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Abstract

Deciphering the crosstalk between cancer stem cells and the tumor immune microenvironment †

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Abstract: Immune checkpoint blockade therapies aim to re-establish the antitumor immune response of effector lymphocytes. Although these therapies have revolutionized cancer treatment, only a minority of patients benefits from them. Two major aspects obstacle the effectiveness of immune-checkpoint inhibitor therapies, the composition of the tumor microenvironment and the quiescence of cancer cells including cancer stem cells (CSCs). Understanding the molecular mechanisms underlying these problems is key to boost antitumor immunity.

Eukaryotic cells have evolved complex systems to decipher and respond to signals that come from the environment. One of the second messengers widely used in nature by both plant and animal cells to interpret environmental stimuli is the Ca2+ ion. In response to extracellular stimuli, the intracellular concentration of Ca2+ increases. Ca2+ sensors such as calmodulin and calcineurin (CN) are conserved in evolution from plants to humans. In plants, yeasts and fungi, CN is recognized as a stress sensor that decides on cell proliferation and survival in response to environmental signals. CN, a serine (Ser)/threonine (Thr) phosphatase, serves as an important translator of information from the local calcium rise to the effectors that direct cellular responses. For instance, it is activated in dendritic cells (DCs) downstream of Pattern Recognition Receptors (PRRs) in response to microbial stimuli and is responsible for their terminal differentiation, moreover CN activation in T and B cells is fundamental for their proliferation and differentiation. The tumor-intrinsic role of CN in controlling the formation of the tumor microenvironment, quiescence of CSCs, and the responsiveness to immune checkpoint inhibitor therapies are discussed.

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