11. The Immuno-Carcinogen Theory of Cancer—The Lifelong Dynamic Interface Between the Immune System and the Carcinogen-Driven Carcinogenesis

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Abstract Over the decades, many theories or models of carcinogenesis have been proposed. Based on the systems epidemiology research on gene expression from immune cells in peripheral blood, the concept of the dynamic interface between the immune system and the carcinogen-driven carcinogenesis is put forward. This combines traditional exposure research in cancer epidemiology with upcoming knowledge of the immunological response to cancer, from clones of cancer cells to clones of immune cells.

Keywords Immune system | risk factor | carcinogenesis | tumor tissue | blood | clones

This novel theory of carcinogenesis introduces the concept of a lifelong dynamic interface between the immune system and carcinogen-driven carcinogenesis. Through the analyses of trajectories of gene expression in peripheral blood from immune cells, the introduction of time-dependent changes in functional genomics has documented the responses of the immune system to the carcinogenic process. This dynamic interface could be looked upon as a balance or war between clones of immune cells and tumor cells. In a systems epidemiology design, the two forces can be weighed against each other: the traditional carcinogen-driven model against the immune defense system. The metaphor of war follows from lay state-
ments about cancer: the "war on cancer", “la lutte” (in French) or “sin livs kamp” (Norwegian). In popular speeches, researchers call TD8+ cells “killer cells”.

The aim is to discuss the observational background for the theory, its relation to other models, the need for scientific collaborations between different disciplines, and finally, new challenges.

SYSTEMS EPIDEMIOLOGY STUDIES OF GENE EXPRESSION FROM PERIPHERAL IMMUNE CELLS IN BLOOD

We have demonstrated the potential for studies of trajectories in Chapters 8 and 9, The trajectories before (Lund et al. 2016, see Chapter 8, Holden et al. 2017) and after diagnosis (Chapter 9) demonstrate the time-dependent difference in gene expression from immune cells dependent on stage. Important for the interpretation of the interface is the finding of lack of correlation between gene expression in blood and in tumor tissue in the same individual at time of diagnosis; see Dumeaux et al. 2017. Blood is not a surrogate for tissue studies. The findings tell us that there is a dynamic interface between the immune system and the effect of carcinogens on the tissue cells changing over time. While invasive cancer shows few changes, in metastatic cancer relatively rapid changes are seen around and before diagnosis. More dramatic are the changes in gene expression after diagnosis in metastatic cases, with a second, transient increase. This effect can be found even more clearly in cases where the patient later dies (Lund submitted PLOS).

In other studies we found that hundreds of genes change their gene expression in blood as a consequence of increasing parity, the major protective factor for breast cancer; the more pregnancies, the more experiences of the immune system of the semi-allograft or fetus (Lund et al. 2018a). Here, the fetus is protected through a redirection of response away from the adaptive system towards the innate, a balance that is restored just before, at and after birth. The proposal that later the immune system will consider the cancer as a pseudo-semi-allograft, and with more experience immune cells or clones of cells, the better the success rate of elimination (Lund et al. 2018b).

HISTORICAL THEORIES

Over the last century, many theories of causes of cancer have been proposed by basic researchers and epidemiologists. In a review of carcinogenic models (Vinei
et al. 2010), five different models with their statistical methods were proposed: the mutational, genome instability, non-genotoxic, Darwinian, and tissue organization. Over the years, epidemiologists tried to use incidence rates to estimate the necessary number of stages for a cancer to develop, starting with the Armitage-Doll assumption of at least five stages (Armitage and Doll 1954). The number of stages was later reduced to two, the two-hit model proposed by Knudson (Knudson 2001). Today, most epidemiologists argue that cancer is caused by environmental carcinogens like smoking and radiation. In the paper by Peto and Doll in the early 1980s, “bad luck” was not necessary to explain the cancer epidemic (Doll and Peto 1981). Epidemiologists primarily use the relative risk between a carcinogen and cancer to discuss causality and prevention, but with no information on time dependency in the semi-parametric proportional hazard models. In basic research, the Hansemann-Boveri aneuploidy theory (Holland and Cleveland 2009) was based on observations of asymmetric mitoses in skin cancer. Warburg’s theory was based on observations that cancers metabolize glucose via glycolysis (Hsu and Sabatini 2008). Today, basic researchers propose multistep carcinogenesis, such as the “bad luck” hypothesis explaining cancer as intrinsically random, and, therefore, unavailable, mutagenic events that dominate tumorigenesis (Tomasetti and Vogelstein 2015). This theory is unsupported by individual data and has been rejected by epidemiologists (Perduca et al. 2019).

Clinical researchers have mostly relied on basic research findings for new therapies. Now there is increasing concern about analogies from mice to human, from constructed diseases to human conditions (for further detail see Chapter 7).

