HCG AND HYPERGLYCOSYLATED HCG IN HEMOCHORIAL IMPLANTATION: 1. PARALLEL EVOLUTION

Laurence A. Cole

All mammals prior to Cercopithecidae (Old World Monkey) had small brains, including Lemur and primitive primates. These were limited in size by the efficiency of epitheliochorial and other basic non-invasive placenta transport systems (Gibbons A, Solving the brain's energy crisis. Science 1998;280:1345-1347). The small brains varied from 0.07% to 0.15% of body weight. Beginning with the appearance of Cercopithecidae came the evolution of hemochorial placentation, in which the placenta invades through the decidua accompanied by extension of decidual and myometrial spiral arteries to the placental villi. With the improved efficiency of placentation, development of larger and more complex brains occurred, 0.17% (mass/mass) in Cercopithecidae, 0.74% in the advanced primate or orangutan, and then 2.4% in the human. Hemochorial implantation advanced from invasion of the decidua in Cercopithecidae, to invasion through the decidua and 1/10th the width of myometrium in orangutan, to invasion though the decidua to 1/3rd the width of the myometrium in humans (Gibbons A, Solving the brain's energy crisis. Science 1998;280:1345-1347, Martin RD, J Reprod Immunol 2003;59:111-135, Pijnenborg R, Hypertens Pregn 1996;15:7-23). With advancing depth of invasion and spiral artery angiogenesis came the improved placental nutritional efficiency needed for advanced primate and human brain development.

As discussed in the previous presentation, in humans hCG and hCG-H are the signals driving angiogenesis and driving invasion. Intriguingly, CG evolved with Cercopithecidae, the first species with invasion and angiogenesis. It is therefore not unreasonable to infer that CG and CG-H were the signals initiating hemochorial placentation in this species. The Cercopithecidae CG (and presumably CG-H) had only 2 O-linked oligosaccharides with a pI of 6.3. Such an hCG form is estimated to have a circulating half life of 100 minutes. CG evolved further with advanced primates, gaining 3 O-linked oligosaccharides with a pI of 4.9 and an estimated circulating half life of 600 minutes. Finally, with the evolution of humans CG gained a 4th O-linked oligosaccharide, yielding an average pI of 3.9 and a circulating half life of 2300 minutes. Clearly, with increasing circulating half life the serum concentrations of CG and CG-H became proportionally elevated, as did the their activity and abilities to push hemochorial implantation from the myometrial periphery in Cercopithecidae to a remarkable 1/3rd the width of the myometrium in humans. We conclude that the advancing evolution of CG and CG-H with 2, 3 and 4 O-linked oligosaccharides was the signal driving the increased development of hemochorial implantation. Considering that the progressive evolution of increasingly advanced hemochorial implantation permitted the development of the human brain, it would not be unreasonable to attribute the development of humans to the evolution of CG and CG-H.

The placental implantation system needed for the development of the human brain was a biological extreme. Like other extremes it is accompanied by subsequent problems. Almost every mammalian species has a pregnancy failure rate of approximately 10%, yet humans, with their extreme implantation, have a 41% failure (25% early pregnancy loss plus 16% miscarriage) rate (Jauniaux E et al. Human Reprod Updt 2006;12:747-755). As a complication of incomplete advanced hemochorial placentation, humans develop anoxia causing PIH, preeclampsia and eclampsia in pregnancy (Pijnenborg R, Hypertens Pregn 1996;15:7-23, Burton GJ. J Soc Gyn Invest 2004; 11:342-352). This is unique to humans. Choriocarcinoma or invasive gestational trophoblastic disease is also unique to humans and is driven by the high levels of hCG-H unique to humans. The free ß-subunit of hCG is expressed by retrodifferentiation in advanced human malignancies. The gene for this molecule is solely present in humans as an artifact of the placentation requirements. As shown, expression of free ß-subunit makes a malignancy worse, advancing growth and invasion (Iles RK, Tumor Marker Upd 1995;7161-166). Reviewing as we do here the roles of CG and CG-H in placental development and development of the human brain, we explain for the first time their evolutionary roles and how they are at the root of pregnancy failure, preeclampsia, choriocarcinoma and poor outcome malignancies. We conclude, that putting CG and CG-H into their complete perspectives may be a first step in developing new therapies and possible cures for many of these complications (CG-H therapy and hCGß vaccine cures).