Minisymposia no 26 on

Tumor-immune interactions

Wednesday, June 18

11:40 – Mark Robertson-Tessi
12:00 – Philippe Robert
12:20 – Heiko Enderling
12:40 – Ardith El-Kareh

Abstract 1:
The effect of T-cell homeostasis on solid and liquid tumors
Mark Robertson-Tessi

T-cell populations are subject to homeostatic control from cytokines and microenvironmental signaling. Disruption of homeostasis can cause changes to the dynamics of the system that have implications for the progression of cancer. Here we present two mathematical models that examine the progression of tumors in the context of T-cell homeostasis. Model 1: During a chronic disease such as cancer, T cells often become tolerant to the antigens presented by the disease. This tolerant state effectively limits the response of the immune system to the tumor. Experimental evidence has shown that depletion of T-cells can lead to a loss of T-cell tolerance. During the homeostatic phase of T-cell compartment repopulation, there is a temporary window of opportunity during which T cells lose their tolerant state, allowing them to respond to tumor antigens. In addition, clonal expansion of the tumor-specific T-cell clone may be enhanced during the regrowth phase due to increased stimulation. We use an ordinary differential equation (ODE) model to explore the effect of T-cell depletion and homeostatic repopulation on the loss of tolerance in the T-cell compartment and subsequent effectiveness of immune-mediated tumor cytotoxicity. The model predicts different outcomes for the tumor and T-cell compartment, dependent on the strength and schedule of the depletion therapy. The optimal regimen can lead to tumor control in some cases, but T-cell exhaustion is also common dynamic predicted by the model. By understanding the effects of T-cell depletion, immune depleting therapies can be optimized to enhance immune potential. Model 2: Large Granular Lymphocytic Leukemia (LGLL) is a T-cell lymphoproliferative disorder that exhibits clonal expansion of a subset of T cells. Since there are no clinical biomarkers to predict the aggressiveness of the disease, treatment decisions are often made on a watch and wait approach. Using a set of ODEs, we develop a model of LGLL that uses clinical patient data from diagnosis to predict the timeframe for progression of the disease. Our experimental results have suggested that the disease is caused by a change in sensitivity to both positive and negative regulators of T-cell homeostasis. The model incorporates these cell-specific mechanisms to investigate their effect when placed in a homeostatic setting. The level of dysregulation as measured from patient-specific data determines the rate of outgrowth of the diseased T-cell clone, and therefore serve as a useful predictive tool for managing treatment decisions in the clinic.

Abstract 2:
Different modelling approaches for T helper differentiation and applications to anti-tumor therapy.
Philippe Robert

During the onset of an acquired immune response, antigen presenting cells (APCs) are able to activate and differentiate T helper lymphocytes (CD4+ T cells) through triggering their T cell receptor (TCR) and producing different chemical signals (cytokines). For instance, a viral infection leads to the production of the cytokine IL12 by APCs, which promotes the differentiation of T helper cells into IFN-gamma-producing cells (Th1), which in turn amplifies the killing of infected cells by Cytotoxic T cells (CD8+ T cells). Similarly, in the case of extracellular parasites, or allergy, differentiated T helper cells produce IL4, IL5 and IL13 (Th2 phenotype), boosting the B cell response and production of antibodies. Other T helper subsets have been described based on their cytokine production profile, such as Th17, Th9, Tfh (T follicular helper), or their suppressive capacity (Tregs). Therefore, a proper differentiation of T helper cells is required to appropriately direct and control the immune response. T helper cells subtypes (Th1 and Th17) are also involved in tumor rejection, Th17 cells showing positive or pathogenic effect depending on the tumoral context. Here, we'll discuss different computational approaches used to model the complexity of intracellular signaling and cytokine communications controlling T helper cell differentiation, and how it can be applied to tumor microenvironment, in the context of new findings regarding the behaviour of T cells in different metabolic environments.

Abstract 3:
Immunoediting of cancer stem cell-driven solid tumors
Heiko Enderling

The role of the immune system in tumor progression has been a subject for discussion for many decades. Numerous studies suggest that a low immune response might be beneficial, if not necessary, for tumor growth, and only a strong immune response can counter tumor growth and thus inhibit progression. We discuss a cellular automaton model that captures the dynamical interactions between the cancer stem and non-stem cell populations of a tumor through a process of self-metastasis. By overlaying on this model the diffusion of immune reactants into the tumor from a peripheral source to target cells, we simulate the process of immune-system-induced cell kill on tumor progression. A low cytotoxic immune reaction continuously kills cancer cells and, although at a low rate, thereby causes the liberation of space-constrained cancer stem cells to drive self-metastatic progression and continued tumor growth. With increasing immune system strength, however, tumor growth peaks, and then eventually falls below the intrinsic tumor sizes observed without an immune response. With this increasing immune response the number and proportion of cancer stem cells monotonically increases, implicating an additional unexpected consequence, that of cancer stem cell selection, to the immune response. Cancer stem cells and immune cytotoxicity explain the three-step “immunoediting” concept – the modulation of tumor growth through inhibition, selection and promotion.

Abstract 4:

A mathematical model for effect of tumor stroma on rate of metastasis formation

Ardith El-Kareh

Analysis of the NIH SEER database suggests that the volume-dependence of the rate of metastasis formation is slight. One possible explanation is that metastases arise only from a slowly-proliferating sub-population of tumor cells. However, a large part of the volume of many solid tumors consists of stromal cells, including immune cells, among which macrophages are often the most populous, as well as fibroblasts and myofibroblasts. Experimental evidence points to a cooperative role of tumor-associated macrophages and myofibroblasts in tumor cell migration into the circulation; tumor stroma may therefore also significantly affect the metastatic rate. The effect of factors secreted by these cells, as well as cooperativity, appears in many cases to be quite local; hence spatial distribution of the cell populations has an effect on the interactions. A spatially-distributed model is developed for rate of metastatic formation from a solid tumor mass, including macrophages, myofibroblasts, and cell-derived factors involved in recruitment of these cell populations to the tumor, as well as migration and intravasation. Matrix metalloproteinases and the biphasic effect of nitric oxide are considered. The role of TGF-beta , both in promoting EMT (epithelial-to-mesenchymal transition) at the tumor site and inhibiting MET (mesenchymal-to-epithelial transition) at the metastatic site is included. The model is used to predict rate of metastasis formation as a function of growing tumor volume. While a few damping effects exist in the system, overall it is difficult to explain a weak dependence on volume. The model provides insight into the important role of stroma in metastasis.