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Hypothesis: Bacterial induced inflammation disrupts the orderly progression of the stem cell hierarchy and has a role in the pathogenesis of breast cancer

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ABSTRACT

Background: The hierarchical model of stem cell genesis is based on the idea that the number of cell divisions between the zygote and fully differentiated epithelial cells is kept close to the minimum, which is log to the base 2 of the total number of cells produced in a human lifetime. The model assumes the orderly progression of stem cell divisions requires precise control at every stage in development. If the orderly progression is maintained then cancer will be rare. A prediction of the model is that if the orderly progression of the stem cell hierarchy is disturbed by trauma, ulceration or inflammation then cancer will occur.

Hypothesis: Bacterial induced inflammation in breast ducts disturbs the stem cell hierarchy and is a cause of breast cancer.

Evidence: Mammalian milk is not sterile. It contains a range of bacteria, derived endogenously by the entero-mammary circulation. The dominant flora consists of lactose fermenting bacteria. Pregnancy and breast feeding reduce the risk of subsequent breast cancer. The implication is that a lactose fermenting bacterial flora in breast ducts is protective. Malignant and benign breast tissue contains bacteria derived endogenously, but studies so far have not revealed a specific flora associated with malignancy. Periodontitis is associated with oral, oesophageal, colonic, pancreatic, prostatic and breast cancer. The pathogenic bacteria which cause periodontitis spread endogenously to cause inflammation at other epithelial sites. Meta-analysis of epidemiological studies shows that the consumption of yoghurt is associated with a reduction in the risk of breast cancer.

Conclusion: The hypothesis, although not proven, is supported by the available evidence. Lactose fermenting bacteria protect but pathogenic bacteria which induce inflammation raise the risk of breast cancer. The consumption of yoghurt also appears to be protective.

Introduction

The prevalence of carcinoma rises as a power function of age with an exponent of approximately seven. This observation led epidemiologists in the 1950s and 1960s to propose multi-stage or multi-hit models of carcinogenesis [1,2]. Subsequently molecular biologists showed that the multiple hits were independent deleterious mutations in genes concerned with growth control [3–5]. Even though there are billions of stem cell mitoses occurring every day within our bodies, the chance of a single stem cell acquiring the *m* specific deleterious mutations for malignancy is sufficiently low that cancer is rare until near the end of our lifespan. The value of *m* is approximately four for the common cancers such as colon, lung, breast and prostate [6,7]. Once a stem cell has acquired the specific set of mutations it will grow out of control to form a monoclonal malignant tumour.

Differentiated epithelial cells are produced from stem cells. This process has been studied most intensively in the crypts of the colon and the small intestine [8,9]. The conventional view is that stem cells divide asymmetrically every few days. One daughter cell becomes the new stem cell and the other undergoes up to 8 successive divisions producing up to 256 differentiated cells that line the crypt for one or two days before they are replaced by the products of the next stem cell division. This model, however, leads to a paradox [10]. Men are a thousand times larger than mice and live 30 times as long. This means that the prevalence of cancer in men should be 30 raised to the power *m* multiplied by 1000 (i.e approximately one billion) times higher than in mice. In fact the prevalence in men and mice is similar, rising in both species to similar levels at the end of their respective lifespans.

The hierarchical model of stem cell genesis differs fundamentally from the conventional model of stem cell genesis [11–15]. In the

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hierarchical model all differentiated epithelial cells are produced in fewer than 60 divisions from the zygote. The result is that cancer will be rare in both mice and men unless the orderly progression of the hierarchy is disrupted [Appendix A]. Imagine a zygote undergoing 30 successive divisions to produce one billion stem cells. These stem cells are labelled generation A. It is possible for each stem cell of generation A to produce 256 fully differentiated cells of generation Y every day for at least 100 years. The process involves the production of a linear hierarchy of quiescent stem cells which awake in strict order to provide the terminally differentiated cells (Appendix A).

If the number of cell divisions between the zygote and fully differentiated cells is below 60 then cancer will be rare. But if the orderly progression of the hierarchy is disrupted and the stem cells start to cycle every few days then the risk of cancer will rise. Inflammation is one process that could disrupt the hierarchy by destroying quiescent stem cells and the surrounding stromal cells. Repair of the hierarchy is likely to be effective in the first half of life but perhaps less effective in the second half as ageing impairs the repair process.

