Hyperglycosylated hCG Drives Malignancy in Most or All Human Cancers: Tying All Research Together

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Abstract: *Objectives*: Two forms of hCG are produced, the hormone hCG binding a luteinizing hormone/hCG joint receptor and the autocrine hyperglycosylated hCG binding a TGF-ß receptor. In pregnancy, hyperglycosylated hCG drives placental cell growth and invasion in implantation of pregnancy. It also blocks apoptosis. Human cancer cells steal the hCG ß-subunit gene and use hyperglycosylated hCG and its ß-subunit to drive malignancy. Here we examine research into hyperglycosylated hCG and its ß-subunit, and show that these molecules drive malignancy in most or possibly all human cancers.

Methods: Mouse monoclonal antibody B152was raised against intact hyperglycosylated hCG, batch C5. The antibody binds hyperglycosylated hCG and its ß-subunit but does not bind the hormone hCG or its subunits. Total hCG was measured using the Siemens Immulite hCG assay, hyperglycosylated hCG and its ß-subunit were measured using the antibody B152 assay.

Results: Eight independent center show that the hCG ß-subunit produced by cancers promotes malignancy, enhances cancer cell growth, cancer cell invasion and blockage of apoptosis in cancers. A study of 42 choriocarcinoma cases shows that percentage hyperglycosylated hCG exactly correlates with weekly doubling rate of cancer. It is concluded that hyperglycosylated hCG drive malignancy in this cancer. In a study with 7 separate cancers it is shown that increasing concentrations of hyperglycosylated hCG enhance all cancers. Increasing concentration of monoclonal antibody B152.

Hyperglycosylated hCG and its ß-subunit drives cancer growth, cancer invasion and blocks apoptosis in cancer cells. Antibody B152 suppressed cancer cell growth creating a non-malignant-like state (no growth, no invasion), with no cancer growth over a starting 70% confluency.

Conclusions: Choriocarcinoma is an example of cancer driven in malignancy by hyperglycosylated hCG, cancer aggression (weekly doubling rate) exactly correlating with percent hyperglycosylated hCG. In examining cancers, antibody B152 suppresses malignancy totally halting cancer growth in 7 of 7 cancer. This confirms that only the antigens, hyperglycosylated hCG and its ß-subunit drives malignancy in cancer cases.

Keywords: hCG, hyperglycosylated hCG, malignancy.

INTRODUCTION

Human chorionic gonadotropin (hCG) α-subunit and ß-subunit genes produce two unique proteins, the hormone hCG produced by placental syncytiotrophoblast cells, and the autocrine hyperglycosylated hCG produced by placental cytotrophoblast cells [1,2]. The two forms hCG share a common amino acid sequence and common N-linked sugar side chains [3-5], and are structurally 97% the same [6]. They only differ in their O-linked sugar structures. The hormone hCG having type 1 sugar side chains, and the autocrine hyperglycosylated hCG having type 2 larger sugar side chains [3-5]. Sugar side chain differences that only change the three-dimensional folding of hCG [6], permitting the autocrine hyperglycosylated hCG to be nicked or cleaved and blocking nicking/cleavage of the hormone hCG [6]. The hormone hCG binds and functions through a luteinizing hormone (LH)/hCG joint hormone receptor. In contrast, the autocrine hyperglycosylated hCG binds a transforming growth factor-ß (TGF-ß) autocrine receptor [7-9], with no cross-reactivitybetween the two 97% identical molecules [6].

During human evolution, the hormone hCG and autocrine hyperglycosylated hCG evolved as potent, more-potent and super-potent molecules. They are isoelectric point (pI) 6.3 in Aotus and Callicebus, early primates, circulating ½-life 2.4 hours [10,11]; pI=4.9, circulating ½-life 6.0 hours in Orangutan and advanced primates and pI=3.5, circulating ½-life 36 hours in humans [10,11].

Hyperglycosylated hCG drives invasion, cell growth, implantation and deep implantation in pregnancy. Implants placenta in Aotus/Callicebus, Orangutan and Humans at 1.0% (potent CG), 10% (more-potent CG) and 30% uterine depth (super-potent hCG) [12,13]. Cancer cells literally steal this super-potent hyperglycosylated hCG from the human genome and use it to drive invasion, cell growth and blockage of apoptosis in malignancy [14].

