of an hCG ß-subunit gene on chromosome 21, and expressing this gene and a cancer cell TGF-ß2 receptor to drive the malignancy.

There are as many as 8 hCG ß-subunit genes on chromosome 19. While cancers express genes 1 and 2, pregnancies express genes 3-8 [59]. This may cause amino acid sequence differences on cancer hCG.

Superglycosylated cancer hCG free ß-subunit is produced by non-trophoblastic cells. Trophoblastic cells contain a trophoblast and gonadotrope cell specific disulfide isomerase that form the last two disulfide linkages on hCG ß-subunit, ß93-100 and ß26-110. Without these linkages ß-subunit does not bind beta-subunit and form a dimer [60]. As such, non-trophoblastic cancers do not form a dimer, they form a free ß-subunit, superglycosylated cancer hCG free ß-subunit (hCG-4ß). This antagonizes the TGF-ß2 receptor as well as the dimer. As shown, using superglycosylated cancer hCG (hCG-4) and superglycosylated cancer hCG free ß-subunit (hCG-4ß) to drive malignancies is interchangeable [61].

Superglycosylated cancer hCG free ß-subunit contains triantennary N-linked sugar structures include structures NNM, NNN and NNNF (Figure 3) [26-28]. It also contains Type 2 O-linked sugar structures include Type 2A and Type 2B (Figure 3) [26-28].

Multiple authors have shown, confirmed and double confirmed that non-trophoblastic malignancies are driven by...
a variant of hCG free ß-subunit, superglycosylated cancer hCG free ß-subunit [8,20-22,61]. Driven to grow, driven to block apoptosis and driven to enzymatically invade.

Figure 7 illustrates a malignancy invasion and how superglycosylated hCG (hCG-4) and its free ß-subunit (hCG-4ß) are autocrines driving cancer tissue growth, blocking apoptosis and using collagenase and metalloproteinases to force invasion.

While it is a little unclear whether superglycosylated hCG (hCG-4) and its free ß-subunit (hCG-4ß) drive all human cancers or just most human cancers. All I know is that hCGß is the tumor marker for a very wide range of cancers [62,63], and a very wide range of cancer have been demonstrated to be promoted by these drivers [8,20-22,61,64]. I have yet to discover a human cancer that is not promoted by these driver.

Fetal hCG (hCG-5)

Multiple researchers have identified hCG receptors on fetal organs, and have located a fetal source of hCG production [23-25,65,66]. What promotes fetal growth during pregnancy has always been a conundrum. Growth hormone is inactive in pregnancy, and human placental lactogen and human placental growth factor are maternal hormones that have very limited action on fetal growth. Multiple studies by different investigators show that fetal organs contain hCG receptors [23-25,65]. LH/hCG receptors have been demonstrated in fetal kidney, fetal lung, fetal pancreas, fetal small and large intestine and fetal adrenal tissues [23-25,65,66]. It is inferred that a form of hCG (structure unknown) is a fetal growth factor and that hCG promotes fetal growth during pregnancy.

Fetal hCG and fetal LH/hCG receptors have been shown to disappear at pregnancy parturition, so that they are not present in human infants [23-25,65,66]. The fetus has been demonstrated to produce its own variant of hCG in the fetal liver and kidney [23-25,65,66]. Data currently is limited, and the amount of fetal hCG tested very limited. As such we do not know how fetal hCG may compares to the hormone hCG (hCG-1), or the structure of fetal hCG. Control of fetal growth may be a major functions of fetal hCG (hCG-5).

We assume that the unknown structure of fetal hCG may be a fifth independent form of hCG. Thus the name hCG-5 is assumed. There are multiple oddities about fetal hCG. If it is made by fetal liver and fetal kidney it is made in the absence of trophoblastic disulfide isomerase, and combination of subunits should not occur [60]. As such fetal hCG should be a free ß-subunit! Yet authors claim that it uses a regular LH/hCG hormone receptor [23-25,65,66]. But a regular LH/hCG receptor does not bind hCG free ß-subunit [67-69]! Is the hCG form hCG free ß-subunit and is the receptor the regular LH/hCG receptor?

