Appendix 1 Glossary of terms

Tumor microenvironment: A combination of normal cellular and tumor elements and key factors that interact at a microscopic level. Including different cell types and various growth factors and cytokines secreted by these cells that act on one another.

Cell of origin: Refers to the original cell that a diffuse large cell lymphoma originates in. The two basic cell types are either cells located outside the germinal center (lymphoma is known as ABC or "activated B-cell" type) or cells that are located within the germinal center (lymphoma is known as GC or "Germinal Center" type).

Digital gene expression measurements: Described as a sequence-based study of the way genes are transcribed to synthesize functional RNA species or protein products for gene expression that generates a digital output.

Components of caveolae: Caveolae are specialized subdomains of the plasma membrane that can bud from the plasma membrane to form an endocytic vesicle or can flatten into the membrane to help cells withstand mechanical stress.

Extracellular matrix: Defined as a non-cellular component of a tissue, it provides not only essential physical scaffolding for the cellular constituents but also initiates crucial biochemical and biomechanical cues that are required for tissue morphogenesis, differentiation, and homeostasis. Extracellular matrix components can be put into three categories: adhesive proteins, structural proteins, and proteoglycans.

Housekeeping genes: are defined as genes that are consistently expressed across tissues, essential for carrying out cellular maintenance, and conserved across species. These genes, including β-actin, β-tubulin, and GAPDH, are used most often as protein loading controls or internal references to normalize the target protein expression.

Nanostring-based GEP profiling study: Nanostring is a piece of DNA (probe) attached to a linear sequence of fluorophores made up of four different colors (barcode). Each probe is complementary to a unique target oligonucleotide. NanoString Technologies has developed automated workflow platforms enabling researchers to visualize and quantify gene and protein expression in tissue sections down to single-cell and subcellular resolutions.

Immune checkpoint molecules: Immune checkpoint molecules are expressed on different immune cells, tumor cells, or other cell types and are defined as ligand-receptor pairs that exert inhibitory or stimulatory effects on immune responses. When the checkpoint and partner proteins on other cells bind together, they send an "off" signal to the T cells. They are crucial for maintaining self-tolerance and modulating the duration and amplitude of physiological immune responses to minimize collateral tissue damage.

Tumor-infiltrating lymphocytes: Tumor-infiltrating lymphocytes include T cells and B cells and are part of the larger category of 'tumor-infiltrating immune cells', which consist of both mononuclear and polymorphonuclear immune cells in variable proportions. They are implicated in killing tumor cells. The presence of lymphocytes in tumors is often associated with better clinical outcomes.

Immune surveillance: Cancer immune surveillance is an important host protection process to inhibit carcinogenesis and maintain cellular homeostasis. This response is mainly given by T cells and natural killer cells.

Small-molecule inhibitors: Small-molecule inhibitors inhibit the target proteins' function by binding to the "pocket" on their surface. Small-molecule inhibitors can bind a wider range of extracellular and intracellular targets.

CAR-T therapy: Chimeric antigen receptors (CARs) are receptor proteins that have been engineered to give T cells the new ability to target a specific antigen. The receptors are chimeric in that they combine both antigen-binding and T cell activating functions into a single receptor. CAR-T cell therapy uses T cells engineered with CARs to treat cancer. T cells are modified to recognize cancer cells and destroy them.

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