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Eight completely independent separate laboratories have all shown, confirmed, and double confirmed, that hyperglycosylated hCG or its ß-subunit promotes malignancy, promotes cell proliferation, promotes cell-cell invasion, and blocks apoptosis in a wide variety of different human cancer cells, cancer cell lines and human patient tissue samples, Gilott *et al*., London, UK, 1996 [15]; Butler *et al*., London, UK, 2000 [7]; Devi *et al*., Oregon, USA, 2002 [16]; Cole *et al*., Albuquerque, USA, 2006 [17]; Jankowska *et al*., Poznan, Poland, 2006 [18]; Li *et al*., Enfield, UK, 2008 [19]; Guo *et al*., Guangzho, China, 2011 [20]; Kawamaja *et al*., Sapporo, Japan, 2018 [21].

Here I take this confirming and double confirming data [7,15-21], examining a wide range of different human cancers, 23 of 23 human cancers (Table **1**), and take my own published findings that hyperglycosylated hCG and its ß-subunit promote human cancer cell malignancy in Jar and JEG-III choriocarcinoma cells [14], in NTERA germ cell testicular cancer cells [14], in Hec-1-a endometrial carcinoma cell line [14], in ScaBER squamous bladder cancer cell line [14], in KLE endometrial adenocarcinoma cell line [14], in SK-MES-1 epithelial lung carcinoma cell line [14], in KM-H2 Hodgkin's lymphoma cell line [14], in T24 epithelial bladder cancer cell line [14], and in CasKi epithelial cervical carcinoma cell line [14]. I conclude that hyperglycosylated hCG and its ß-subunit must drive most or possibly all human malignancies, whether cancer cell growth, cancer cell invasion or cancer cell blockage of apoptosis in most or all human cancers [14].

I here investigate malignancy in choriocarcinoma and the action of hyperglycosylated hCG in this invasive disease. I also examine the actions of a monoclonal antibody against human hyperglycosylated hCG and its ß-subunit in 7 human cancers [22]. Antibody B152 binds hyperglycosylated hCG and its ß-subunit and has no affinity for the hormone hCG or its ß-subunit [22]. I use this data to determine if this monoclonal antibody blocks malignancy, and thus confirms the assumed association of hyperglycosylated hCG and its ß-subunit with malignancy.

MATERIALS AND METHODS

USA hCG Reference Service Customers

All customers of the USA hCG Reference Service completed a form giving the USA hCG Reference Service permission to blindly publish total hCG and hyperglycosylated hCG results, and to use them for research. Three clients refused this option, their results are omitted from this report. Result for 42 choriocarcinoma cases are presented.

Cell Culture Experiments

Cell lines, JEG-3 choriocarcinoma cell line, JAr choriocarcinoma cell line, NTERA testicular germ cell cancer, T24 epithelial bladder carcinoma cell line, KLE endometrial adenocarcinoma cell line, CaSki epidermoid cervical cancer cells, ScaBER squamous bladder cancer cell, Hec-1-a endometrial cancer cells, SK-MES-1 lung epithelial cancer cells and KM-H2 Hodgkin's lymphoma cancer cells were all maintained continuously in culture in T75 flasks using high glucose Dulbecco's modified Eagle's medium with 10% fetal bovine serum.

Cells were cultured in flasks 3 – 5 days in quadruplicate until they reach approximately 70% flask confidence. Then medium was changed and replaced with median containing 0 pmol/ml, 10 pmol/ml and 100 pmol/ml hyperglycosylated hCG (JAr, JEG-3 and NTERA cell lines), or 0 pmol/ml, 10 pmol/ml and 100 pmol/ml hyperglycosylated hCG free ß-subunit (T24, KLE, CaSki, ScaBER, Hec-1-a, SK-MES-1 and KM-H2 cell lines), or 0 µg/ml, 0.5 µg/ml, 1.0 µg/ml and 2.0 µg/ml monoclonal antibody B152. Cells were cultured for 24 hours and the cell number determined in each flask using a hemocytometer.

