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# The Coevolution of Placentation and Cancer

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## Abstract

Analogies between placentation, in particular the behavior of trophoblast cells, and cancer have been noted since the beginning of the twentieth century. To what degree these can be explained as a consequence of the evolution of placentation has been unclear. In this review, we conclude that many similarities between trophoblast and cancer cells are shared with other, phylogenetically older processes than placentation. The best candidates for cancer hallmarks that can be explained by the evolution of eutherian placenta are mechanisms of immune evasion. Another dimension of the maternal accommodation of the placenta with an impact on cancer malignancy is the evolution of endometrial invasibility. Species with lower degrees of placental invasion tend to have lower vulnerability to cancer malignancy. We finally identify several areas in which one could expect to see coevolutionary changes in placental and cancer biology but that, to our knowledge, have not been explored.

## 1. INTRODUCTION

All multicellular organisms can develop tumors, i.e., populations of cells that escape the growth control of the organism. These have been found in plants, corrals, many invertebrates, and of course vertebrates (1, 2). Placentation exists in a small subset of animals, mostly known from vertebrates but also described in many invertebrates, ranging from cnidarians to insects and others. Given this taxonomic distribution of cancers[1] and placentas, it is clear that cancers existed before placentas originated. The question discussed here, therefore, is how the evolution of the placenta affected cancer biology. Also, the "evolution of the placenta" has at least two dimensions, namely, the origin of the placenta and the subsequent evolution of different forms of placentation. This prompts at least two further questions: What is the impact of the evolutionary origin of placentation, which happened many times in animals, on tumor biology? And how did the evolution of different forms of placentation, after its origin, affect cancer biology? The scope here is, unfortunately, limited to mammals. That is because the knowledge about nonmammalian cancers is limited, as is that of nonmammalian placentation, with the exception of reptilian placentation, which attracted a good amount of attention from zoologists but is unfortunately unmatched with sufficient data on reptilian cancers (3–5).

The idea that there might be a mechanistically relevant connection between trophoblast and cancer biology is usually ascribed to the Scottish embryologist John Beard (1858–1924) (6). Although Beard's core idea that cancer cells are ectopic trophoblast cells turned out to be wrong, his ideas still inspire research. In the second part of the twentieth century, theories about a connection between cancer and placental biology were based mostly on the mechanistic similarities between implantation and placentation and tumor progression to malignancy (7–13). Although these observations are valuable, their evolutionary interpretation is complicated because cancers arose earlier than placentation.

The field of evolutionary or comparative cancer biology is a relatively recent development, which arose largely around the turn from the twentieth to the twenty-first century (14–18). Before that, evolutionary thought with respect to cancer was limited to the rather obvious fact that cancer is a breakdown of multicellular organization (e.g., 19, 20). Evolutionary or comparative cancer biology consists of two research programs. First is the field of somatic evolution of the tumor itself, i.e., studying the progression of tumor cells toward malignancy within a patient as an evolutionary process (e.g., 21, 22). This is an important field of research with implications for cancer treatment (23). The other dimension could be called comparative cancer biology and is the study of species differences in cancer biology across the tree of life. The latter focuses on understanding species differences in vulnerability to cancer and cancer malignancy (15, 22, 24–27). We review ideas and facts pertaining to the question of whether the evolution of the fetal–maternal interface (e.g., the trophoblasts, the placenta, and the decidua) in mammals affected the biology of mammalian cancers.

## 2. THE PLACENTA–CANCER NEXUS

Here we want to briefly outline how a cancer–placenta nexus can be understood at both the cell biological as well as the evolutionary level. At the cell biological level, three areas of overlap exist between cancer and placentation: (*a*) Both a neoplastic tumor and a (hemochorial) placenta can

[1] In the title and introduction of this article, the term cancer is used in its generic sense for any form of tumor, regardless of whether it is of epithelial (carcinoma sensu stricto) or mesenchymal (sarcoma) origin. This is to facilitate communication with readers who are not aware of this distinction, as is generally the case outside of the biomedical sciences. After all, the main US federal institution dedicated to the study of tumors is called the National Cancer Institute, even though it also covers the study of sarcomas.

be viewed as a sustained lesion, a "wound that does not immediately heal" (28, 29); (*b*) both trophoblasts and cancer cells require immune evasion; and (*c*) both placentation and malignant cancer growth involve cells invading into the surrounding stroma (12, 30). A fourth relationship between cancer and placentation is a little less straightforward, namely, the involvement of inflammation. In the case of cancer, inflammation can be a key part of the process of cancer onset and progression. In the case of placentation, inflammation (31, 32), or processes derived from inflammation (33), plays an essential role in embryo implantation but must be locally suppressed after implantation to sustain pregnancy. The involvement of inflammation is understandable given that both cancer and placentation compromise tissue integrity, i.e., generate wounds; however, the nature and control of the inflammatory processes may be different in cancer and placentation.

Beyond the cell biological similarities between cancer and placentation, the question is how the evolution of placentation may have influenced cancer biology. So far, three models have been proposed in the literature: (*a*) the co-option, by growing tumors, of mechanisms of embryo implantation and placentation (7, 8, 10, 34), (*b*) pleiotropic effects of the evolution of the uterine stroma on stromal biology in the rest of the body (35–37), and (*c*) the evolution of the immune system in response to the origin of placentation (38).

Co-option by the tumor of placentation mechanisms assumes that the evolution of mammalian placentation involved mechanisms employed by the trophoblast to evade the maternal immune response. Once in place, a tumor can gain access to these genetic programs and itself evade detection by the host immune system. Evidence for this is discussed in Section 5.

The second model, pleiotropic effects of the evolution of endometrial stroma onto the rest of the body, assumes that eutherian species that differ in their degree of placental invasiveness differ in their endometrial invasibility (35, 36). Evidence for this is discussed in Section 6.

## 3. THE EVOLUTIONARY ORIGIN AND DIVERSIFICATION OF MAMMALIAN PLACENTATION

Mammalia consists of three main clades: the monotremes, marsupials (i.e., metatheria), and placental (eutherian) mammals, where the marsupials and the eutherians form the clade of Theria, i.e., they are related to each other more closely than either is to monotremes (**Figure 1**). The three mammalian clades differ fundamentally with respect to their female reproductive biology. Monotremes are known as the egg-laying mammals, even though they already have some degree of matrotrophy via diffusion of nutrients from the uterus through the eggshell to the embryo (39). Both marsupials and eutherians are live bearing and have placentae; thus, the most parsimonious hypothesis is that viviparity evolved in the stem lineage of therians. Nevertheless, the placental biology of marsupials is fundamentally different from that of eutherian mammals.

