Theoretical and computational analysis of the evolution of immunogenicity in tumour clones

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Abstract

The dynamics of immune system cells chasing cancer clones is of paramount interest with deep biomedical and clinical implications. In this thesis we aim at developing a theoretical body and computational studies to understand the evolution of immunogenicity in heterogeneous tumor cell populations. Clinical and experimental data have revealed the huge heterogeneity (both genotypic and phenotypic diversity) of tumor cell populations. This heterogeneity has been described within-tumours and between patients suffering the same type of cancer. We aim at modelling the immune response against tumor cells considering key populations of the immune system, such as the so-called regulatory immune cells, considering the evolutionary and coevolutionary traits.

Scientific project

The dynamics of reaction of the immune system against tumor cells is extremely complex. However, efforts in modelling these responses have been developed within the fields of nonlinear dynamical systems and computational biology. A key aspect of the interactions between immune system cells and tumour cells is given by a pool of cells including regulatory T cells, effector cells, and antigen presenting cells (APCs) (Bacher-Allan 2006; Fontenot et al. 2003; Hori et al. 2003). In this thesis we will aim to get a better insight on the impact of regulatory CD25+CD4+ T cells in tumor immunobiology by means of simple mathematical model. Specifically, the models will focus on the dynamics of autoreactive regulatory cells and effector cells that interact upon their co localized activation APCs. Typically, it is assumed that tumor growth stimulates the activation and migration to the adjacent lymph node of fresh APCs loaded with tumor antigens. These APCs stimulate the growth of both effector and regulatory T cells, which may then migrate to the tumor site and induce tumor cell destruction. This give place to interesting nonlinearities which may involve the appearance of dynamics governed by periodic orbits or strange attractors.

A key feature of tumor cells is their genotypic and phenotypic plasticity which allow them to escape form the action of the immune system. Different tumor cell clones may trigger different immunogenic responses, also considering that the immune cells have also evolutionary potential. One of the main goals of this project will be to introduce evolution and co-evolution phenomena in previous mathematical models considering a more static picture of tumor immunobiology (see Leon et al. 2007). Recently, dynamical systems analysing phenotypic traits of tumor cells have been developed (Sardanyés & Alarcón 2018). Within the framework of co-evolution, several mathematical (Sardanyés & Solé 2007) and computational (Sardanyés and Solé 2007; Sardanyés & Alarcón 2018) models have allowed

to investigate the evolutionary dynamics of replicating cells under different settings which are also useful tom model the immunogenic response of tumor clones.

We will use dynamical systems theory to investigate the dynamics of these systems, seeking for bifurcation phenomena which might impair tumour cells persistence.

References

Baecher-Allan, C., Anderson, D.E., 2006. Regulatory cells and humancancer. Semin. Cancer Biol. 16, 98–105.

Fontenot, J.D., Gavin, M.A., Rudensky, A.Y., 2003. Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. Nat. Immunol. 4, 330–336.

Hori, S., Nomura, T., Sakaguchi, S., 2003. Control of regulatory T cell development by the transcription factor Foxp3. Science 299, 1057–1061.

Leon, K., Garcia, K., Carneiro, J., Lagem A., 2007. How regulatory CD25+CD4+T cells impinge on tumor immunobiology? On the existence of two alternative dynamical classes of tumors. J. Theor. Biol- 247, 122-137

Sardanyés J., Alarcón T. Noise-induced bistability in the fate of cancer phenotypic quasispcies: a bit-strings approach. Nature Scientific Reports 8:1027 (2018)

Sardanyés J., Solé R.V., Red Queen strange attractors in host-parasite replicator gene-for-gene coevolution. Chaos, Solitons and Fractals 32(5): 1666-1678 (2007)

Sardanyés J., Solé R. V., Chaotic stability in spatially-resolved host-parasite replicators: The Red Queen on a lattice. International Journal of Bifurcation and Chaos 17(2): 1-18 (2007)