Immunoassays

All samples were tested by immunometric 96 well microtiter plate assays using Immulon-1 flat bottomed plates, manufactured by Thermo-Scientific Inc. These are plates exhibiting a high affinity for binding proteins such as antibodies. For B152 hyperglycosylated hCG and hyperglycosylated hCG free ß-subunit plates were coated with 1/1000 B152, or 15 µl antibody in 22 ml coating buffer. The secondary antibody used was 4001-POD. Coated plates were incubated with 0.2 ml sample or standard and incubated 2 hours at room temperature. Finally, 200µl of substrate (TMB reagent, dilute 50% with water [Sigma part # T8665]) is added to each well. After approximately 15 min incubation reaction is topped by the addition of 50µl of 2N HCl. Absorbance is then read on the titerplate reader at 450nm.

Specificity studies show that the B152 assay detect hyperglycosylated hCG, hyperglycosylated hCG

Table 1: Eight independent reports that hyperglycosylated hCG and hCG ß-subunit promotes cancer cell malignancy [6,12-18], and one concluding report by Cole showing that hyperglycosylated hCG and its ß-subunit drives all malignancies [11]

Year	Author	Cancer cell tested	Promotes cancer cell growth	Promotes cancer cell invasion	Blocks cancer cell apoptosis	Ref
1996	Iles *et al*.	T24 Epithelial bladder cancer cell line	X		X	[12]
		ScaBER squamous bladder cancer cell line	X		X	
		RT112 bladder carcinoma cell line	X		X	
		5637 adherent bladder carcinoma cell line	X		X	
2000	Butler *et al*.	ScaBER squamous bladder cancer cell line	X		X	[6]
2002	Devi *et al*.	DU145 prostate carcinoma cells	X			[13]
2006	Cole *et al*.	Jar choriocarcinoma cell line	X	X		[14]
		JEG-III choriocarcinoma cell line	X	X		
2008	Jankowska *et al*.	12 patients with planoepithelial cervical cancer			X	[15]
		1 patient with glossy cell cervical cancer			X	
		1 patient with Basaloid cell cervical cancer			X	
		1 patient with Intraepitheliate cervical cancer			X	
		15 patients with endometrial cancer			X	
2008	Li *et al*.	81 patients with uterine cervical cancer			X	[16]
2011	Guo *et al*.	T29 ovarian epithelial carcinoma cell line	X		X	[17]
		T80 ovarian epithelial carcinoma cell line	X		X	
		15 patients with ovarian carcinoma	X		X	
2018	Kawamata *et al*.	80 patients with colorectal cancer	X	X		[18]
		Caco-2 epithelial colorectal cancer	X	X		
		LoVo epithelial colorectal cancer	X	X		
		HCA-7 epithelial colorectal cancer	X	X		
		WiDr colorectal adenocarcinoma	X	X		
		T84 epithelial colorectal cancer	X	X		
2017	Cole	Jar choriocarcinoma cell line	X	X		[11]
		JEG-III choriocarcinoma cell line	X	X		
		NTERA germ cell testicular cancer cell line	X			
		Hec-1-a endometrial carcinoma cell line	X			
		ScaBER squamous bladder cancer cell line	X			
		KLE endometrial adenocarcinoma cell line	X			
		SK-MES-1 epithelial lung carcinoma cell line	X			
		KM-H2 Hodgkin's lymphoma cell line	X			
		T24 epithelial bladder cancer cell line	X			
		CasKi epithelial cervical carcinoma cell line	X			

ß-subunit, nicked hyperglycosylated hCG and nicked hyperglycosylated hCG ß-subunit. With <0.2% detection of the hormone hCG, and its dissociated hCG ß-subunit.

Serum samples were also tested for total hCG (hCG, + nicked hCG, + nicked hCG missing ß-subunit C-terminal peptide, + hCG free ß-subunit, + nicked ß-subunit, + nicked ß-subunit missing ß-subunit C-

terminal peptide, + hyperglycosylated hCG, + nicked hyperglycosylated hCG, + nicked hyperglycosylated hCG free ß-subunit) using the automated Siemens Immulite assay. Tests were run according to manufacturer's instruction using a total hCG standard mass curve, recombinant hCG (4ng/ml, 1 ng/ml, 0.25 ng/ml, 0.5 ng/ml, 0.2 ng/ml and 0.09 ng/ml), run with all tested samples.