In basally branching lineages of marsupials, such as the opossums and the Peramelidae, placentation is present but limited in scope and complexity. Here we use the term placentation as defined by Grosser (40) and Mossmann (41) as a direct intimate apposition or attachment between fetal membranes and maternal (or paternal in the case of pipe-fishes) tissue for the purpose of nutrient transfer, waste product removal and gas exchange. Apposition between fetal and maternal tissue occurs late in the 14-day gestation of the gray short-tailed opossum, *Monodelphis domestica*, and lasts for only two days (42, 43). During the short attachment period, inflammatory mediators are induced and increase in expression until parturition (42, 44). This inflammation-like process is induced by the presence of the fetus, as it is not observed during the estrus cycle if no fertilization had occurred, i.e., during pseudopregnancy (45).

Opossum placentation does not lead to sustained implantation and thus remains superficial. The trophoblast is nevertheless invasive, as it penetrates between the uterine luminal epithelial

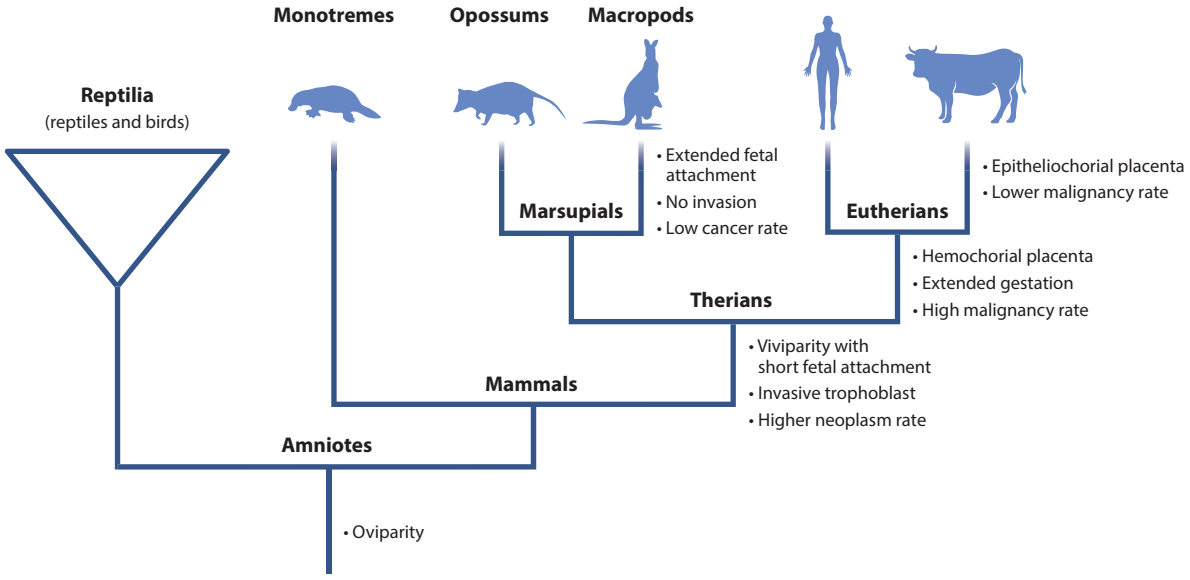


**Figure 1**

Simplified phylogeny of amniote vertebrates. The sister taxon of mammals is Reptilia, consisting of conventional "reptiles" and birds. The mammals consist of three main clades: monotremes, marsupials, and eutherian (placental) mammals. Major changes in reproductive biology are noted at the phylogenetic branches where they occurred (also see text for more detail).

cells (46), but does not lead to implantation because of the brevity of pregnancy. This is also the case for most non-macropod marsupials (47). This observation is important when considering the cancer rate among mammals (see below). Macropodids (kangaroos and wallabies) are remarkable in having both a longer gestation period and not-even-slightly invasive trophoblasts (48). Given the derived status of macropodids in the marsupial tree (49), this is likely a derived characteristic within marsupials.

In eutherians, three types of tissue organization at the fetal–maternal interface can be distinguished (40). The least invasive is called epitheliochorial, where the epithelium of the placenta, the trophoblast, is attached to the uterine luminal epithelium. This form is found in hoofed animals and their relatives, as well as in tarsiers, i.e. in an early branching primate lineage. In endotheliochorial placentation, the uterine epithelium is eroded and the trophoblast is next to the maternal blood vessels, but the maternal blood vessels remain intact. This form is found, for instance, in carnivores. Finally, the most invasive placenta type is hemochorial, as seen in humans and most other primates, as well as rodents, where the maternal blood is in direct contact with the trophoblast.

Surprisingly, in the 2000s it was found that the most likely ancestral form of eutherian placenta was hemochorial, or at least endotheliochorial (50–52). A corollary of this finding is that the less invasive forms of placentation, as found in hoofed animals, secondarily evolved from a more invasive condition. The latter fact is important for the placenta–cancer connection with respect to malignancy rate (see Section 6).

From this short overview, we can conclude that trophoblast invasiveness is an ancestral condition for therian mammals (marsupials and eutherians) (**Figure 1**). This follows from two observations: (*a*) that the opossum trophoblast penetrates the uterine epithelium shortly before birth and elicits a quasi-inflammatory process (42, 44) and (*b*) that the ancestral condition for eutherian mammals is a hemochorial or endotheliochorial placenta (50–52), i.e., one where maternal tissue

is greatly modified by the embryo. Marsupials and eutherians deal with trophoblast invasiveness quite differently. In basal marsupials, the invasion of the uterus is ended by parturition, whereas in basal eutherians, the mother evolved mechanisms to tolerate the injury caused by placentation (42). In summary, the evolutionary history of mammalian placentation involves the origin of an invasive trophoblast early in therian phylogeny; then, in eutherians, the evolution of maternal tolerance mechanisms, as a prerequisite for extended placentation (anti-inflammatory activity and delay of the wound healing process); and finally, the elaboration of the placenta, including adaptations for immune evasion (**Figure 1**).

