**Tissue restricted antigens (TRAs)**

Tissue-restricted antigens (TRAs) are genes which are highly expressed in a few tissues of the body in comparison to other tissues. They stand in contrast to housekeeping genes, which are expressed in many tissues of the body.

These genes are up-regulated in the medullary part of the thymus (mTECs) in order to teach developing T-cells in a process called negative selection not to react to them. These T cells are out selected by apoptosis. Only 5% of all T cells survive these selection procedures (positive selection and negative selection). While they are tested in the positive selection on self-MHC they are tested in the negative selection on self-antigens-self MHC. If these selection procedures don’t work well, human suffer of multiple autoimmune diseases.

**Promiscuous gene expression (pGE):** expression of a highly diverse set of genes in mTECs, which are otherwise expressed in a strictly tissue-restricted fashion (Kyewski, 2004)  
-> Thymic epithelial cells (TECs) express wide host of TRAs   
-> phenomenon unique to TECs and poorly understood  
-> Self-antigens expressed by mTECs represent basically all parenchymal (peripheral) organs

AIRE is a transcription factor that activates the expression of TRA genes in mTECs (Žumer, 2013). Therefore, responsible for negative selection -> reduces threat of auto-immunity.

**T-cell selection**

A mature T-cell needs to be able to bind to the MHC molecule ("positive selection"), and not to react against antigens that are actually from the tissues of body ("negative selection") (Kyewski, 2004).

Loss of over 95 % of thymocytes in selection process

Positive selection: Thymic cortex (Hiroyuki, 2017)

* TCRs generated by DNA rearrangement: functional -> Thymocyte expresses CD4 and CD8 simultaneously
* Tested for their capacity to engage host MHC molecules: functional -> MHC class I or II results in mature CD4+ or CD8+ cells
* Most apoptotic death attributed to failure of positive selection (death by neglect)

Negative Selection: Thymic medulla (Hiroyuki, 2017)

* Diversity of TCRs important for protection against pathogens, but TCR rearrangement also generates a certain number of T-cells that recognize self-antigens
* Auto-reactive T-cell negatively selected to ward of self-reactivity -> avoidance of autoimmune diseases
* Major mechanism for central tolerance

**TRAs and cancer**

For some reason these genes are often up-regulated in cancer, although this atopic gene expression should not take place and can due to the negative selection of T cells in the thymus not react to these genes. The tumor down regulates the MHC molecules and escapes the immune system.

For this reason, tissue-restricted antigens (TRAs) are potentially good drug targets both in cancer therapy as also in cancer immunotherapy. Among these genes, there are several gene groups, which have been already in focus of cancer immunotherapy, such as testis-specific antigens (CTAs), but also oocyte-specific genes, others are still very unknown, such as kallikrein genes, casein genes, skin-specific genes, pancreas-specific genes, and the role of TRAs in developmental processes in general.

**Central tolerance in cancer (Kyewski, 2004)**

Depending on the nature of the target antigens, the immune response to tumors can be categorized either as a response directed against self or foreign:

* Foreign: tumor antigens arising from genetic alterations specific to a tumor  
  -> immune response through pathogen-driven immunity (“normal”)
* **Self: Tumor-associated self-antigens (induced or upregulated in tumor cells)**  
  -> central or peripheral self-tolerance should eliminate threat

Problem of self-tolerance through pGE: several categories of tumor-associated self-antigens are reproducibly detectable in mouse or human mTECs  
-> e.g. differentiation antigens, cancer germ cell antigens, onco-fetal antigens (e.g. CEA)

Expression of for example CEA antigens in mTECs induce central tolerance. Only T cells of low avidity escape the central tolerance induction, and this blunted repertoire is incapable of eradicating CEA-expressing mouse tumor cells even after repeated immunization.

Possible therapy: specific elimination of Tregs holds great promise to recruit the available T-cell repertoire   
-> clinical trails on humans