**Context dependent selection as the keystone in the somatic evolution of cancer**

Abstract:

Somatic evolution of cancer involves a series of mutations and accompanying genomic, epigenomic and physiological changes in one or more clones of cells. Whether the mutations accumulate by chance alone (bad luck hypothesis) or owing to selection of intermediate mutants leading to clonal expansion is an unresolved question. An implicit assumption in clonal expansion is that any mutation leading to partial loss of regulation of cell proliferation will give a selective advantage to the mutant. However, a number of experiments show that an intermediate precancer mutant has only a conditional selective advantage. Accordingly the selective advantage to a mutant will be different in every individual depending upon the genetic, developmental, dietary, behavioural, habitual and physiological background. Thus the selective advantage to a mutant will be widely distributed across individuals in the population. We comparatively evaluate the three models namely bad luck, context independent selection and context dependent selection with respect to their ability to predict patterns in total incidence, age specific incidence, tissue specific incidence and their ability to explain Peto’s paradox and related paradoxes. Results show that context dependence is necessary and sufficient to explain all the observed patterns whereas the number of cells and mutation rates are not necessarily rate limiting. This implies that the susceptibility to cancer can be substantially different across individuals and cancer is not sheer bad luck. This has important implications for the prevention of cancer by identifying and targeting the micro-environmental factors that influence the dynamics of selection.

**Context dependent selection as the keystone in the somatic evolution of cancer**

An old debate in the theory of evolution is how the simple process of random mutations and natural selection can lead to complex structures such as the eye that needs coordinated action of several genes. This problem is often perceived as a monkey on a typewriter paradox (1-4). How probable it is that a monkey sitting on a typewriter and hitting keys at random would end up typing a meaningful sentence? The problem of cancer is qualitatively similar to this but quantitatively even more difficult. No single mutation is known to make a cell cancerous. All cancers are necessarily a combination of different types of genomic changes including point mutations, aneuploidy and other chromosomal aberrations. The cancer phenotype has a large number of distinguishing characters that include independence from growth factor signalling, insensitivity to growth suppressing signals, evading apoptosis, telomere maintenance, sustained angiogenesis, evasion of contact inhibition, genomic instability, inflammation, altered glucose metabolism, co-option of other cell types, tissue invasion and metastasis (5). It is astonishing that so many alterations in cell properties come together in cancers. Moreover, cancer has to evolve independently in each individual suffering from it. Since mutation accumulation is recognized to be central to carcinogenesis, increased rate of mutagenesis is said to be responsible for carcinogenesis.

A population level process implicated in carcinogenesis is clonal expansion. After every component mutation in the cancer process the mutant clone expands and as the mutant population increases, the probability of second component mutation increases proportionately. Implicit in this theory is the assumption that every component mutation has a selective advantage over the normal cell. Since most changes involved in carcinogenesis are about evading the growth regulation mechanisms, it is considered logical that any such mutant will have a selective advantage within a tissue.

However, not all experiments support the view that cells with component mutations are always at an advantage. ------. It is possible therefore that the fitness advantage to a mutant is largely dependent on the tissue microenvironment and therefore selective forces can vary considerably across different individuals.

We examine the three models namely (i) chance accumulation of mutations or the bad luck hypothesis, (ii) unconditional or context independent clonal selection and (iii) context dependent clonal selection to see whether they predict the epidemiological picture of cancer observed in human population. In addition we will also examine how the different models possibly explain the well-known Peto’s paradox (6-9), the red cell paradox () and the observed relationships with stem cell number () and mutation rates ().

It is also important that while undergoing a series of genomic alterations, the cell should not experience a lethal or deleterious mutation. Since a greater proportion of mutations would be deleterious to the cell, it is highly unlikely that a cell would acquire the specific combination of alterations that make it neoplastic without undergoing any deleterious mutation. In addition an evolving cancer cell would also be subject to Muller’s ratchet and thereby progressively reduce its fitness. We examine how the three models can incorporate these phenomenon.