## 4. PHYLOGENETIC PATTERNS OF CANCER AND MALIGNANCY INCIDENCE

The main sources of information about the incidence rate of cancer and malignancy are necropsy reports from farm and zoo animals (53–55). Although these reviews contain a lot of detailed data, the quantitative aspects of data reporting are often incomplete; for instance, the data sets often lack numbers of total necropsies per species. In addition, zoo necropsies tend to be done on older animals that die of natural causes, whereas slaughterhouse data cover mostly young animals with the occasional exception of milk cows, for instance. Nevertheless, these are the data we have to interrogate for species and clade differences in neoplasm and malignancy rates. This is also the only evidence we have to investigate correlations with the evolution of placental biology. Here we focus first on comparisons between species with and without a placenta to assess whether the evolutionary origin of placentation affected cancer incidence. Then we compare species with different forms of placentation to assess whether these affect malignancy rates.

### 4.1. Incidence of Neoplasms in Mammals Compared with Other Amniotes

Neoplasm incidence rates for broad taxonomic groups, such as mammals (mostly therian mammals) and birds, are problematic because incidence rates can vary greatly between species. For instance, the Virginia opossum (*Didelphis virginiana*), in some data sets, has a reported neoplasm incidence rate of above 60%, but only two neoplasms and no malignancies out of 67 necropsies (3%) were reported in the armadillo (*Dasypus novemcinctus*) (56), and even lower rates were reported in the naked mole-rat (57, 58). Hence, the average reported cancer incidence rate for large taxonomic groups will be influenced by nonrandom sampling of taxa (i.e., whatever animals happened to live and die in a particular zoo). Nevertheless, some remarkably robust patterns arise.

Let us first compare the neoplasm incidence rate of therian mammals with that of birds. Birds never in their evolutionary history had viviparous ancestors. In addition, both mammals and birds have higher metabolic rates than reptiles and thus should be expected to have higher cancer rates than other reptiles (birds are technically reptiles), given the genotoxic effects of high metabolic rate and the incidental production of reactive oxygen species. Here we review two summaries of necropsy reports from two zoos (54, 55).

Ratcliffe (55) reported pathology data from the Philadelphia Zoo and found a 2.6% (89/3,400) neoplasm incidence rate for mammals and a rate of 1.2% (81/6,898) for birds (Fisher's exact test $p < 10^{-4}$).[2] Effron et al. (54) reported necropsy results from the San Diego Zoo and found a neoplasm incidence rate for mammals of 2.9% (92/3,127) and 1.9% (111/5,957) for birds.

[2]Using standard statistical tests on data from different species is problematic because the degrees of freedom are less than the number of observations (minus whatever the test requires), as observations from different species are not stochastically independent. Nevertheless, the majority of the observations in these pathology

The data for mammals in these two papers are statistically indistinguishable (Fisher's exact test $p = 0.451$), whereas the data for birds are distinguishable ($p = 0.0016$). Both studies suggest a higher incidence of neoplasms in mammals than in birds, which is consistent with, though not proof of, an effect of the origin of placentation on cancer rate, where mammals have a higher rate than birds (from 1.5× to 2×). Specifically, the data are consistent with the idea that the evolution of placentation makes available to cancer cells molecular pathways that are beneficial, in one way or another, to cancer cell viability (see below).

A recent analysis of newer San Diego Zoo necropsy data by Boddy et al. (56) reported a high 10% neoplasia incidence rate for eutherian mammals, with an average of 21% for marsupials and 13% for therian mammals overall. This neoplasm rate for mammals is much higher than that reported by Ratcliffe (55) and Effron et al. (54). The reason for this difference is unclear, but more thorough necropsy standards in recent years could be a factor. The most striking feature of the data reported by Boddy and colleagues is the difference between macropodid marsupials and other marsupials, such as opossum and koala. Whereas the overall neoplasm incidence in the 229 marsupial necropsies was 21%, the macropodids had a rate of only 3.7% (4/109), and the other marsupials had a rate of 38% (46/120). This is interesting given the fact that the placental biology of macropodids is quite different from that of other marsupials, as mentioned above. Macropodids have evolved a longer gestation period (48) and have a not even minimally invasive placenta (47) and no clear inflammatory reaction to the presence of the embryo/fetus (Oliver Griffith, personal communication). Although whether the lack of invasion is due to evolutionary changes in the maternal tissue or the trophoblast is unclear, that such a striking difference in cancer rate coincides, evolutionarily, with this change in placental biology is nevertheless intriguing.

### 4.2. Malignancy Rate Among Mammals with Different Placentas

Malignant cancer frequency was reported by Priester & Mantel (53) for farm animals and pets [analyzed by D'Souza & Wagner (35)] and Effron et al. (54) for mammals and birds (as well as reptiles, but with too small a sample size) and in Boddy et al.'s (56) recent study on mammals. Malignancy rates can be reported in two ways. On the one hand, Boddy et al. (56) reported the incidence rate of malignant cancers, estimated as the number of malignant cancers divided by the total number of necropsies. On the other hand, one can calculate the malignancy rate, estimating the probability that a benign cancer turns into a malignant cancer. Malignancy rate can be estimated by dividing the number of malignant cancers by the total number of neoplasms found. In this way, one avoids conflating the malignancy rate and neoplasm rate, which is confounded in calculating the malignancy incidence rate. Still, estimating the true malignancy rate is complicated given the fact that animals with malignant cancer are more likely to die than those that had benign tumors but died for other reasons. But without additional detailed information, the malignancy rate is the closest we can get to estimating a tumor's propensity to become malignant.

Priester & Mantel (53) summarized necropsy data from 202,277 animals with 8,634 tumors classified into 4 broad categories of neoplasms: skin cancer and glandular epithelial, nonglandular epithelial, and connective tissue tumors. Enough data were available to calculate malignancy rates for four species: cattle, horse, dog, and cat (35). These species represent two forms of placentation, endotheliochorial (cat and dog) and epitheliochorial (cattle and horse). For three of the classes of neoplasms, the malignancy rate was statistically higher in cats and dogs compared with in cattle

reports are independent reports about different animals from the same species, and thus the use of Fisher's exact test is not entirely irrational. We interpret the calculated $p$-values as lower limits of the true $p$-values.

and horses. Only in nonglandular cancers was the malignancy rate statistically the same across all four species. This pattern suggests that species with more invasive placentation have a higher malignancy rate than species with less invasive placentation, at least with respect to certain classes of neoplasms. The evolutionary and mechanistic explanations for this pattern are discussed in Section 6.

Effron et al. (54) reported overall malignancy rates for mammals (42%, 39 malignant out of 92 neoplasms), birds (64%, 71/111), and reptiles (54%, 15/28). The difference between mammals and birds is significant (Fisher's exact test, $p = 2.9\ 10^{-3}$), but comparisons with reptiles are not significant owing to the small number of reptiles examined. These data seem to indicate a lower malignancy rate in mammals compared with birds, whereas the number of neoplasms is higher in mammals (see above). Further stratification of the mammalian data into groups with different placental biology leads to sample sizes too small to be meaningful.

