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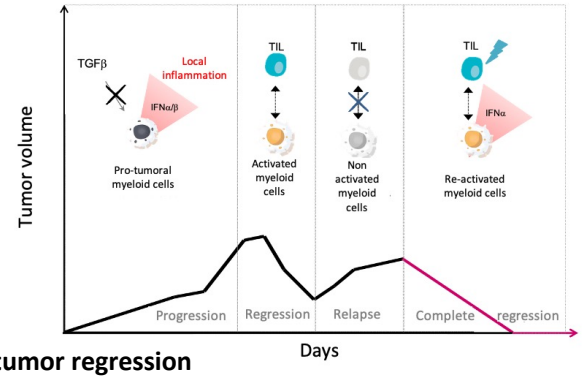

Dynamic of immune cells interactions during tumor regression

Despite significant advances, cancer immunotherapy does not systematically cause tumor regression. In addition, if regression is achieved, it is often followed by relapse. It is therefore urgent to better understand and characterize what conditions an effective immune response against solid tumors.

In the context of tumors, cytotoxic T lymphocytes (CTL) and tumor associated macrophages (TAM) are often presented as having antagonistic functions: activated CTLs can specifically kill cancer cells while TAMs inhibit their cytotoxic function and promote tumor growth. Nevertheless, considering the importance of macrophages in anti-infectious immune responses, one can predict that effective anti-tumor reactions could benefit from TAM reactivation. Indeed, TAMs are both a major source of T cell chemoattractants, but also cells capable of presenting tumor associated antigens to locally reactivate CTLs. This is why the team proposed that the induction of local and transient inflammation is crucial both to increase the efficiency of cellular cooperation but also to build an appropriate anti-tumor immune response (Bercovici and Trautmann, 2012).

Based on this hypothesis, two models of transplanted solid tumors were set up, one using TC1 lung cells, the other using PyMT breast cells. To induce tumor regression, two distinct modes of action were chosen. On the one hand, the use of a vaccination (Sx-TB-E7 + IFNa) for the TC1 model and on the other hand, that of DMXAA, an agonist of the STING receptor (Stimulator of interferon genes) involved in controlling infection. These two therapies induce local inflammation via the presence of interferons (IFN). Thanks to this, we were able to show in a robust way that TAMs can act in synergy with CTLs in regressing tumor and that this cooperation, essential to induce tumor regression, involves complex cellular and molecular interactions that vary over time and in space (Weiss, Guérin et al., 2017). Indeed, it has been shown that TAMs isolated from regressing tumors are capable of killing tumor cells by producing TFNα and that this tumoricidal activity is enhanced in the presence of CTL producing IFNg. In return, TAMs have been shown to be important for the recruitment and activation of CTLs. This view challenges the widely held view that interactions between myeloid cells and T lymphocytes are detrimental to anti-tumor immunity.

Following this, we wondered if it was possible to observe these tumor regressions, induced by the CTL / TAM cooperation, in a model of a spontaneous breast tumor, similar to a human carcinoma. Very surprisingly, DMXAA does not induce this same tumor regression in mice which spontaneously develop PyMT tumors. We have shown that this is due to an inhibition of the production of IFNα/β by TGFβ. However, IFNs are the key cytokines in tumor regression since they condition both the first wave of cell death but also the rapid recruitment of different immune cells in the tumor mass. Mechanistically, it turns out that TGFβ, by accumulating in spontaneous tumors, biases the polarity of myeloid cells towards an immunosuppressive phenotype which prevents the phosphorylation of IRF3 downstream of STING and therefore, the production of IFNα/β. Finally, the blocking of TGFβ in spontaneous tumors is sufficient to induce the regression of spontaneous mammary tumors (Guérin et al, 2019).

Despite very fine tumor regressions observed in our three tumor models, the majority of tumors relapse. We hypothesized that it is possible to prevent these relapses, obtained in the TC1 and PyMT tumor models after incomplete tumor regression, by maintaining T cell / myeloid cell cooperation.

To prevent these relapses, we used a anti-PD1 i.p treatment combined with IFNα injected locally, in order to respectively re-stimulate the CTLs and TAMs still present in the tumors. Our data indicate that the administration of this treatment after the initial regression phase very strongly reduces the relapse rate which drops from 70 to 15%. We suggest that the anti-PD1 + IFNα combination works by preventing the depletion of CTLs and allowing the maintenance of cytotoxic TAMs in the tumor since the CTLs and TAMs, purified from tumors treated with the anti-PD1 + IFNα combination are de novo cytotoxic when we put them in the presence of TC1 cells.

Thus, all of this work allowed me to highlight the importance of the induction of acute and local inflammation at the tumor site, necessary to mobilize the myeloid cells alongside the T and allow the regression of tumors. Finally, these results make it possible to propose new therapeutic anti-tumor combinations, which will take advantage not only of T lymphocytes, but also of myeloid cells which constitute the main population infiltrating human tumors.