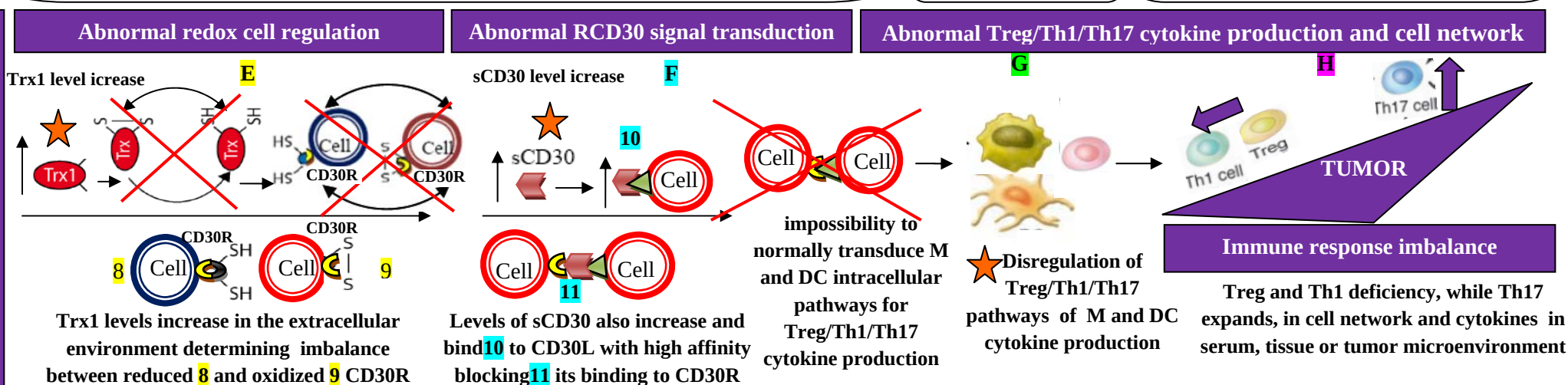
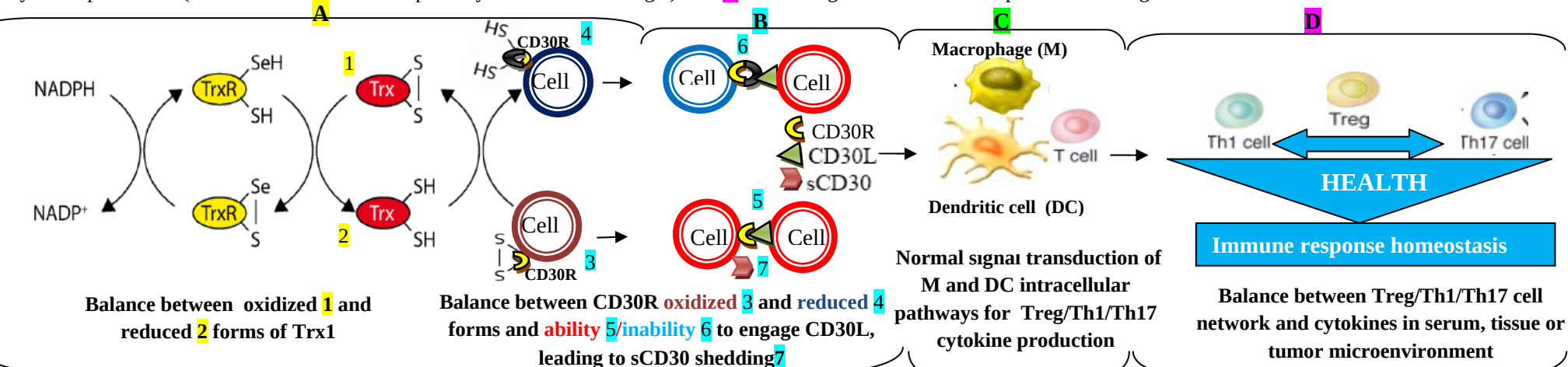


Online Resource 1 The Trx1/CD30 system is a promising new target for tumor therapy aimed at the simultaneous optimization of redox and immune system regulation: serum, tissue or tumor microenvironment levels of Trx1 and soluble(s) CD30 and Treg/Th1/Th17 cytokine production are functional biomarkers ★ of the extracellular and intracellular pathways. In tumor disease, levels of Trx1 and sCD30 and Treg/Th1/Th17 cytokines within physiological normal ranges are potentially positive (benefit) biomarkers of immunological function and therapeutic response, while significant increases in their levels reflects immunological deficit and a lack of therapeutic response and can therefore be considered a potentially, negative (risk) biomarker. Trx1 has a conserved catalytic site (-Trp-Cys-Gly-Pro-Cys-Lys) that undergoes reversible oxidation to the cysteine-disulfide (Trx-S₂) form through the transfer of reducing equivalents to a disulfide substrate (X-S₂). **A**: in health, the oxidized (1) Trx1 form (Trx-S₂) is converted back to the cysteine-thiol reduced (2) form [Trx-(SH)₂] by the NADPH-dependent flavoprotein thioredoxin reductase (TrxR), so maintaining balance between oxidized and reduced Trx1 forms, and catalytically interacts with CD30 cell membrane receptor (CD30R) on the immune cells (9). **B**: the consequent oxidized (3) and reduced (4) states of CD30R determine its respective ability (5) or inability (6) to engage its ligand CD30L. In this way it is possible to transduce signals of **C** M and DC intracellular pathways for Treg/Th1/Th17 cytokine production, leading to **D** balance of Th differentiation into Treg/Th1/Th17 cells, for immune response homeostasis. **E**: in tumor, an increase in Trx1 levels leads to abnormal redox cellular regulation related to tumor aggressiveness (23-25) and immunological deficit. **F**: when levels of sCD30 (shed from the plasma membrane upon CD30L binding 7) increase, sCD30 binds to CD30L with high affinity blocking CD30/CD30L transmembrane signalling (36). Thus, abnormal increases in the levels of Trx1 and sCD30 (biomarkers of extracellular pathways of Trx1/CD30 target) result in both **G** dysregulation of M and DC pathways of Treg/Th1/Th17 cytokine production (biomarkers of intracellular pathways of Trx1/CD30 target) and **H** immunological deficit: Th17 expansion and Treg and Th1 cell functional deficit



HEALTH

DISEASE

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