All data was entered into Microsoft Excel spreadsheets and analyzed and sorted by diagnosis code.

RESULTS AND DISCUSSION

As proven previously [14], cancer cells only produce hyperglycosylated hCG and its ß-subunit. Trophoblastic malignancies produce hyperglycosylated hCG, and non-trophoblastic cancer produce hyperglycosylated hCG free ß-subunit. As also previously shown [14], all cancers seemingly produce these molecule, whether in tiny amounts (0.1-20 fmol/ml) as a simple TGF-ß autocrines, or in larger concentrations (100-10,000 fmol/ml) as a complex TGF-ß autocrine [14].

The USA hCG Reference Service examines trophoblast disease cases from all around the world. In the past 19 years the USA hCG Reference Service has consulted on 45 choriocarcinoma cases, these are all summarized in Table **2**, Three of 45 cases omitted at the request of patients, to preserve their privacy, although no names were mentioned. The cases included 12 cases with maximally aggressive disease (weekly doubling rate <3.0), 11 cases with aggressive or suppressed disease (weekly doubling rate <4.5), 10 cases with minimally aggressive or chemorefractory disease (weekly doubling rate <6.0, and 8 cases with quiescent or inactive disease (weekly doubling rate >6.0).

As shown in Table **2**, the proportion hyperglycosylated hCG as a percentage of total hCG, was determined using the B152 assay. This percentage exactly correlated with the weekly cancer doubling rate, ttest P=0.996. For the proportion hyperglycosylated hCG to correlate with the cancer doubling rate, hyperglycosylated hCG would have to control cancer growth rate, or to be the malignancy governing molecule. As published [14], hyperglycosylated hCG in trophoblastic malignancies seemingly controls malignancy. It was inferred that hyperglycosylated hCG was the malignancy factor or the malignancy controlling molecule in choriocarcinoma cases. Physicians and other centers managing choriocarcinoma cases should consider using proportion hyperglycosylated hCG as a measure of cancer aggressiveness.

Eight independent published research articles show that hyperglycosylated hCG (trophoblastic malignancies) and hyperglycosylated hCG ß-subunit (non-trophoblasic malignancies) controls malignancy in cancer patient tissues and cancer cell line, controls cancer growth, controls cancer invasion of other tissues, and blocks cancer cell apoptosis in a wide range of cancers (Table **1**) [7,15-21]. In addition, I demonstrated that hyperglycosylated hCG and its ß-subunit control malignancy in 9 widely varying cancer cell lines (Table **1**) [14]. Putting all this data together it appears that hyperglycosylated hCG and its ß-subunit are molecules that control malignancy in most or possibly all cancers.

To support this hypothesis, I investigated the action of antibody B152, a specific monoclonal antibody against hyperglycosylated hCG and its ß-subunit, on growth of 7 of 7 widely varying cancer cell lines (Table **3**).

Cancer cells were grown to 70% confluency and counted (Table **3**). Then cultured for a further 24 hours with 0, 10 and 100 pmol/ml hyperglycosylated hCG (trophoblastic malignancies), or 0 10 and 100 pmol/ml hyperglycosylated hCG ß-subunit (non-trophoblastic malignancies), or with 0, 0.5, 1.0 or 2.0 µg/ml monoclonal antibody B152. As shown in Table **3**, hyperglycosylated hCG and its ß-subunit very much expanded cell growth to 164 ± 16% - 242 ± 2.6% over the 70% confluency growth. B152 monoclonal antibody treatment seemingly totally blocked carcinogenesis, reducing growth (2.0 µg/ml) to the static 70% confluent levels (Table **3**).

It appeared that B152 2.0 µg/ml diminished malignancy action back to the benign disease or non-growing level. That this worked in 7 of 7 cancers tested, proves that in these cancers hyperglycosylated hCG and its ß-subunit must be the malignancy factors, since all malignancy is totally blocked. This very much confirms the 7 independent studies (Table **1**) [7,15-21] and my study of 9 cancers (Table **1**) [14], confirming that hyperglycosylated hCG and its ß-subunit are the malignancy factors in most or possibly all human cancers.

