Lactic Acid Suppresses Anti-Cancer Immunity

Subjects: Oncology

Contributor: Yuzhuo Wang

Lactic acid is no longer considered a waste product of the Warburg effect. Lactic acid in the TME is responsible for suppressing anticancer immunity. A number of recent studies provide evidence explaining how lactic acid impedes immune cell functions. In this section, we summarize its role in 1) inhibiting immune cell proliferation and survival; 2) inducing immune cell de-differentiation; and 3) signaling of downstream processes (Figure).

Keywords: Lactic acid ; Cancer-induced immunosuppression ; Epigenetic reprograming ; De-differentiation ; Anticancer immunotherapy ; Acidic tumour microenvironment

1. Introduction

Despite much research, success rates in treating advanced cancers have changed relatively little. One reason for this is that most research is highly specific and thus narrowly focused, often neglecting more widely fundamental aspects of cancer biology. In the last decade, cancer immunotherapy has become one of the most promising types of treatment. However, currently available immunotherapies focus only on restoring or enhancing isolated components of the immune system, often being directed at a single immune cell type. For example, there are over 2000 clinical trials investigating PD-1/PD-L1-targeted drugs**, yet** only a minority of patients will respond to these agents.

2. Influence and application

Lactic acid is considered a key “oncometabolite” that plays an important role in cancer biology both directly and through its acidification of the TME. It can promote angiogenesis, cancer cell migration, and metastasis. Furthermore, the excessive production of lactic acid by cancer cells and the resultant acidification of the TME suppress a whole host of innate and adaptive immune cells, leading to a critical hallmark of cancer – evasion of anticancer immunity. This is manifested in the inhibition of immune cell proliferation, induction of de-differentiation via epigenetic regulation, and alteration of cell functions via autocrine and paracrine signaling. By overcoming immune surveillance in low pH environments, cancer cells become better adapted for survival and metastasis.

We have previously reported that the role of lactic acid in cancer cell immune evasion seems to be evolutionarily conserved. It is also a mechanism utilized by pathogenic bacteria, endoparasites, and virus-infected host cells.

Lactic acid has complex effects on a wide spectrum of innate and adaptive immune cells that contribute to anticancer immunity. As described in this review, the effector functions that are inhibited by lactic acid and an acidic TME have been experimentally demonstrated as reversible in a variety of immune cell types across different cancers. Thus, if the acidic TME can be buffered back to a physiological condition, the anticancer functions of various immune cells can likely be restored. This has the potential to become an extremely powerful form of immunotherapy, although our proposed paradigm has not yet entered the mainstream of cancer discovery and therapy.