Boddy et al. (56) analyzed data from 37 species and 852 necropsies of animals that died at the San Diego Zoo between 1964 and 2015. The authors tested for a relationship between placenta type and malignancy incidence and found no statistical relationship. However, this study used malignancy incidence rather than malignancy rate; the former again conflates malignancy rate and tumor incidence. Wagner et al. (59) reanalyzed these data by estimating the malignancy rate (rather than incidence) for species with at least four reported neoplasms and combined it with the data from Priester & Mantel (53). These combined data suggest a nominal trend in eutherians toward higher malignancy rate from epitheliochorial to hemochorial placenta type. This result is consistent with a model in which the species with less invasive placentation are also, on average, less vulnerable to a transition to malignancy.

This brief overview of data about species differences in neoplasm incidence and malignancy rates illustrates that more and higher-quality data are needed to arrive at a firm understanding of the evolutionary patterns of cancer and malignancy rates. At this point, any associations between placental and cancer biology must be considered as preliminary. Within these limits, though, it seems that mammals have a higher incidence of neoplasms than birds, suggesting that neoplasm incidence increases coincident with the origin of the mammalian placenta. Comparative data on reptiles with and without placentotrophic development are currently too sparse to invite scrutiny and must be evaluated in light of the differences between reptilian placental biology and therian placentas. With respect to malignancy rate, the preliminary data are consistent with, but not proof of, a positive relationship between placental invasiveness and malignancy rate. Finally, placental biology is just one factor influencing malignancy rate, and patterns of variation between species need not directly reflect the impact of placental evolution on tumor biology.

## 5. THE CO-OPTION BY THE TUMOR OF TROPHOBLAST MECHANISMS

The core idea of a connection between the evolutionary origin of the eutherian placenta and tumor biology consists of a two-step argument. First is the realization that the evolution of invasive placentation, which is the ancestral form of placentation for eutherian mammals (see above), required the evolution of mechanisms enabling and supporting trophoblast cell invasion into the maternal tissue and the avoidance of immune rejection of the fetus by the maternal immune system. Second, the argument assumes that adaptations that enable the trophoblasts to invade and avoid immune recognition can become co-opted by cancer cells to enhance their chance to escape immune surveillance. Under this model, the evolution of eutherian placentation would have increased the vulnerability of eutherians for developing manifest neoplasms as compared with, say, birds. This is consistent with reports reviewed above that mammals tend to have higher average

neoplasm incidence than birds. Here we summarize some of the mechanistic evidence in support of this model.

The genetic theory of cancer emergence suggests that micro-tumors arise all the time but become manifest only if the tumor escapes immune surveillance. Both tumors and trophoblasts express a relatively large repertoire of tumor-associated antigens and present a remarkably high cellular diversity relative to other tissues (60). However, most early-stage nonviral tumors do not necessarily acquire neo-antigens, which could be recognized by neo-antigen-specific T cell receptors (61).

## 5.1. Which Tumor Hallmarks Are Associated with Placental Evolution?

Several authors have pointed out similarities between the molecular biology of trophoblast cells and tumor cells (7–11, 62–64). In evaluating these claims in the context of placenta–cancer coevolution, we must consider that not all similarities between placenta and cancer may be attributable to placental evolution. Some mechanisms that are shared between cancer cells and trophoblast cells are also shared with other, phylogenetically older, biological processes. For instance, the migratory behavior of cancer cells and extravillous trophoblast cells (EVTs) is shared with mesenchymal cells in general, which is a pan-metazoan cell phenotype. Only mechanisms used by trophoblast cells that evolved in the context and for the purpose of establishing a sustained fetal–maternal interface are relevant for the topic at hand, i.e., whether and how the evolution of the placenta has affected tumor biology. Below, we summarize the claims of placenta–cancer similarities and evaluate whether they are likely the result of placenta–cancer coevolution.

In a recent review, Lala et al. (10) adopted a systematic approach to consider trophoblast–tumor similarities. They used Hanahan & Weinberg's (65) list of 10 cancer hallmarks as a reference and asked which of these are also found in trophoblasts. Of the 10 cancer hallmarks, Lala and colleagues identified 6 that have counterparts in trophoblast biology (**Table 1**). Of these 6, "avoiding immune destruction" is most likely to be related to the evolution of invasive placentation. A caveat of this assertion is that we are unaware of any evidence as to whether or how tumors in nonmammalian species can avoid destruction by the adaptive immune system. The adaptive immune system is a shared derived characteristic of jawed vertebrates (all vertebrates derived from the most recent common ancestor of sharks and humans) (66, 67). Hence, in all vertebrates that possess jaws, i.e., gnathostomes, tumors should be subject to immune attack by the host, and the question is how tumors can escape immune surveillance in nonmammalian species. Interestingly, cancers in amphibians are considered rare and difficult to induce with known cancerogenic agents (68).

The cancer hallmark "tumor-promoting inflammation" is harder to assess. Both tumors and embryo implantation disrupt tissue integrity, in either the uterus or the tumor site. One can thus expect that both will trigger damage-induced inflammation (69). There is evidence that the

**Table 1 Six cancer hallmarks shared with trophoblast, according to Lala and colleagues (10)**

| Cancer hallmark shared with trophoblast | Placenta-related innovation? |
|---|---|
| Sustained proliferative signaling | No |
| Avoiding immune destruction[a] | Yes |
| Tumor-promoting inflammation | Insufficient data |
| Invasiveness | Unlikely, but insufficient data |
| Angiogenesis | No/may be vascular mimicry |
| Aerobic glycolysis | No, a sign of proliferation |

[a]Only "avoiding immune destruction" is clearly a placenta-related innovation co-opted by cancer cells.

inflammatory processes related to embryo implantation are necessary for successful implantation (31) and that they represent an evolutionarily modified inflammatory process, in both eutherians (69, 70) and the opossum, a marsupial (33, 42). The question is thus whether the inflammatory processes at the tumor site borrow mechanisms that evolved in the context of embryo implantation or, alternatively, represent generic damage-induced inflammation. Answering this question will require understanding both the way implantation-related and damage-induced inflammation differ and how inflammation in the tumor-associated stroma differs from generic inflammation. Modified inflammation pathways could be part of the tumor–stroma interaction in eutherian mammals, but we lack evidence that would address this question directly.