THE IMMUNE SYSTEM AND CANCER—A LONG HISTORY

Accounts of the effects of the immune system on cancer patients have been recorded for centuries, such as the spontaneous regression of cancer, mostly in relation to serious infection (Hoption Cann et al. 2002). One of the first treatments of cancer was introduced in 1850 by French doctors, and they succeeded in treating two patients (Kaplon and Dieu-Nosjean 2018). Before and after the First World War, researchers performed systematic experiments on humans by injecting various bacteria, viruses and toxins (Kucerova and Cervinkova 2016). The high mortality due to the virulent disease used in the injections killed many patients, although many were cured too. After the Second World War, these accounts were dismissed and the spontaneous elimination of tumors in patients was considered impossible. Due to vaccinations and the more effective treatment of infectious diseases, it is possible that such cases were no longer seen. From basic research, many
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Studied pointed towards the concept of immune evasion (Hanahan and Weinberg 2011, Wang et al. 2017, Steven and Seliger 2018). This concept is partly compatible with the novel theory, but lack information on the exposures that are the driving forces. It is hard to imagine that the carcinogenesis of hormone-related breast cancer should be similar to smoking-induced lung cancer or HPV-induced cervical cancer. Thus, due to the different methods, observational confirmation has been lacking. New therapies called immunotherapies are based on several mechanisms in the tumor and the use of immune cells to kill the tumor cells. The new immunotherapies (De la Cruz and Czarnecki 2018) have changed the direction of cancer treatment towards immunology. Today, "hot" and "cold" cancers refer to the number of immune cells in the matrix around the cancer and the consequences for prognosis.

Another important aspect in understanding the role of the immune system in cancer and the novel theory is the increasing understanding of the role infections play in cancer development as causes or co-factors. In an overview the PAF (population-attributable factor) risk was calculated to be around 16% worldwide, but with large geographic differences (de Martel et al. 2012).

Infection is the main cause of HPV in cervical (Cohen et al. 2019) and pharyngeal cancer (Chen et al. 2019), some lymphomas (Molyneux et al. 2012), hepatitis C (Mina et al. 2015), and partly act as co-factors for helicobacter pylori in stomach cancer (Pereira-Marques et al. 2019). Research has been ongoing to link cancer of colon to the biota (Collins et al. 2011). The importance of chronic inflammation as an additional driver in many cancer sites has become a major research area (Qu et al. 2018). Other aspects of immunology and cancer promise new immunotherapies (De la Cruz and Czarnecki 2018) such as monoclonal antibodies and checkpoint inhibitors. Both cancer vaccines and oncolytic immunotherapy have the potential to improve survival (Guo et al. 2019). Epidemiologists should include inflammatory biomarkers in cancer research in order to obtain some indications of the reaction of the immune system towards the carcinogenic process (Brenner et al. 2014).

THE NEED FOR COLLABORATION ACROSS SCIENTIFIC DISCIPLINES

The different carcinogenic paradigms still exist side by side due to the lack of interaction between scientists of the differing traditions. The main reason has been the lack of models that might incorporate information from all three research disciplines in cancer (basal, clinical, and epidemiological research). Basic research uses
reductionist experiments with little option for experiments with different exposures over extended time, as in humans. In addition, the mice model is usually based on animal experiments in non-pathogenic laboratories, leaving the adult mice with an immune system comparable to a newborn human. We postulated that the experiences of the immune system could be important for the power of protection against transformed cancer cells. Clinicians almost only have studies of the cancer patient, with no possibility of looking back on lifestyle.

Obviously, new designs and technologies are necessary for an understanding of the dynamic interface between the immune system and the effect of carcinogens on tissue cells around the body. Through the systems epidemiology concept we have built a new biobank giving us the opportunity to follow up on gene expression in the blood from before diagnosis, at diagnosis, and after diagnosis. At the same time, we can collect either fresh tumor or normal tissue cells, or collect biopsies from the paraffin-embedded samples used for diagnostics of cancer. From the basic traditional prospective design, we can introduce different lifestyle factors through questionnaire information or the use of biomarkers. It is easy to add genomic information such as single nucleotide polymorphisms (SNPs).

The crucial difference between the dynamic interface theory and previous proposals is the willingness to view the different scientific disciplines as equally important. A novel theory must be able to synthesize previous ones.

The strength of the proposed theory is the combination of information from all three cancer research disciplines with the core concepts of dynamics over time and an interface in which tumor cells encounter the immune cells struggling for life. Here, immunology as both a basic research discipline and well-accepted disease-related research meets new possibilities in epidemiology that also include basic cell studies.

**CHALLENGES OF THE DYNAMIC INTERFERENCE THEORY**

This novel theory has some important implications or new hypotheses:

- Any substance inhibiting the immune system will work as a carcinogen. Carcinogens are the drivers of change from normal to cancer tissue cells. The immune system acts on the interface of the tissue to attack transformed cells. This illustrates the balance or war on cancer, but any substance inhibiting the immune system could act as driver of carcinogenesis.

- What is the effect of previous experiences of the immune system? The accumulated experiences of the immune system could be important for later resistance towards cancer development.
• An interesting hypothesis could be to search for the memory cells in the immune system, for the immune cells’ victories, or the carcinogens’ lost battles. Should we expect to find successful clones of immune cells, and if yes, how many different clones over a long life?

**EPILOGUE**

The metaphor of clone wars was chosen without knowledge of the clone war in *Star Wars*. Still, the metaphor is a nice one: The good guys create clones of 12 000 soldiers to defend their empire, but the bad ones among them implant a chip into the heads of the soldiers. When the command "Order 66" is given, the soldiers kill the good guys, the officers or the leaders. Fortunately, however, one good guy survives.

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