The finding that hyperglycosylated hCG and its ß-subunit are the malignancy factor in most or possibly all human cancers is very important. Identifying the

Table 2: Serum samples from 42 choriocarcinoma cases. hCG-H is the B152 hyperglycosylated hCG result, converted to hCG equivalents mIU/ml (X11) and the percentage hCG-H of total hCG. The cancer doubling rate is the consulting physician's estimated time for the cancer mass to double

Age	Diagnosis made by	Total hCG	hCG-H	hCG-H	Percent hCG-H	Cancer Doubling
	USA hCG Reference Service	(mIU/ml)	(ng/ml)	(mIU/ml)	hCG-H/hCG (%)	rate (weeks)
25	Maximally Aggressive Choriocarcinoma	40,256	4,400	48,400	100%	2.6
32	Maximally Aggressive Choriocarcinoma	80,400	8,050	88,550	100%	3.0
21	Maximally Aggressive Choriocarcinoma	314,000	429,000	390,000	100%	<2
34	Maximally Aggressive Choriocarcinoma	399,500	37,270	401,000	100%	<2
21	Maximally Aggressive Choriocarcinoma	932,000	85,090	936,000	100%	<2
19	Maximally Aggressive Choriocarcinoma	50,053	4,333	47,663	95%	Not determined
34	Maximally Aggressive Choriocarcinoma	116,620	10,011	110,121	94%	<2
37	Maximally Aggressive Choriocarcinoma	596,000	50,931	560,240	94%	2.8
N/A	Maximally Aggressive Choriocarcinoma	37,500	3,110	34,210	91%	2.4
35	Maximally Aggressive Choriocarcinoma	14,1627	11,034	12,1374	86%	<2
26	Maximally Aggressive Choriocarcinoma	45,000	3,400	37,400	83%	<2
N/A	Maximally Aggressive Choriocarcinoma	40,644	3,012	33,132	82%	2.6
			Mean ± SD		94% ± 6.9%	2.30 ± 0.38
N/A	Aggressive choriocarcinoma	6,016	436	4,796	80%	3.5
20	Aggressive choriocarcinoma	821	58	638	78%	4.2
N/A	Aggressive choriocarcinoma	2500	176	1,936	77%	<3
N/A	Aggressive choriocarcinoma	80,699	5,560	61,160	76%	Not determined
N/A	Aggressive choriocarcinoma	2450	140	1,540	63%	4
43	Aggressive choriocarcinoma	1208	66	726	60%	4.4
34	Aggressive choriocarcinoma	901	49	539	60%	4
37	Aggressive choriocarcinoma	21,590	982	10,802	50%	3.5
29	Aggressive choriocarcinoma	454	19.2	211.2	47%	2.8
36	Aggressive choriocarcinoma	521	20.2	222.2	43%	3.5
34	Aggressive choriocarcinoma	2,362	91	1001	42%	3.8
			Mean ± SD		60% ± 13%	3.85 ± 0.58
37	Minimally Aggressive choriocarcinoma	27,688	982	10,802	39%	5.5
27	Minimally Aggressive choriocarcinoma	440	15.1	166.1	38%	5.2
42	Minimally Aggressive choriocarcinoma	542	17	187	35%	4.5
50	Minimally Aggressive choriocarcinoma	1596	42	462	29%	Not determined
29	Minimally Aggressive choriocarcinoma	214	5.6	61.6	29%	5.5
32	Minimally Aggressive choriocarcinoma	5290	112	1,232	23%	4
30	Minimally Aggressive choriocarcinoma	20,440	4,025	44,275	22%	5
31	Minimally Aggressive choriocarcinoma	639	11.7	128.7	20%	5.5
37	Minimally Aggressive choriocarcinoma	735	7.8	85.8	12%	>6
46	Minimally Aggressive choriocarcinoma	238	2	22	9.2%	>6
			Mean ± SD		26% ± 10%	5.20 ± 0.66
46	Quiescent choriocarcinoma	18	0.01	0.11	0.61%	5.5
40	Quiescent choriocarcinoma	35	0.02	0.22	0.62%	>6
26	Quiescent choriocarcinoma	3.4	Not detected		<1%	>6

(Table 2). Continued.