**A. The bad luck model**: This hypothesis assumes that the set of driver mutations accumulate in a cell by chance alone. This may happen over a time course or in one go as in chromothripsis. In either case the probability that the necessary cancer causing mutations come together without any lethal mutation happening in the same cell can be written as, *Pca.(1-PL)L*

Where, Pc is the probability of a carcinogenic/driver mutation, *a* the number of mutations required for carcinogenesis, PL the probability of a lethal mutation in the same cell and L is the number of possible mutations that can be lethal or detrimental to the cell. As a baseline assumption, Pc and PL can be assumed to be equal. The probability of transforming a cell into a cancer cell by mutation accumulation depends upon the number of mutational events required for developing cancer which have been variously estimated between 2 and 20 for different types of cancers (ref). It can be seen that the probability of turning cancerous is non-monotonic and at higher mutation rates the probability of incurring a lethal mutation prevails bringing down the probability of cancer. The probability of an individual having 10 14 life time cell divisionsdevelops cancer has a threshold relationship with the mutation rate such that at a given m, the probability is near zero or near one with a sharp transition. By this model, epidemiologically one would expect a zero incidence or 100% life time incidence of some or the other form of cancer (fig 1). The model also gives a threshold relationship with the number of cells in a tissue. This means that the incidence of cancer would be near zero in some tissues and near one in others. Gradation, if any would be very sharp.

Fig 1

1. The probability that a cell accumulates the necessary mutations to transform it to a cancer cell without incurring a lethal mutation, as a function of the mutation rate.
2. The probability that a given individual develops a cancer at different rates of mutation. Note that cancer probability holds a threshold relationship with mutation rate. Above a threshold rate the probability approaches one.
3. The relationship between cell number and probability of cancer in a tissue.

It can be seen that the bad luck model predicts a threshold relationship with the cell number. T and V (2015, 2017) claimed a linear relationship between life time stem cell divisions and incidence of cancer in different tissues as a supportive evidence for the bad luck hypothesis. A simple model based on chance mutations does not predict a linear or log linear relationship and therefore unless a threshold relationship between LSCD and cancer incidence is observed the bad luck model is not supported.

**B: The context independent selection model**:

This model assumes that all component mutations that lead to cancer give some selective advantage to the mutant. As a result the mutant clone expands and as the number of mutant cells increase, the probability of second mutation in at least one of cells from the clone increases. This linear process leads to accumulation of mutations that make a cell cancerous. Since this is a stochastic and time course dependent process we use simulations to predict cancer incidence in a population.

We begin by considering ………

**C: The context dependent selection model**:

**Incorporating mutational melt down, Muller’s ratchet in the two selection models**: Does passenger mutation accumulation in a context independent model give predictions similar to context dependent model?

Testing predictions of the three models:

1. total incidence in the realistic range?
2. age incidence pattern
3. relationship with cell number,
4. relationship with mutation rates
5. explaining non-mutagenic carcinogens
6. Peto’s paradox and other paradoxes.

Compatibility with branched evolution, polyclonality, clonal synergies: We used a linear evolution model for examining the predictions of context independent and context-dependent selection. The models can incorporate branched evolution, polyclonality or clonal synergies. But this incorporation does not change the mainstream predictions of the models.

Implications for cancer control: Identifying the microenvironmental factors that influence the selection dynamics and studying their regulation should be the main focus of translational cancer research. If we can maintain a microenvironment that gives a selective advantage to the normal cell over an intermediate pre-cancer mutant, cancer is unlikely to develop. By this strategy cancer should be largely preventable.