A key component of the conventional model of carcinogenesis is that malignant tumours are monoclonal because the accumulation of *m* specific mutations is sufficiently unlikely that only one, at most, of a large set of stem cells will acquire the full set. Thus it came as a surprise when Sir Nicholas Wright's group in London, UK, found that many gastro-intestinal neoplasms are oligoclonal at inception [13]. This observation, however, fits with the hierarchical model. The orderly progression of the hierarchy is disturbed, many stem cells start to cycle daily, several stem cells independently acquire the mutations for malignancy but only one clone survives to produce an invasive malignant tumour.

These ideas lead to the prediction that most carcinomas have a local cause in which trauma, ulceration or inflammation disrupts the orderly progression of the hierarchy and leads to cancer [15]. In this article we explore the extent to which these ideas could apply to breast cancer. Lancastrian scientists have previously presented evidence that trauma can cause breast cancer [16], and also suggested that viral induced inflammation could have a role [15]. But in this paper we specifically propose the hypothesis that bacterial induced inflammation also has a role in the pathogenesis of some cases of breast cancer.

Mammalian milk is not sterile

Human breast milk in healthy women contains bacteria including staphylococci, streptococci, corynebacteria, lactic acid bacteria, proprionibacteria and bifidobacteria. These organisms have been demonstrated using standard culture techniques. More recently bacterial DNA and RNA in milk have been analysed and these studies have shown a broader range of bacteria including anaerobes [17–19].

The analysis of bacterial DNA and RNA is not without problems. Contamination is common and demonstrating genetic material does not mean the bacteria are viable. It is not always possible to identify species and quantitation is difficult. However in spite of these problems there is a general consensus that mammalian milk has evolved through millions of years to provide the infant with optimal nutrition and an optimal microbial flora. Milk contains lactose fermenting bacteria which form a commensal flora in the upper and lower gastro-intestinal tract of the infant. In addition there are many other bacteria, not only commensals but also pathogens, in low dose, which will prime the immune system. The bacteria in milk are carried through the blood stream from other epithelial surfaces. They are not mere contaminants that enter the milk after it has been ejected from the nipple [20–24].

Milk from humans, cows, sheep and goats contains a similar range of bacteria but there is variation by species, and within a species by geography, season and length of gestation. Lactose fermenting bacteria are commonly found in milk and are likely to occupy the breast ducts of women during lactation and for an unknown period after lactation.

Human lactation protects against breast cancer

The epidemiology of breast cancer has been extensively studied [25,26]. Risk factors include age, late age at first birth, nulliparity, early age at menarche and late age at menopause. Pregnancy and lactation are protective. The collaborative group study [27] performed a meta-analysis of 50,302 women with breast cancer and 96,073 controls. The relative risk of breast cancer decreased by 4.3% (95% CI 2.9–5.8%, $p < 0.0001$) for every year of breast feeding and 7% (95% CI 5–9%, $p < 0.0001$) for each birth. The authors state that "It is estimated that the cumulative incidence of breast cancer in developed countries would be reduced by more than half, from 6.3 to 2.7 per 100 women by age 70, if women had the average number of births and life time duration of breast feeding that had been prevalent in developed countries until recently."

The breast duct flora in non-pregnant women

The bacterial composition of aseptically collected human breast tissue and nipple aspirates has been determined in patients with breast cancer and benign breast disease [28–34]. These studies have been undertaken in the last few years using next generation sequencing techniques. The key findings are:

- Benign and malignant breast tissue and nipple aspirates, from patients with benign and malignant disease, are not sterile.
- The bacterial composition within the breast tissue is different from the flora of the skin and nipple, and from the infant's oral cavity. Thus it appears that the bacteria within the breast are derived endogenously from other epithelial surfaces and are not derived directly from the skin around the breast or from the infant's mouth.
- The range of bacteria differs between benign and malignant tissue in some of the studies, but there is no consistent pattern across the studies undertaken so far.
- There is no specific dysbiotic flora that can be directly linked with cancer or carcinoma in situ at this stage, but further work is underway.