Age	Diagnosis made by	Total hCG	hCG-H	hCG-H	Percent hCG-H	Cancer Doubling
	USA hCG Reference Service	(mIU/ml)	(ng/ml)	(mIU/ml)	hCG-H/hCG (%)	rate (weeks)
24	Quiescent choriocarcinoma	7.2	Not detected		<1%	>6
17	Quiescent choriocarcinoma	11	Not detected		<1%	>6
23	Quiescent choriocarcinoma	7.8	Not detected		<1%	>6
27	Quiescent choriocarcinoma	3.3	Not detected		<1%	>6
32	Quiescent choriocarcinoma	17	Not detected		<1%	>6
35	Quiescent choriocarcinoma	20	Not detected		<1%	>6
			Mean ± SD		<1 ± 0.013%	5.94 ± 0.17
			T test		P=0.996	

Table 3: Cancer cells cultured to 70% flask confluency (confl), then cultured 24 h with hyperglycosylated hCG (hCG-H), or 24 h with antibody B152 in quadruplicate and cells counted. hCG-H is hyperglycosylated hCG and hCG-H-ß is hyperglycosylated hCG ß-subunit, and B152 is antibody B152. Values are percent change from 70% confl. Inherant changes following 0 pmol/ml or 0 µg/ml incubations due to hyperglycosylated hCG or ß-subunit produced by cells

70% confl	hCG-H 0 pmol/ml	hCG-H 10 pmol/ml	hCG-H 100 pmol/ml	B152 0 µg/ml	B152 0.5 µg/ml	B152 1.0 µg/ml	B1522.0 µg/ml
A. Trophoblastic malignancies							
JAr choriocarcinoma cell line, 70% confl = 334,500±33,000 cells							
100 ± 10%	128 ± 8.4%	149 ± 18%	183 ±10%	128 ± 8.4%	110 ± 23%	105 ± 15%	101 ± 0.9%
JEG-3 choriocarcinoma cell line, 70% confl = 430,000 ± 33,110 cells							
100 ± 7.7%	123 ± 11%	145 ± 8.5%	164 ± 16%	123 ± 11%	115 ± 7.6%	103 ±2.4%	101 ± 8.1%
NTERA testicular germ cell malignancy, 70% confl = 391,000± 10,160 cells							
100 ± 2.6%	114 ± 19%	130 ± 10%	168 ± 12%	114 ± 19%	119 ± 10%	117± 2.4%	100 ± 0.7%
70% confl	hCG-H-ß 0 pmol/ml	hCG-H-ß 10 pmol/ml	hCG-H-ß 100 pmol/ml	B152 0 µg/ml	B152 0.5 µg/ml	B152 1.0 µg/ml	B152 2.0 µg/ml
B. Non-trophoblastic malignancies							
SCaBER bladder epithelial carcinoma cells, 70% confl = 334,000 ± 17,000 cells							
100 ± 5.1%	147 ± 2.0%	169 ± 12%	193 ± 3.7%	147 ± 2.0%	129 ± 16%	120 ± 3.7%	100 ± 2.9%
T24 bladder epithelial carcinoma cells, 70% confl = 559,000 ± 24,000 cells							
100 ± 4.2%	120 ± 4.4%	162 ± 2.6%	172 ± 5.4%	120 ± 4.4%	114 ± 12%	103 ± 1.1%	100 ± 3.5%
Hec-1-a endometrial carcinoma cells, 70% confl = 390,500 ± 12,800 cells							
100 ± 3.3%	140 ± 11%	169 ± 5.6%	171 ± 7.2%	140 ± 11%	128 ± 7.7%	132 ± 8.2%	103 ± 3.1%
KLE endometrial adenocarcinoma cells, 70% confl = 331,000 ± 6,950cells							
100 ± 2.1%	182 ± 16%	222 ± 1.7%	242 ± 2.8%	182 ± 16%	142 ± 1.3%	118 ± 3.3%	102 ± 2.5%

molecules that drive malignancy is probably the first step in the synthesis of a new group of cancer drugs that potentially cures cancer, prevents malignancy or blocks malignancy, or that keep people alive with history of advancer cancer. It is now the job of readers to generate these agents and to cure cancer or disease caused by hyperglycosylated hCG and its ß-subunit. One approach might be preventing the expression of

hCG ß-subunit gene expression by cancer cells, or preventing or blocking the expression of gonadotropin releasing hormone (GnRH), hCGß's promoter [23-25], or preventing or blocking opiate stimulation of GnRH [26-28] which controls the expression of hCGß.