**References:**

1. Behe, M.J., and Snoke, D.W. Simulating evolution by gene duplication of protein features that require multiple amino acid residues. Protein Sci. (2004). *13*, 2651–2664.
2. Johnson, P.E., and Behe, M.J. Darwin on trial (InterVarsity Press). (2010).
3. Borel, É. La mécanique statique et l’irréversibilité. J Phys Theor Appl (1913). *3*, 189–196.
4. Dawkins, R. The blind watchmaker: Why the evidence of evolution reveals a universe without design (WW Norton & Company). (1986).
5. Schäfer, M., and Werner, S. Cancer as an overhealing wound: an old hypothesis revisited. Nat. Rev. Mol. Cell Biol. (2008). *9*, 628–638.
6. Caulin, A.F., and Maley, C.C. Peto’s Paradox: evolution’s prescription for cancer prevention. Trends Ecol. Evol. (2011). *26*, 175–182.
7. Caulin, A.F., Graham, T.A., Wang, L.-S., and Maley, C.C. Solutions to Peto’s paradox revealed by mathematical modelling and cross-species cancer gene analysis. Phil Trans R Soc B (2015). *370*, 20140222.
8. Nagy, J.D., Victor, E.M., and Cropper, J.H. Why don’t all whales have cancer? A novel hypothesis resolving Peto’s paradox. Integr. Comp. Biol. (2007). *47*, 317–328.
9. Roche, B., Hochberg, M.E., Caulin, A.F., Maley, C.C., Gatenby, R.A., Misse, D., and Thomas, F. Natural resistance to cancers: a Darwinian hypothesis to explain Peto’s paradox. Bmc Cancer (2012). *12*, 387.
10. Klapper, L.N., Kirschbaum, M.H., Sela, M., and Yarden, Y. Bio chemical and clinical implications of the ErbB/HER signaling network of growth factors. Adv Cancer Res (2000). *77*, 25–78.
11. Mendelsohn, J., and Baselga, J. The EGF receptor family as targets for cancer therapy. Oncogene (2000). *19*, 6550–6565.
12. Olayioye, M.A., Neve, R.M., Lane, H.A., and Hynes, N.E. The ErbB signaling network: receptor heterodimerization in development and cancer. EMBO J. (2000). *19*, 3159–3167.
13. Witsch, E., Sela, M., and Yarden, Y. Roles for Growth Factors in Cancer Progression. Physiol. Bethesda Md (2010). *25*, 85–101.
14. Zhang, X., and Chang, A. Somatic mutations of the epidermal growth factor receptor and non‐small‐cell lung cancer. J. Med. Genet. (2007). *44*, 166–172.
15. Lemmon, M.A., and Schlessinger, J. Regulation of signal transduction and signal diversity by receptor oligomerization. Trends Biochem. Sci. (1994). *19*, 459–463.
16. Yu, J., Liu, X.-W., and Kim, H.-R.C. Platelet-derived growth factor (PDGF) receptor-α-activated c-Jun NH2-terminal kinase-1 is critical for PDGF-induced p21WAF1/CIP1 promoter activity independent of p53. J. Biol. Chem. (2003). *278*, 49582–49588.
17. Reis-Filho, J.S., Steele, D., Di Palma, S., Jones, R.L., Savage, K., James, M., Milanezi, F., Schmitt, F.C., and Ashworth, A. Distribution and significance of nerve growth factor receptor (NGFR/p75NTR) in normal, benign and malignant breast tissue. Mod. Pathol. (2006). *19*, 307–319.
18. Tsang, J.Y., Wong, K.H., Lai, M.W., Lacambra, M.D., Ko, C.-W., Chan, S.K., Lam, C.C., Alex, M., Tan, P.-H., and Gary, M.T. Nerve growth factor receptor (NGFR): a potential marker for specific molecular subtypes of breast cancer. J. Clin. Pathol. jclinpath (2012)..
19. Ahmad, I., Iwata, T., and Leung, H.Y. Mechanisms of FGFR-mediated carcinogenesis. Biochim. Biophys. Acta BBA-Mol. Cell Res. (2012). *1823*, 850–860.