Periodontitis

Chronic periodontitis is a bacterial induced chronic inflammation of the gums which leads to destruction of the cementum that holds the teeth firmly in their sockets. It is caused by a number of bacteria that interact to cause tissue damage. Key pathogens involved in the process include *Porphryomonas gingivalis*, *Fusobacterium nucleatum*, *Treponema denticola*, *Aggregatibacter actinomycetemcomitans* and *Tannerella forsythia.* These organisms produce various toxins that enable them to survive within the body and resist immune destruction. For instance *P. gingivalis* secretes gingipain proteases which protect the organism against intracellular destruction. Periodontitis is the commonest cause of tooth loss in middle and later life. This condition is associated with a wide range of chronic conditions including senile dementia, atherosclerosis, rheumatoid arthritis and cancer. The last includes cancers of the gastrointestinal tract including oral, oesophageal, gastric, and colonic [35]. There is also an association with cancer of the breast, pancreas and prostate [36,37]. In all these conditions inflammation is thought to play a key role. Inflammatory cytokines are released at the site of inflammation in the gums and do have a general effect. But it is much more likely that organisms from the mouth are carried through the blood to distant sites and cause direct tissue destruction and inflammation. In the breast we envisage that the pathogenic bacteria directly damage epithelial cells and lead to disruption of the stem cell hierarchy.

Dairy consumption and breast cancer risk

Zang et al. [38] undertook a systematic review and meta-analysis of the association between dairy intake and breast cancer. They analysed 22 prospective cohort studies with 1,566,940 participants and five case control studies with 33, 372 participants. High and modest dairy consumption significantly reduced the risk of breast cancer compared with low dairy consumption (RR 0.9 (95% CI 0.83–0.98) and 0.94 (95% CI (0.91–0.98) respectively). High consumption was greater than 600 g daily, modest was 400–600 g and low less than 400 g. Conversions involved estimates of one serving equals 200 g, one cup equals 237 g and one glass equals 200 g. Subgroup analysis showed that yoghurt (RR 0.91, 95% CI 0.83–0.99) and low fat dairy (RR 0.85, 95% CI 0.75–0.96) reduced the risk of breast cancer but other dairy products did not.

Dong et al. [39] also undertook a meta-analysis of prospective cohort studies of the association between dairy consumption and breast cancer. They analysed 18 prospective cohort studies with 24,187 cases and 1063, 471 participants. There is obviously considerable overlap between this analysis and that undertaken by Zang et al. [38]. They found essentially similar results. The relative risk of breast cancer for the highest intake of dairy food compared with the lowest was 0.85 (95% CI 0.76–0.95). For milk consumption the relative risk was 0.91 (95% CI 0.8–1.02). There was a significant dose-response relationship of total dairy food, but not milk, with breast cancer risk.

Discussion

The idea that bacteria, which are mutagenic, can cause cancer is not new. Indeed there has long been suspicion that the colonic bacterial flora has a role in the pathogenesis of colonic cancer [40]. The number of stem cells and stem cell mitoses is greater in the small intestine than in the colon, but cancer is much more common in the colon. Furthermore bacterial dysbiosis is often invoked as a cause of ulcerative colitis which is a pre-malignant condition. More recently *Fusobacterium nucleatum* has received attention. It is consistently associated with both ulcerative colitis and colonic cancer [41]. This organism can invade epithelial cells and inhibit growth control mechanisms. The best evidence linking bacteria to cancer, however, is *Helicobacter pylori* [42] which are the accepted cause of both gastric adenocarcinoma and gastric lymphoma. *H. pylori* are attached to the surface of gastric epithelial cells and damage their tight junctions so that the bacteria are in direct continuity with the gastric tissues (i.e. water soluble molecules can diffuse passively between the bacteria and cells in the gastric mucosa).

The relationship between the colonic bacterial flora and colonic mucosa has been extensively investigated in both mice and men [40–49]. Bacteria are required for the host to develop a full repertoire of immunity and are capable of inducing both inflammation and tolerance, presumably to promote their own survival and to protect their niche. Bacteria have the power to turn cellular gene expression on and off at the genomic level. Bacterial products such as short-chain fatty acids modulate epigenetic programming of cells, through (de)methylation and (de)acetylation of DNA [43,44]. This can lead to over expression of oncogenic or under-expression of anti-cancer e.g. anti-apoptotic, genes in a specific tumour microenvironment. Infectious agents can also utilise immunosuppressive pathways to promote their survival. One such pathway is the induction of indolamine-2,3 dioxygenase (IDO) [45]. IDO is upregulated in cancer and high expression is linked to poor prognosis [46,47] as the cancer cells are shielded from anti-cancer immunity [50]. This complex interaction of bacteria, epithelial cells and the immune response can then lead to mutations in stem cells. But cancer is a consequence of the accumulation of mutations in stem cells over a long period of time and that cannot occur if strict control of the hierarchy is maintained. This is simply because any mutations that do form in the stem cells will be lost after a few days when the stem cell and its progeny are shed. Thus the mechanism proposed in this article is that the bacteria which cause cancer induce inflammation which leads to the destruction of the stem cells and the surrounding stromal cells. If repair fails and the stem cells start to cycle then bacteria can cause the accumulation of mutations in stem cells. But if stem cells cycle beyond 60 divisions genetic instability will occur even in the absence of bacterial induced mutagenesis. This model fits with *H. pylori* induced neoplasia because the bacteria are more likely to induce inflammation if they are in direct continuity with the immune system. The model also fits with the putative role for *F. nucleatum* in colonic neoplasia as this organism is also capable of invading epithelial cells.