I know that I have developed antibody B152, a monoclonal antibody to hyperglycosylated hCG and its ß-subunit [29]. When cancer is transplanted into nude mice, B152 suppresses the cancer, creating a state of oncostasis [29]. When humanized, such an antibody could be a treatment for advanced cancer, placing the mass into a benign-like state and allowing life to continue post cancer or longevity. When humanized It may also have an application in blocking cancer growth and invasion during therapy.

REFERENCES

[1] Cole LA, Dai D, Leslie KK, Butler SA, Kohorn EI. Gestational trophoblastic diseases: 1. Pathophysiology of hyperglycosylated hCG-regulated neoplasia. Gynecol Oncol 2006; 102: 144-149.

[2] Kovalevskaya G, Genbacev O, Fisher SJ, Cacere E, O'Connor JF. Trophoblastorigin Elliott MM, Kardana A, Cole LA. Carbohydrate and Peptide structure of the α- and β-subunits of human chorionic gonadotropin from normal and aberrant pregnancy and choriocarcinoma. Endocrine 1997; 7: 15-32. https://doi.org/10.1007/BF02778058

[3] Elliott MM, Kardana A, Cole LA. Carbohydrate and Peptide structure of the α- and β-subunits of human chorionic gonadotropin from normal and aberrant pregnancy and choriocarcinoma. Endocrine 1997; 7: 15-32. https://doi.org/10.1007/BF02778058

[4] Valmu L, Alfthan H, Hotakainen K, Birken S, Stenman UH. Site-specific glycan analysis of human chorionic gonadotropin beta-subunit from malignancies and pregnancy by liquid chromatography - electrospray mass spectrometry. Glycobiol 2006; 16: 1207-1218. https://doi.org/10.1093/glycob/cwl034

[5] Cole LA. hCG and Hyperglycosylated hCG Carbohydrate Structures Corrected. J Glycobiol 2014; 3: 1000114.

[6] Cole LA. The Minute Structural Difference between the Hormone hCG and the Autocrine Hyperglycosylated hCG. J Glycobiol 2017; in press. https://doi.org/10.4172/2168-958X.1000127

[7] Butler SA, Ikram MS, Mathieu S, Iles RK. The increase in bladder carcinoma cell population induced by the free beta subunit of hCG is a result of an anti-apoptosis effect and not cell proliferation. Brit J Cancer 2000; 82: 1553-1556.

[8] Berndt S, Blacher S, Munuat C, Detilleux J, Evain-Brion D, Noel A, Fournier T, Foidart JM. Hyperglycosylated human chorionic gonadotropin stimulates angiogenesis through TGF-ß receptor activation. FASEB J 2013; 12-213686.

[9] Ahmud F, Ghosh S, Sinha S, Joshi SD, Mehta VS, Sen E. TGF-ß-induced hCG-ß regulates redox homeostasis in glioma cells. Molec Cellul Biochem 2015; 399: 105-112. https://doi.org/10.1007/s11010-014-2237-6

[10] Cole LA, Khanlian SA, Kohorn EI. Evolution of the Human Brain, Chorionic Gonadotropin and Hemochorial Implantation of the Placenta: Origins of Pregnancy Failures, Preeclampsia and Choriocarcinoma. J Reprod Med 2008; 53: 449-557.

[11] Cole LA. The evolution of the primate, hominid and human brain. Primatology 2015; 4: 100124.

[12] Sasaki Y, Ladner DG, Cole LA. Hyperglycosylated hCG the source of pregnancy failures. Fertil Steril 2008; 89: 1871-1786. https://doi.org/10.1016/j.fertnstert.2007.03.010

[13] Cole LA. Hyperglycosylated hCG and Pregnancy Failures. J Reprod Immunol 2012; 93: 119-122. https://doi.org/10.1016/j.jri.2012.01.001

[14] Cole LA. Hyperglycosylated hCG drives malignancy in cancer cases. J Molec Oncol Res 2017; 1: 53-63.