Recently, a new genetic disorder was identified by Laurence Cole, familial hCG syndrome [70-72]. It is a dominant syndrome in which women and men produce an hCG form during the duration of their lives. In all cases identified a primary male or female patient was identified and a mother or father was shown to be producing similar hCG forms proving the dominant genetic nature of the disorder [70-72]. In all cases the production site must be outside the placenta, and is unknown. As demonstrated a mutated form of hCG free ß-subunit is detected in these cases [70-73]. It is postulated that this maybe a lifetime remnant of fetal liver and kidney hCG, assuming that fetal kidney produces a free ß-subunit. It is postulated that the genetic disorder is failure to stop production at birth [70-73]. This is a strange syndrome with production of an hCG-form being the only symptom. No infertility has been reported in that the molecule is an inactive free ß-subunit [70-73]. If this postulate is true then cases of familial hCG syndrome may be a site for future study of fetal hCG (hCG-5) outside of the fetus.

hCG Genetics

hCG forms are dimeric molecules comprising an beta-subunit and a ß-subunit joined non-covalently. The beta-subunit is the common subunit to hCG, LH, FSH and TSH. This is coded by a single gene on chromosome 6. The unique ß-subunit, in contrast, is coded for by 6 multiple copies of the gene on chromosome 19. These multiple copies lie back to back with the single gene coding for LH ß-subunit o chromosome 19.

It is thought that while pregnancy hCG is coded for by genes 3-8, that genes 1 and 2 may code for the cancer cell ß-subunit, the hCG-4ß [59].

hCG Therapeutics

As discussed in the section “Sulfated hCG a pituitary gonadotropin,” sulfated hCG functions alongside LH in promoting ovulation. It functions by binding joint LH/hCG receptors. Placental hCG (circulating half-life 36 hours) is approximately 150-fold more potent than LH (circulating half-life 0.33 hours) [74,75]. As such, hCG has been used for over 40 years to induce ovulation in women, and more recently to induce poly-ovulation of potential in-vitro fertilized pregnancies [76]. Mutiple hCG preparation have been produced for this application, Serono Profasi (Chinese Hampster Ovary cell recombinant hCG, 100% pure), Serono Ovidrel (human pregnancy urine, 92% pure), Ferring Choragon (human pregnancy urine, 40% pure), and Organon Pregnyl (human pregnancy urine, 31% pure), as examples.

Unfortunately, by far the biggest uses of hCG are inappropriate quackery use as a dietary aid, and ilicit sports use as an anabolic steroid promoter. In 1954 Simeons published in the Lancet that a diet combining hCG shots with calorie restrictions worked incredibly well [77]. As claimed, hCG mobilized fat and
suppressed appetite. This false claim is still plastered on diet clinic walls and on hundreds of internet sites to this day. The dietary claims of fat mobilization and appetite suppression have been disproved by scientists over and over again in dozens of papers [78-80], but still the “Simeons diet” gets pushed and widely use all over the world, with no science and no clinical studies to support it. hCG induces a state of hyperemesis or morning sickness, Do people lose hundreds of pounds weight by constantly inducing vomiting? I do not think so.

Weight loss hCG preparations include injectables, nose sprays and regular tablets. It is one false thing claiming that hCG promotes diet, it is another even more ridiculous thing claiming that hCG tablets are absorbed as bioactive hCG and continues to function. Previous chapters in this review show hCG variants to be cancer promoters, hCG free β-subunit and hyperglycosylated hCG. All urinary hCG preparations contain a mixture of regular hCG and hyperglycosylated hCG. hCG normally dissociates with time in the serum, so that even recombinant hCG generates hCGß in serum. As shown, these hCG variants can be carcinogenic. In all likelihood they can promote a pre-malignancy to become a malignancy, or a questionable malignancy that would normally be suppressed by the immune system to reach cancer status. The use of hCG as a questionable dietary agent needs to be carefully avoided, consider the cancer relationship.

hCG promotes steroidogenesis in men, or testosterone formation. Testosterone tablets are hepatotoxical in men, as such, to promote testosterone-enhanced anabolism or muscle growth in men, men take hCG shots [81-83]. This has become completely banned by all sports authorities. Today, the World Anti-Doping Agency (WADA) and United States Anti-Doping Agency (USADA) check sports players and athletes all over the world by random urine screening. Illegal testosterone anabolism is one of the biggest uses for hCG as a therapeutic. Once again, considering the cancer side of hCG variants, anabolism as an hCG application needs to be halted. Unfortunately, hCG’s biggest uses today are for illicit or questionable purposes, diet and testosterone anabolism.

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