"Activation of invasion" is another cancer hallmark where Lala and colleagues see a similarity with trophoblast biology, in particular for EVTs. In humans and other great apes, EVTs are a prominent component of the placental bed and effect, in interaction with uterine natural killer cells, the remodeling of the spiral arteries. EVT formation is reported for all hemochorial placentas (71), with the possible exception of that in the armadillo (72, 73). Formally, the armadillo has a hemochorial placenta, but it is minimally invasive and consists only of placental villi growing into preformed maternal blood sinuses. However, the connection between the mechanisms of EVT invasion and cancer invasion is complicated by the fact that epithelial–mesenchymal transitions are common during animal development. As in the case of inflammation, the open question is whether there are invasive mechanisms that are specific to EVTs rather than shared with other invasive cell behavior in development or pathology, like wound healing.

"Induction of angiogenesis and vascular mimicry" is another cancer hallmark that Lala et al. (10) see as overlapping with placental biology. However, mechanisms that induce angiogenesis by parenchymatic cells are a regular feature of tissue homeostasis. Thus, the trophoblast likely co-opted angiogenetic pathways existing prior to the evolution of eutherian placentation. Mechanisms for eliciting angiogenesis by tumors may not be the product of placenta–cancer coevolution. However, the fact that EVTs can replace endothelial cells of the maternal spiral arteries (74, 75) may be a putative derived characteristic, which could be related to the remarkable ability of tumors to perform "vascular mimicry" (75, 76).

Finally, Lala et al. (10) find a similarity in the so-called Warburg effect, i.e., aerobic glycolysis, between cancer cells and the cyto-trophoblast, but only the undifferentiated cyto-trophoblast cells. The Warburg effect was long understood as a cancer hallmark. But more recently, it became broadly accepted that the Warburg effect is typical of proliferating cells rather than only tumor cells (77). Hence, this cancer hallmark is also unlikely to be the product of placenta–cancer coevolution.

Therefore, out of the six similarities between cancer and placental biology, only the escape from immune surveillance by cancer cells is a likely product of placenta–cancer coevolution. This is because the problem of immune tolerance in an adult organism, long after self-tolerance has developed, is quite specific for the evolution of invasive placentation. It is thus plausible that additional immune-modulating mechanisms had to evolve with the origin of invasive placentation.

## 5.2. The Similarities Between Cancer and Trophoblast Immune Modulation

Similarities between trophoblast (placenta) immune modulation and cancer "immune editing" have been described in several recent reviews (7, 10, 78), and only a brief overview is given here. A widely recognized shared mechanism of immune modulation is the lack of expression of the most specific type 1 major histocompatibility complex genes, such as *HLA-A* and *HLA-B*. Suppression of these genes prevents the recognition of trophoblast cells by the mother's cytotoxic T cells. The suppression of *HLA-A* and *-B* genes is complemented by expression of *HLA-C* and

*HLA-G* (79), which is thought to prevent their recognition by natural killer cells, which would otherwise attack cells that "refuse to reveal their identity" by not displaying HLA-A and HLA-B. Further shared mechanisms are the expression of the indoleamine 2,3 dioxygenase (IDO) enzyme (80); the expression of the inhibitory programmed cell death protein 1 (PDCD1, also known as PD1) receptor ligand, CD274 (also known as PDL1) (81); and the extrathymic differentiation of regulatory T cells in the uterus and the tumor stroma (peripheral Treg or pTreg). The latter aspect of immune tolerance, however, already points beyond the trophoblast or cancer cell because, as we see in the next section, the differentiation of the tolerogenic immune environment in the uterus depends on evolutionary changes in the maternal cells rather than the trophoblast cells and thus implies that placenta–cancer coevolution involves the coevolution of the trophoblast with its maternal environment (82).

IDO is one of the enzymes involved in tryptophan catabolism. IDO has been implicated in maternal immune tolerance since it was discovered that pharmacological inhibition of IDO can lead to the resorption of allogenic fetuses in mice (83, 84). The effect of IDO was ascribed initially to local tryptophan depletion. Tryptophan depletion specifically affects T cells, but the mechanistic involvement of IDO in maternal immune tolerance seems to be more complicated (85). IDO expression has also been linked to immune tolerance toward tumor cells (86, 87). Kynurenine is a natural ligand of arylhydrocarbon receptor and may aid cancer progression through this mechanism (88).

PD1/PDCD1 is an immune checkpoint that, when engaged with its ligand, PDL1/CD274, causes apoptosis in cytotoxic T cells. PDL1 expression has been detected in both trophoblast and malignant cancer cells, explaining their resistance to maternal and host immune surveillance (89). Other immune checkpoint controls also contribute to the immune tolerance (90).

The problem in explaining this convergence of immunomodulatory mechanisms between placental and cancer cells is that cancer, as such, is not an adaptive trait, because, with the exception of a few transmissible cancers, cancer cells die with their host. One possible explanation, however, is that cancer itself is a somatic evolutionary process whereby the somatic fitness of a cancer cell is enhanced by its ability to escape immune surveillance. Thus, the similarity between cancer and placenta immune modulation could be thought of as convergent adaptive evolution of cancer cells and trophoblast cells. If that were true, one would expect that cancers of nonmammalian vertebrates also evolve the same immune-editing properties as eutherian cancers. We are not aware of evidence for noneutherians or nonmammalian animals expressing the same immune-modulatory genes.

A complementary possibility for the similarity between placental and cancer immune editing is that the convergence between placental and cancer gene expression is made more likely because of shared gene regulatory mechanisms (i.e., parallel evolution). Costanzo et al. (7) proposed one such model for the similarity between trophoblast and cancer biology, noting that trophoblast and cancer cells share functional genomic features, namely, widespread demethylation and derepressed chromatin. This shared feature also explains the fact that both cell classes experience transposable element activation owing to the removal of suppressive marks that normally silence transposable elements. For cancer cells, Costanzo et al. explain these DNA and chromatin features as a consequence of replicative and DNA damage stress that cancer cells tend to experience. The authors cite evidence that these forms of stress tend to induce widespread erasure of repressive chromatin marks (91). The core argument is that replicative stress leads to a genomic state similar to that which exists naturally in trophoblast cells, and thus cancer cells. This similarity in genomic regulatory state may allow cancer cells to gain access to gene regulatory networks that evolved in the trophoblast cell. This model neatly explains how cancer cells can converge to a functional profile that is similar to trophoblast cells serving their parallel needs, namely, to escape from maternal/host immune surveillance.