20. Katoh, M., and Nakagama, H. FGF receptors: cancer biology and therapeutics. Med. Res. Rev. (2014). *34*, 280–300.
21. Koziczak, M., Holbro, T., and Hynes, N.E. Blocking of FGFR signaling inhibits breast cancer cell proliferation through downregulation of D-type cyclins. Oncogene (2004). *23*, 3501–3508.
22. Goel, H.L., and Mercurio, A.M. VEGF targets the tumour cell. Nat. Rev. Cancer (2013). *13*, 871–882.
23. Nexø, E., Hollenberg, M.D., and Bing, J. Aggressive behaviour in mice provokes a marked increase in both plasma epidermal growth factor and renin. Acta Physiol. Scand. (1981). *111*, 367–371.
24. Nexø, E., Olsen, P.S., and Poulsen, K. Exocrine and endocrine secretion of renin and epidermal growth factor from the mouse submandibular glands. Regul. Pept. (1984). *8*, 327–334.
25. Roberts, M.L. Testosterone-induced accumulation of epidermal growth factor in the submandibular salivary glands of mice, assessed by radioimmunoassay. Biochem. Pharmacol. (1974). *23*, 3305–3308.
26. Davison, J., Befus, A., and Mathison, R. The cervical sympathetic trunk—submandibular gland neuro-endocrine axis: its role in immune regulation. Biomed Res (2003). *14*, 30–37.
27. Aloe, L., Bracci-Laudiero, L., Alleva, E., Lambiase, A., Micera, A., and Tirassa, P. Emotional stress induced by parachute jumping enhances blood nerve growth factor levels and the distribution of nerve growth factor receptors in lymphocytes. Proc. Natl. Acad. Sci. (1994). *91*, 10440–10444.
28. Wilson, S.E., Chen, L., Mohan, R.R., Liang, Q., and Liu, J. Expression of HGF, KGF, EGF and receptor messenger RNAs following corneal epithelial wounding. Exp. Eye Res. (1999). *68*, 377–397.
29. Berker, B., Emral, R., Demirel, C., Corapcioglu, D., Unlu, C., and Kose, K. Increased insulin-like growth factor-I levels in women with polycystic ovary syndrome, and beneficial effects of metformin therapy. Gynecol. Endocrinol. (2004). *19*, 125–133.
30. Bulló, M., Peeraully, M.R., Trayhurn, P., Folch, J., and Salas-Salvadó, J. Circulating nerve growth factor levels in relation to obesity and the metabolic syndrome in women. Eur. J. Endocrinol. (2007). *157*, 303–310.
31. Mraz, M., Bartlova, M., Lacinova, Z., Michalsky, D., Kasalicky, M., Haluzikova, D., Matoulek, M., Dostalova, I., Humenanska, V., and Haluzik, M. Serum concentrations and tissue expression of a novel endocrine regulator fibroblast growth factor‐21 in patients with type 2 diabetes and obesity. Clin. Endocrinol. (Oxf.) (2009). *71*, 369–375.
32. Rasmussen, M., Hvidberg, A., Juul, A., Main, K., Gotfredsen, A., Skakkebaek, N., Hilsted, J., and Skakkebae, N. Massive weight loss restores 24-hour growth hormone release profiles and serum insulin-like growth factor-I levels in obese subjects. J. Clin. Endocrinol. Metab. (1995). *80*, 1407–1415.
33. Morrison, S.J., Shah, N.M., and Anderson, D.J. Regulatory Mechanisms in Stem Cell Biology. Cell (1997). *88*, 287–298.
34. Reya, T., Morrison, S.J., Clarke, M.F., and Weissman, I.L. Stem cells, cancer, and cancer stem cells. Nature (2001). *414*, 105–111.
35. Sasaki, T., Hiroki, K., and Yamashita, Y. The Role of Epidermal Growth Factor Receptor in Cancer Metastasis and Microenvironment. BioMed Res. Int. (2013). *2013*, 546318.
36. Coutu, D.L., and Galipeau, J. Roles of FGF signaling in stem cell self-renewal, senescence and aging. Aging (2011). *3*, 920–933.