The key concept in this model is that bacteria cause cancer by interfering with the orderly progression of the stem cell hierarchy and this involves local destruction of stem cells and the surrounding stromal cells by locally induced inflammation. But once the hierarchy is disturbed the subsequent progression of cancer can be influenced by bacteria in a number of ways as indicated above. Furthermore, the bacteria might be in direct contact with the aberrant cells or they might act from more distant sites. In particular there is evidence that the composition of the microbial flora can influence tumour progression and the response to chemotherapy [48,49]. The bacteria which cause cancer could also induce tolerance and thereby protect the dysplastic and malignant cells against immune rejection.

Breast ducts are not sterile [17–24]. Following pregnancy and lactation they will have a flora which is dominated by lactose fermenting bacteria. This appears to be protective against the development of cancer [25–27]. However, the process of bacterial transportation between epithelial surfaces appears to continue following pregnancy and the ducts acquire a different flora over time [28–34]. Bacteria enter the body in food and water and in inspired air. Thus the initial reservoir of bacteria is on and between the non-keratinised stratified squamous epithelium of the oral cavity, oropharynx and oesophagus. One route is through the stomach to the small and then large intestine, but many bacteria are destroyed by stomach acid. The other route is by the blood to other epithelial surfaces, and this appears to be much more common than previously assumed.

Transient bacteraemia due to oral alpha haemolytic streptococci has been recognised for many years. It is the cause of sub-acute bacterial endocarditis [51,52]. But more recently the role of pathogenic oral bacteria in causing periodontits has been defined [35,36]. A number of pathogens including *Porphrymonas gingivalis* invade the tissues around the teeth and cause destruction of the cementum which holds the teeth firmly in their sockets. The pathogens are present within and between the squamous epithelial cells and in the soft tissue adjacent to the cementum. Low grade inflammation over many years leads to gum retraction and eventually tooth loss. These pathogenic bacteria are transported through the blood to other sites where they also initiate low grade inflammation. Periodontitis is associated with Alzheimer's disease, atherosclerosis, and carcinoma at several sites including the breast and pancreas. Breast tissue rarely shows marked chronic inflammation as seen in ulcerative colitis and *H. pylori* associated gastritis. But low grade inflammation induced by organisms such as *P. gingivalis* would not be clinically apparent. These organisms, however, are invasive and could disrupt the stem cell hierarchy in the breast.

Breast carcinoma in situ is an oligoclonal proliferation of potentially malignant cells. The cells are clearly abnormal as assessed by microscopy and this must be apparent to the immune system. Why are the cells not eliminated? Perhaps because the bacteria that caused the problem are still present and still inducing a degree of tolerance. The idea that bacterial induced inflammation causes cancer and bacterial induced tolerance subsequently protects the aberrant cells against rejection is worthy of serious consideration [53]. Indeed there is evidence that dysbiosis in mice promotes invasion and metastasis of breast cancer and this may act through the mechanism of tolerance.