The remaining problem with these models is to explain why trophoblast cells, in contrast to other specialized cell types, have a gene regulatory landscape characterized by widespread removal of repressive chromatin and specific DNA modifications. Costanzo et al. explain this via the fact that the trophoblast cell fate commitment is the first to develop after the cleavage divisions of the fertilized egg. The alternative cell fate to that of the trophoblast is the inner cell mass, which is the paradigm of a totipotent cell population. High potency to differentiate into many possible cell-type identities is also associated with very few repressive chromatin modifications. Costanzo and colleagues argue that the trophoblast has these features because of its close developmental relationship to the totipotent inner cell mass. Finally, demethylation and transposable element activation can lead to higher mutation rates. In this context, it is interesting that Coorens et al. (92) recently highlighted the extensive mutations that happen in the human placenta, including even aneuploidy, similar to the high mutation loads in cancer.

A slightly different model arises from the detailed comparison of epigenomic profiles of mouse extraembryonic tissues (ExEs) with those of human cancers (34). Although in the blastocyst the inner cell mass and the trophoblasts are characterized by global hypomethylation, the subsequent differentiation of the inner cell mass into the epiblast (leading to the embryo proper) and the ExE leads to specific epigenomic features in the EXE that are shared with many cancer cells. During epiblast–ExE differentiation, the ExE acquires hypermethylation of a subset of CpG islands. This subset of CpG islands are found in promoter sequences that remain unmethylated in somatic tissues. These promoters preferentially belong to developmentally regulated genes and thus seem to be repressed by DNA methylation in the ExE. Interestingly, such a pattern has also been found in many human cancers, suggesting a convergence of epigenetic regulation between placental and cancer cells, specifically of developmental genes belonging to the *Gata* and *Hox* gene families (34). In ExE, this methylation pattern is induced by FGF and Wnt signals, which is shedding light on the role of these signaling pathways in cancer (93, 94).

To complement the models of Costanzo et al. (7) and Smith et al. (34), we note that the trophoblast, as well as the differentiation between ExE and the embryo proper, as understood in mouse and human embryology, is a eutherian or at most a therian novelty. As mentioned above, in eutherian mammals, the first cell-fate decision after fertilization and cleavage divisions is that between the trophoblast and inner cell mass (95). An embryo consisting of an inner cell mass and a trophoblast is called a blastocyst. Next, the inner cell mass divides into an epi- and a hypoblast, which also give rise to additional ExEs, such as the amnion and yolk sac. Only then does the embryo proper start to form. Already in marsupials, the sister taxon of eutherian mammals, the early developmental stages are different (96–98). The opossum first forms a blastula-like stage (i.e., a hollow ball of cells) without an inner cell mass and then segregates cells to populate the inner space of the blastula. In nonmammalian amniotes, development follows a completely different schedule. There, the rudiments of the embryo proper develop immediately from the cells produced during cleavage divisions, and the ExEs (amnion, chorion) come later from the yolk sac material around the developing embryo. Hence, the outermost layer of fetal membranes is derived from the embryonic ectoderm, whereas in eutherians, the trophoblast is never in continuity with the embryonic ectoderm. We are not aware of molecular studies that investigate the identities of the nonmammalian chorionic cells, but we anticipate that they might be very different from eutherian trophoblast cells, given their different developmental histories. Hence, early eutherian development resulted from a radical reorganization of the ancestral condition: a yolk-rich egg with discoidal cleavage from which an embryo emerges and where the ExEs form gradually after gastrulation and the start of somitogenesis of the embryo proper. In eutherians, ExEs form first, and the embryo proper forms later.

Based on the comparative embryological evidence outlined above, we must understand the phrase "the origin of the eutherian placenta" as "the origin of the precocious segregation of the extraembryonic cell lineages from the embryo," and the trophoblast as a new cell type or cell-type family (consisting of the cyto-trophoblast, syncytio-trophoblast, and extravillous trophoblast, where they exist). The trophoblast cell-type family has strong similarities with cells under replicative or DNA damage stress. One may speculate that the gene regulatory identity of trophoblast cells may have evolved from modifying the replicative stress response network similar. If that is the case, the origin of trophoblasts would fit into a growing pattern of evidence that shows that other cell types also likely evolved from the co-option of stress response mechanisms. Examples are the somatic cells of multicellular *Volvox* algae, the shaft cells of slime molds, the components of the eye, and the decidual stromal cell of eutherian mammals (99–103).

In summary, a closer evaluation of the evolution of mammalian placentation suggests that the situation in eutherians is not correctly characterized by referring to the "evolution of placentation," because placentas of various forms have evolved in many vertebrate lineages (see 104, 105). Rather, one must consider that the early eutherian embryo, the blastocyst, is unique among amniotes in being the product of a radical reorganization of early developmental events. The evidence summarized above suggests that the evolutionary origin of the trophoblast and ExE cell lineages may have advantaged tumor cells that were modified through the epigenetic modifications caused by either the replicative stress response (7) or FGF/WNT signaling, as various studies (e.g., 34) suggest. In addition, we must remember that reactivation of a trophoblast-like genetic program is not an isolated example of cancer recruitment of developmental genes. This has also been documented for fetal genes, a process known as oncofetal gene expression (106, 107).

## 6. THE COEVOLUTION OF UTERINE AND CANCER-ASSOCIATED STROMA

The process of embryo invasion into the maternal tissue and establishment of immune tolerance is understood primarily as an interaction between trophoblast and maternal cells of the uterus and the maternal immune system. Evolutionary changes in the fetal–maternal relationship can thus be due to both changes in fetal trophoblast cells and evolutionary changes in maternal cell function. Consequently, when considering evolutionary changes in the maternal–fetal relationship, we must ask whether these changes are due to changes in trophoblast cells, or maternal cells interacting with the embryo, or both. In the same vein, cancer progression is the result of an interaction between the neo-plastic cells and the cells that form the cancer-associated stroma (108). Broadly speaking, the cancer stroma, like the endometrial stroma of an implanting embryo, consists of the host immune cells as well as fibroblasts. In the cancer stroma, the tissue fibroblasts assume a special phenotype, called the cancer-associated fibroblast (CAF). In this section, we focus on evolutionary changes in the maternal endometrial stroma and whether these evolutionary changes have correlated effects on the tumor-associated stroma.