37. Discher, D.E., Mooney, D.J., and Zandstra, P.W. Growth factors, matrices, and forces combine and control stem cells. Science (2009). *324*, 1673–1677.
38. Shi, Y., Sun, G., Zhao, C., and Stewart, R. Neural Stem Cell Self-renewal. Crit. Rev. Oncol. Hematol. (2008). *65*, 43–53.
39. Tomellini, E., Touil, Y., Lagadec, C., Julien, S., Ostyn, P., Ziental-Gelus, N., Meignan, S., Lengrand, J., Adriaenssens, E., and Polakowska, R. Nerve Growth Factor and proNGF Simultaneously Promote Symmetric Self-Renewal, Quiescence, and Epithelial to Mesenchymal Transition to Enlarge the Breast Cancer Stem Cell Compartment. Stem Cells (2015). *33*, 342–353.
40. González-Suárez, E., Samper, E., Ramírez, A., Flores, J.M., Martín-Caballero, J., Jorcano, J.L., and Blasco, M.A. Increased epidermal tumors and increased skin wound healing in transgenic mice overexpressing the catalytic subunit of telomerase, mTERT, in basal keratinocytes. EMBO J. (2001). *20*, 2619–2630.
41. Osanai, M., Tamaki, T., Yonekawa, M., Kawamura, A., and Sawada, N. Transient increase in telomerase activity of proliferating fibroblasts and endothelial cells in granulation tissue of the human skin. Wound Repair Regen. (2002). *10*, 59–66.
42. Hunt TK, Conolly WB, Aronson SB, Goldstein P Anaerobic metabolism and wound healing: an hypothesis for the initiation and cessation of collagen synthesis in wounds. Am J Surg. (1978). 135 (3):328-32.
43. Hunt, T.K. The physiology of wound healing. Ann. Emerg. Med. (1988). *17*, 1265–1273.
44. Gurtner, G.C., Werner, S., Barrandon, Y., and Longaker, M.T. Wound repair and regeneration. Nature (2008). *453*, 314–321.
45. Tonnesen, M.G., Feng, X., and Clark, R.A. Angiogenesis in wound healing. (Nature Publishing Group), (2000). pp. 40–46.
46. Mardin, B.R., Isokane, M., Cosenza, M.R., Krämer, A., Ellenberg, J., Fry, A.M., and Schiebel, E. EGF-induced centrosome separation promotes mitotic progression and cell survival. Dev. Cell (2013). *25*, 229–240.
47. Schrevel, M., Gorter, A., Kolkman-Uljee, S.M., Trimbos, J.B.M., Fleuren, G.J., and Jordanova, E.S. Molecular mechanisms of epidermal growth factor receptor overexpression in patients with cervical cancer. Mod. Pathol. (2011). *24*, 720–728.
48. Cao, L., Liu, X., Lin, E.-J.D., Wang, C., Choi, E.Y., Riban, V., Lin, B., and During, M.J. Environmental and Genetic Activation of a Brain-Adipocyte BDNF/Leptin Axis Causes Cancer Remission and Inhibition. Cell (2010). *142*, 52–64.
49. Eysenck, H.J. Cancer, personality and stress: Prediction and prevention. Adv. Behav. Res. Ther. (1994). *16*, 167–215.
50. Kavan, M.G., Engdahl, B.E., and Kay, S. Colon cancer: personality factors predictive of onset and stage of presentation. J. Psychosom. Res. (1995). *39*, 1031–1039.
51. Kune, G.A., Kune, S., Watson, L.F., and Bahnson, C.B. Personality as a risk factor in large bowel cancer: data from the Melbourne Colorectal Cancer Study. Psychol. Med. (1991). *21*, 29–41.
52. Eysenck, H.J. Personality, stress and cancer: prediction and prophylaxis. Br. J. Med. Psychol. (1988). *61*, 57–75.
53. Temoshok, L. Personality, coping style, emotion and cancer: towards an integrative model. Cancer Surv. (1986). *6*, 545–567.
54. Watve, M. Behavioral Deficiencies and Behavioral Supplementation. In Doves, Diplomats, and Diabetes, (Springer), (2013). pp. 305–317.