[15] Gillott DJ, Iles RK, Chard T. The effects of beta-human chorionic gonadotrophin on the *in vitro* growth of bladder cancer cell lines. Br J Cancer 1996; 73: 323-326. https://doi.org/10.1038/bjc.1996.56

[16] Devi GR, Oldenkamp JR, London CA, Iversen PL. Inhibition of human chorionic ß-subunit modulates the mitogenetic effect of *c-myc* in human prostate cancer cells. Prostate 2002; 53: 200-310. https://doi.org/10.1002/pros.10151

[17] Cole LA, Dai D, Leslie KK, Butler SA, Kohorn EI. Gestational trophoblastic diseases: 1. Pathophysiology of hyperglycosylated hCG-regulated neoplasia. Gynecol Oncol 2006; 102: 144-149.

[18] Jankowska A, Gunderson SI, Warchol JB. Reduction of hCGß subunit expression by modified U1 snRNA caused apoptosis in cervical cancer cells. Molec Cancer 2008; 7: 26-29. https://doi.org/10.1186/1476-4598-7-26

[19] Li D, Wen X, Ghali L, *et al*. hCG β expression by cervical squamous carcinoma-*in vivo* histological association with tumour invasion and apoptosis. Histopathol 2008; 53: 147-55. https://doi.org/10.1111/j.1365-2559.2008.03082.x

[20] Guo X, Liu G, Schauerl G, *et al*. Overexpression of the β Subunit of Human Chorionic Gonadotropin Promotes the Transformation of Human Ovarian Epithelial Cells and Ovarian Tumorigenesis. Am J Pathol 2011; 179: 1385-1393. https://doi.org/10.1016/j.ajpath.2011.05.018

[21] Kawamaja F, Nishihara H, Homma S, *et al*. Chorionic gonadotropin-ß modulates epithelial-mesenchymal transition in colorectal carcinoma metastasis. Am J Path 2018; 188: 207-215.

[22] Birken S, Krichevsky A, O'Connor J, Schlatterer J, Cole LA, Kardana A, Canfield R. Development and characterization of antibodies to a nicked and hyperglycosylated form of hCG from a choriocarcinoma patient. Endocrine J 1999; 10: 137-144. https://doi.org/10.1385/ENDO:10:2:137

[23] Siler-Khodr TM, Khodr GS, Valenzuela G, Rhode J. Gonadotropin-releasing hormone effects on placental hormones during gestation: I. Alpha-human chorionic gonadotropin, human chorionic gonadotropin and human chorionic somatomammotropin.Biol Reprod 1986; 34: 245-54. https://doi.org/10.1095/biolreprod34.2.245

[24] Mathialagan N, Rao AJ. Gonadotropin releasing hormone (GnRH) stimulates both secretion and synthesis of human chorionic gonadotropin (hCG) by first trimester human placental minces *in vitro*. Biochem Int 1986; 13: 757-65.

[25] Iwashita M, Kudo Y, Shinozaki Y, Takeda Y. Gonadotropin-Releasing Hormone Increases Serum Human Chorionic Gonadotropin in Pregnant Women. Endocrine J 1993; 40: 539-544. https://doi.org/10.1507/endocrj.40.539

[26] Leung PC, Cheng CK, Zhu XM. Multi-factorial role of GnRH-I and GnRH-II in the human ovary. Molec Cellul Endocrinol 2003; 202: 145-153. https://doi.org/10.1016/S0303-7207(03)00076-5

[27] Schally AV. Luteinizing hormone-releasing hormone analogs: their impact on the control of tumorigenesis. Peptides 1999; 20: 1247-1262. https://doi.org/10.1016/S0196-9781(99)00130-8

[28] Lennon FE, Moss J, Singleton PA. The ψ-opiod receptor in cancer progression: Is there a direct effect? Anaesthesiology 2012; 100: 940-945. https://doi.org/10.1097/ALN.0b013e31824b9512

[29] Cole LA, Butler SA. Cole LA, Butler SA. B152 anti-hyperglycosylated human chorionic gonadotropin free β-Subunit. A new, possible treatment for cancer. J Reprod Med 2015; 60:13-20.

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