### 6.1. Evolutionary Changes in the Maternal Immune System

In the previous section on the co-option of trophoblast mechanisms by the tumor, we argued that the evolutionary changes in the placenta most clearly related to the evolution of invasive placentation are mechanisms that ensure the escape from maternal immune surveillance, such as trophoblast suppression of HLA-A and -B gene expression. Other mechanisms mentioned above include trophoblast expression of IDO and PDL1/CD274. However, the expression of both IDO and PDL1 is part of a more comprehensive cell communication network that contributes to immune tolerance toward the fetus, namely, the creation of a maternal immune environment

dominated by extrathymic (i.e., peripheral) regulatory T cells (109). During embryo implantation, pTreg cells in the uterus interact with invading trophoblast cells via kynurenine, thymic stromal lymphopoietin (TSLIP), and galectin 1 (LGALS1) to stabilize the pTreg population. In turn, Treg cells sequester IL2 and thus prevent the local proliferation of proinflammatory Th1 and Th17 cells. Tolerogenic dendritic cells and uterine natural killer cells are recruited into the immune-tolerant stroma by Treg cells via TGFb, IL10, kynurenine, and other signals.

The most convincing smoking gun showing that the evolution of cells of maternal origin is essential for the evolution of invasive placentation is the evolution of pTreg cells active in the uterus during pregnancy. These cells express the transcription factor FOXP3, a critically important Treg cell-type identity factor. The expression of *Foxp3* in the uterus depends on a *cis*-regulatory element called CNS1 (conserved noncoding sequence 1), which, however, is dispensable for the development of thymic Treg cells or pTreg cells in the digestive system (110). The existence of the CNS1 regulatory element is limited to eutherians, and thus plausibly evolved coincident with maternal immune tolerance (38). In the cancer stroma, it is also the $FOXP3^+$ pTreg cells that contribute to the immune-tolerant niche for the tumor, and their presence in the tumor stroma is associated with worse patient outcomes (110–112). If these tumor-associated pTreg cells express FOXP3 via the CNS1 *cis*-regulatory element, it would be the most direct evidence that genetic elements that evolved for the purpose of maternal immune tolerance toward the fetus have been co-opted for the process of cancer progression. A PubMed search for "(Cancer) AND (FOXP3) AND (CNS1)" did not yield papers that directly tested the involvement of CNS1 in the development of cancer-associated Treg cells. Nevertheless, the evolution of *Foxp3* regulation via the evolutionary origin of CNS1 is the best evidence that maternal stromal cells evolved to create an immune-tolerant environment for the fetus in the uterus, which likely also plays a role in cancer progression.

## 6.2. Evolutionary Changes in the Maternal Stromal Fibroblasts (the ELI Hypothesis)

Another maternal innovation for accommodating an invasive placenta is the evolutionary origin of the decidual stromal cell (DSC). The DSC differentiates from the endometrial stromal fibroblast (ESF) of the uterus, under the influence of either progesterone alone during the secretory phase of the menstrual cycle (apes and old-world monkeys) or signals from the implanting embryo in addition to progesterone. The decidual cells are essential for pregnancy maintenance and regulate the immune environment of the uterus, as well as the degree of placental invasiveness (30, 113, 114). Decidual cells exist only in eutherian mammals and thus likely evolved in the stem lineage of eutherian mammals, coincident with the evolution of invasive placentation (51). Whether DSC evolution has affected CAF biology is unknown currently. Is the transcriptional program for decidualization replicated in the desmoplastic reaction in the tumor microenvironment? Our results also indicate that DSCs resist EVT invasion more strongly than the undifferentiated ESF do, suggesting that decidualization may have been a maternal adaptation to limit placental invasion (36). However, whether these mechanisms are also deployed in cancer stroma is yet to be tested.

As mentioned in Section 3 on the evolution of mammalian placentation, the most recent common ancestor of eutherian mammals likely had an invasive hemochorial placenta (50–52). Within the eutherian clade, however, several clades evolved a noninvasive placenta, most notably among the hoofed animals like the cow, sheep, and pig, as well as horses and their relatives. This loss of invasive placentation has been attributed to evolutionary changes in the endometrium, i.e., owing to the evolution of the maternal tissue, rather than to the evolution of the trophoblast/placenta. Two lines of evidence support this conclusion. On the one hand, ectopic embryos of the pig are still invasive outside the uterus, even though, in the uterus, the placenta is not invasive (115).

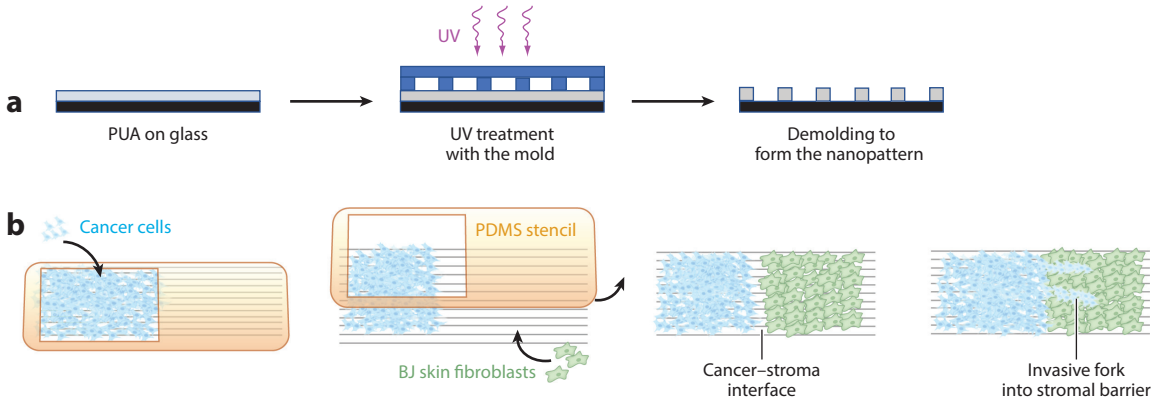


**Figure 2**

Invasibility assay to test whether an invasive cell population (e.g., trophoblast or cancer cells) can invade a monolayer of stromal cells (e.g., endometrial or skin fibroblasts). From the standpoint of the stromal cells, this experiment tests their invasibility, meaning their vulnerability to invasion. (*a*) Production of a nanopatterned surface that mimics collagen fibers. Parallel ridges restrict the migration of the invasive cell population to one dimension, making quantification more sensitive and reproducible. (*b*) Outline of the experimental procedure to test invasibility. A stencil covers part of the nano-surface, and cancer cells are seeded in the open area. After the stencil is removed, the stromal cells are seeded on the remaining surface, creating a cancer–stromal interface. Monitoring of the interface allows one to quantify the invasion of the stromal cell monolayer by the cancer cells. This assay was used to compare the invasability of stromal cells from the cow and human (56) or human stromal cells with altered gene expression (75). BJ cells are a human fibroblast cell line. Abbreviations: PDMS, polydimethylsiloxane; PUA, polyuratane; UV, ultraviolet.