The hierarchical model of stem cell genesis directly predicts that trauma and bacterial induced inflammation will cause cancer. There

seems to be a solid body of evidence to support this idea in relation to breast carcinoma. Furthermore there is a simple, inexpensive potential preventive remedy; which is for women to consume natural yoghurt on a daily basis [54]. Lactose fermenting bacteria have the potential to displace pathogenic bacteria that cause periodontitis in both the oral cavity and in the breast. It is also possible that yoghurt could reverse ductal carcinoma in situ if tolerance inducing bacteria can be displaced.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A

The basic hierarchical model

Consider a single zygote which divides through 30 successive divisions to produce a billion stem cells of generation A. Each stem cell of generation A is placed at the base of an anatomical niche such as a colonic crypt. The generation A stem cell than divides to form two cells of generation B. One of the generation B cells becomes a long lived quiescent stem cell but the other cell of generation B divides to form two cells of generation C. The process then is repeated with one generation C cell becoming quiescent and the other dividing to form two cells of generation D. This process continues until there is a linear hierarchy of quiescent stem cells and two cells of generation Q:

BCDEFGHIJKLMNOPQQ

Each generation Q cell then divides symmetrically through 8 divisions to form 256 cells of generation Y. The generation Y cells are fully differentiated epithelial cells and occupy the anatomical niche for several days before they are shed and replaced. Thus an anatomical niche will have 2R, 4S, 8T, 16U, 32V, 64W, 128X and 256Y cells at any one time if the division time is 24 h and the fully differentiated cells survive for 24 h. In this case half the cells will be mitotically active and half not. If the differentiated cells survive for more than one day there will be proportionally fewer mitotically active cells in the niche.

Each Q provides 256 cells of generation Y. When both Q cells have been used the quiescent P divides to form two more Q cells. When they have been used quiescent O divides to form PQQ and so on. If 256 cells are required daily, Q maintains the niche for one day, P maintains the niche for 2 days, O for 4 days, N for 8 days, M for 16 days, L for 32 days, K for 64 days, J for 128 days, I for 256 days, H for 512 days, G for 1024 days, F for 2048 days, E for 4096 days, D for 8192 days, C for 16384, B for 32,768 and the original A for 65536 days which is 184 years.

In the first few days the process runs as follows:

BCDEFGHIJKLMNOPQ Q divides to form 256 Y cells
BCDEFGHIJKLMNOP Q divides to form 256 Y cells
BCDEFGHIJKLMNOQ Q divides to form 256 Y cells
BCDEFGHIJKLMNO Q divides to form 256 Y cells
BCDEFGHIJKLMNPQ Q divides to form 256 Y cells

Modifications to the basic model

We do not see 14 quiescent stem cells at the base of anatomical niches such as colonic crypts. Thus it is likely that the longer lived quiescent stem cells are in the bone marrow, For instance if BCDEFGHI are in the bone marrow that would leave JKLMNOP to maintain the anatomical niche for 128 days. Every 128 days the crypt would receive one J cell which would reform the linear hierarchy.

The basic model assumes 54 generations between the zygote and a fully differentiated epithelial cell. But it also assumes there is no death of the quiescent cells. In fact quiescent stem cells could be hit by radiation causing genetic damage and could die when they are activated. This might be less likely in the bone marrow than at the periphery of the body but some cell death will almost certainly occur. In which case a senior cell in the hierarchy will replace the dead cell and one additional division will occur i.e. 55 generations. It is also possible that the long lived stem cells in the bone marrow are activated every few years to cull and replace those that have suffered some damage; in which case we would need to add several divisions to the basic 54. In practice 60 seems a reasonable upper limit.

The basic model assumes that the zygote does not contain any deleterious mutations in genes related to growth control; in which case all m mutations must be acquired somatically to form a cancer. In practice this is unlikely to occur within 60 divisions. But if the zygote does contain a deleterious mutation in a growth control gene only $m - 1$ mutations are required for malignancy and this is much more likely to occur.

Inflammation can destroy the anatomical niche and the surrounding stromal cells. In most cases the area is repaired and the hierarchy reformed using stem cells from the bone marrow. But there is always the possibility that repair is incomplete and the stem cells start to cycle as in the conventional model. Inflammation occurs throughout life but the repair process ages and the risk of failure rises with age.

Another factor to consider is the presence of deleterious mutations in the bone marrow stem cells. Every time DNA is copied in mitosis there will be several base changes and after 30 mitoses the expectation of a deleterious mutation is 0.5 (13). There are 20,000 genes in the haploid set. Thus in the billion stem cells of generation A there will be cells with every possible deleterious mutation. The cells with deleterious mutations in growth control genes might well slowly expand in the stem cell pool (7). Thus in later life some of the stem cells that reform anatomical niches will have mutations in growth control genes. If the anatomical niche is destroyed by inflammation in older individuals then there is the possible combination of failure of repair and stem cells with defects in growth control.

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109530.

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