Sympathetic improvement of cancer vaccine efficacy

Else Marit Inderberg and Sébastien Wälchli

ABSTRACT

The link between stress, other psychological factors and response to cancer, or even the cancer incidence and metastasis, is well established. The inhibition of β-Adrenergic receptors (β-AR) using β-blockers was demonstrated to have an inhibitory effect on cancer recurrence. Direct effects on the stress-induced suppression of anti-tumor immune responses were also shown. In a recent issue of Cancer Immunology Research, Daher and colleagues studied the molecular mechanism behind this protective effect in the context of cancer vaccination. They provided evidence that the β-AR signaling affected the priming of naïve CD8 + T cells in their myeloma model, rather than effector CD8 + T cells which downregulated the expression of β-AR after activation and became insensitive to such signaling. Blocking the β-AR signaling during vaccination led to increased expansion and effector functions of antigen-specific CD8 + T cells and reduced tumor growth. This has implications for the clinical use of β-blockers as adjuvants to enhance cancer vaccination and other types of immunotherapy.

There is still an important debate around the clinical efficacy of therapeutic cancer vaccines. A main issue resides in the various influence of the tumor microenvironment (TME) that will determine the therapeutic outcome. The type of cancer, the immune infiltration or “temperature” of the tumor (hot versus cold), the immune status of the patient and their HLA genotype can all actively influence the clinical response to vaccination. However, an aspect that is rarely mentioned is the psychological status of the patient; more precisely their stress level. Indeed, our sympathetic autonomous nervous system controls our response to external aggression by releasing catecholamine molecules, primarily leading to a “fight-or-flight” response. These molecules bind to β-AR and regulate quick response mechanisms. Thus, it is accepted that this stimulation should be sporadic rather than continuous. Therefore, in case of prolonged or chronic stimulation, deleterious effects have been reported. This is especially dramatic in the case of tumor growth where activation of β-AR has been shown to affect gene expression inducing tissue invasion and metastasis.

Immune cells such as lymphocytes also express β-AR, and have been reported to react to sympathetic nervous system stimulation, but only little was known on the implication, in particular during cancer treatment. β-blockers, or β-adrenergic blocking agents, work by blocking the binding of stress hormones (epinephrine and norepinephrine) to the β-AR. Different generation β- blockers interact with various β-ARs; β-1 adrenergic receptor (ADRB1), β-2 adrenergic receptor (ADRB2) and third generation β-blockers also have vasodilative effects. ADRB1 is predominantly expressed in cardiac tissue whereas ADRB2 is more widely expressed in other tissues, predominantly in lymphocytes in blood and frequently upregulated in cancer cells (source: Human Protein Atlas). The most widely tested β-blocker, the first generation propranolol, is nonselective and inhibits both ADRB1 and ADRB2. This was the first blocker to show clinical effect in cancer treatment as a single agent, both in retrospective and prospective studies. The effects of β-blockers can be measured by normalizing NK cell distribution and cytotoxicity, endothelial nitric oxide (NO) production and the effect on CD8 + T cells. β-blockers are mainly used to treat cardiac diseases such as ischemic heart disease, hypertension, arrhythmia and heart failure, but also have other clinical applications such as glaucoma, migraines and anxiety. The use of β-blockers can cause major side effects as β-ARs are expressed on many tissues and their blockade affects multiple metabolic and physiologic functions. They can prevent bronchodilation in asthmatic subjects, exacerbate peripheral artery disease with cold extremities, absent pulses, and, in some cases, cyanosis and gangrene. As β-ARs are also important in glucose metabolism, nonselective β-blockers can facilitate hypoglycemia which can be severe for diabetic patients. Furthermore, catecholamines have important effects on potassium balance and blockade of β-ARs can therefore cause hyperkalemia. Finally, depression, fatigue, and sexual dysfunction are commonly reported side effects of β-blockers, but have been shown to be rare in randomized studies. The use of β-blockers, like any drug, carries the risk of side effects, and any complicating factors or disease should be examined before use, especially because they also interact with several other drugs and are now likely to have wider therapeutic applications, not only in cancer.

Bucsko and colleagues described how decreasing housing temperature increased stress levels in preclinical mouse tumor models. Using a first generation β-blocker and β-AR knockout mice, the authors demonstrated that the differences in
Human memory CD8+ T cells express higher levels of β-AR receptors. Blocking stress hormone signaling through these receptors improves CD8+ T-cell priming in cancer vaccination.

It would be interesting to investigate the effect of β-AR signaling and its modulation by β-AR antagonists in the context of cancer vaccination. A recent report demonstrated that β-AR antagonists will need further testing as there are several important parameters to consider. First, the expression of β-AR differs between species and can be influenced by other physiological factors such as cytokine levels, and timing. The balance of CD4+ T helper subsets is also influenced by β-AR signaling, whereas a β-AR agonist, terbutaline, was previously shown to modulate the level of IL-17 and IFN-γ in T helper cells. It would be interesting to investigate the effect of β-blockers on CD4+ T-cell priming in vaccination.

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Interestingly, Daher and colleagues actually found that CD8+ TILs were not sensitive to β-AR signaling as previous reports would indicate. Naïve CD8+ T cells, however, seemed to be highly sensitive to stress and β-AR signaling strongly inhibited their activation. The benefit of β-blocker use was therefore seen at the site of priming, namely the tumor-draining lymph node (Figure 1). The β-blocker did not affect dendritic cell (DC) maturation or antigen presentation supporting its action through a direct effect on CD8+ T cells. It was previously proposed that β-AR signaling also affect monocytes and dendritic cells as an anti-inflammatory drug (reviewed in 18) which caused a shift from Th1 to Th2 differentiation of CD4+ T cells. However, here the authors tested the effect of the β-blocker on DCs using a setup with transgenic ovalbumin (OVA)-specific OT-1 cells which may be a system too robust to show subtle differences in priming.

Daher and colleagues further presented data supporting the difference in sensitivity to stress between naïve CD8+ T cells and TILs was due to downregulation of β-AR after activation. This could also be confirmed in vitro where naïve CD8+ T cells became insensitive to β-AR signaling upon activation, in the same manner as TILs.

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In conclusion, this paper paves the way to a better understanding of the influence of our psychological status on molecular mechanisms taking place during T-cell priming and cancer vaccination. An improved understanding of patient stress and how this may affect therapeutic response may support rational design of more efficient treatments. Combining cancer vaccination in patients with the administration of β-blockers as adjuvant could lead to a more powerful anti-tumor immune response.

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