This shows that the pig placenta's noninvasive nature is due to evolutionary changes in the endometrium rather than in the trophoblast. The other line of evidence is based on in vitro tests of invasibility, i.e., experiments that assess the degree to which endometrial stromal cell populations are invaded by trophoblast cells (36) (**Figure 2**). Trophoblast cells placed next to endometrial fibroblasts from the cow are unable to invade the lawn of cow ESF. In contrast, trophoblast cells (from human or cow) placed next to human ESFs can readily invade. Hence, the in vivo difference in terms of placental invasion is reproduced in an in vitro assay of endometrial fibroblast invasibility, showing that the maternal tissue is responsible, at least in part, for the noninvasive nature of the cow placenta. Species with less invasive placentas also have a less invasible endometrium.

The same study found that the invasibility of skin fibroblasts by cancer cells from the same species (human and cattle) parallels that of the invasibility of the endometrial stromal cells. In cattle, the skin fibroblasts are less readily invaded by melanoma cells than the skin fibroblasts of humans. This finding explains, in part, the low malignancy rate found in cattle (35). In humans, melanocytic lesions are highly likely to turn malignant (116), while in cattle very large melanocytic lesions can be benign (117). Furthermore, manipulating the gene expression of human fibroblasts to make them more similar to cattle cells makes human cells less invasible (36, 118). And a comparison of invasibility-regulating genes identified from comparison of several eutherian species with different placental invasion showed them to be correlated to patient survival based on data from the Tumor Cell Genome Atlas (37). These findings suggest that a systematic understanding of differences in gene expression among species with differing placental phenotypes may aid in identifying novel avenues of intervention to prevent malignancy in human patients.

The results of comparative studies of cells from the placental stroma and the cancer-associated stroma show that both placentation and cancer progression result from interaction between the invading cell population (trophoblast or cancer cells) and the surrounding stroma (see also 119 for EVT and 120 for cancer). This idea has been summarized in the ELI (Evolved Levels of

Invasibility) hypothesis (36), which states that *placental mammals evolved different levels of invasibility of their uterine stroma due to maternal changes in the biology of the stromal cells and that these differences have pleiotropic effects on the likelihood of malignant progression*. The prediction is that species with less invasive placentas tend to be less vulnerable to malignant transformation (see Section 4.2 on species differences in malignancy rate). The ELI hypothesis implies that by comparing gene expression and cell biology in cells from species with different placental phenotypes, we can identify genes and mechanisms relevant for controlling disease progression in humans.

## 7. THE ROLE OF GENOMIC CONFLICT IN PLACENTA–CANCER COEVOLUTION

Genomic conflict is considered a driving force of the evolution of reproductive mechanisms and is also discussed in the context of the placenta–cancer coevolution (121–123). The core idea of genomic conflict theory is that the fitness interests of the mother and those of the paternal part of the fetal genome do not necessarily align. This theory is most successful in explaining parental gene imprinting and has been reviewed and discussed extensively (124, 125). Nevertheless, the mathematical theory of genomic conflict predicts that fetal–maternal conflict happens in only a narrow range of maternal investment (126, 127). The use of conflict as an explanation for reproductive phenomena therefore would critically require, in each instance, an argument showing that the situation in question is indeed situated within this narrow range of parameters that lead to genomic conflict. Uncritically assuming genomic conflict as the cause for every feature of the reproductive process puts this theory in danger of becoming a new Panglossian paradigm, i.e., a collection of just-so stories.

Genomic conflict can arise in mammalian evolution whenever there is a direct negotiation between parent and offspring about the amount of resources invested in an offspring and thus is linked to the placental mode of reproduction (or analogous situations in seed plants). Regulation of invasiveness may be a site of conflict and is at the same time a process that might be co-opted for cancer invasion. However, the body of evidence invoked in support of a role of genetic conflict in the evolution of cancer risk can also be explained differently. Evolution of placental invasiveness can affect cancer and malignancy rates (see Section 6) regardless of whether genomic conflict exists in these cases.

## 8. CONCLUSIONS AND OPEN QUESTIONS

Although similarities between invasive placentation and cancer progression are noted widely in the literature, a critical evolutionary evaluation shows that only a small subset of these similarities can actually be explained by the evolutionary origin of the eutherian placenta or its subsequent evolutionary modifications. The fundamental observation is that malignant cancers occur in all multicellular forms of life, many hundreds of millions of years earlier than the evolution of mammalian placentation.

The best-supported links between cancer hallmarks and the evolution of eutherian placentation are (*a*) immune avoidance by trophoblast and cancer cells by suppressing the expression of HLA-A and -B genes and the expression of HLA-C, -E and -G genes; (*b*) the evolution of maternal tolerogenic peripheral regulatory T cells; and (*c*) the evolution of maternal adaptations that restrict or prevent trophoblast invasion with its pleiotropic effects on the host to prevent or limit malignant cancer invasion. Of note, the evolution of placentation seems to contribute to both pro- and anti-malignancy mechanisms, and the role of maternal adaptations is equally important to the evolutionary contributions of the trophoblast.

A systematic review of the evolution of placentation in mammals suggests potential avenues of coevolution with cancer biology that, to our knowledge, have not been explored. These are the questions of (*a*) whether evolutionary changes in uterine inflammatory processes during embryo implantation have affected the nature of the inflammatory processes at the tumor niche; (*b*) whether the evolution of the decidual cell type has affected the nature of the CAFs; (*c*) whether the evolution of highly invasive EVTs has changed the invasiveness of cancer cells compared with cancers from species without EVTs; and (*d*) whether cancer cells from nonmammalian gnathostomes can immune-edit the host immune response. Answering these questions will require comparing the molecular cell biologies of nonmammalian and mammalian cancers to assess whether placental evolution affected mammalian cancer biology. Unfortunately, little effort has been expended to understand the cell biology of nonmammalian cancers. However, a carefully conducted comparative study of cancers and placentas over a wide taxonomic range could lead to a deeper understanding of the human vulnerability to cancer malignancy and identify mechanisms that may be targeted for therapeutic intervention.

## DISCLOSURE STATEMENT

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