

What do STAT proteins transcribe?

Introduction

- The diagram on the next page builds on previous content, including “*How are protein products made from a gene?*” and “*How do STAT proteins work?*”. That content described how STAT proteins are transcription factors; their job is to transcribe target genes. Remember that transcription is when the DNA of a specific gene produces RNA. The analogy: a gene is a recipe, and copying it down is like making RNA.
- This content will go over some genes that STATs can transcribe. STAT proteins cause transcription of many genes. In healthy individuals, STATs cause transcription of genes, however the transcription is turned off at the appropriate time. In LGLL, this process is dysregulated, and STATs continually transcribe target genes. This produces protein products that are now in excess and can cause harmful effects.
- Two classes of proteins that STATs transcribe and are found at increased levels in LGLL are cytokines and survival proteins. Just as transcription factors have a specific job to carry out, so do these proteins. Overall, STATs help promote the survival and function of the cytotoxic (killer) T-cells and NK-cells.
 - Cytokines – these are proteins that are produced by immune cells during an immune response. Some cause inflammation (pro-inflammatory) while others suppress inflammation (anti-inflammatory). You can think of an inflammatory cytokine as a poison. In LGLL, pro-inflammatory cytokines are generally increased compared to a healthy individual, and this can drive the disease. The diagram will show you how this can occur.
 - Survival proteins – these proteins perform functions in the cell that allow the cells to stay alive. In LGLL, these proteins can be upregulated, meaning LGL cells stay alive longer than they should.
 - More information about these types of proteins will be covered in depth in the future.

STATs transcribe cytokines which can cause inflammation and drive cancer

1. A cytokine will bind its specific receptor (Y-shaped in this diagram) on the outside of the cell; this causes changes to happen inside the cell (cell signaling). The gray triangles are JAK proteins (Janus kinase). They associate with the receptor and become activated (phosphorylated, depicted by blue circle).

2. STAT monomers (one STAT protein) need to be modified by phosphorylation in order to become dimers (two STATs bound together) to exert transcriptional effects in the nucleus.

3. Specific JAK proteins will phosphorylate specific STAT proteins. If this occurs, two phosphorylated STATs can form dimers and go into the nucleus.

4. The STAT dimer causes transcription of genes in the nucleus. This produces messenger RNA of a gene. It carries the message of the cytokine gene. Other types of RNA are in the cell but are not discussed here.

8. The cytokine binds its specific receptor, and the process begins again. If STAT signaling becomes dysregulated, this process will be a positive feedback loop: increased STAT causes increased cytokine production, which in turn feeds back to more STAT activation.

7. The cytokine is excreted from the cell. It can now bind the receptor of the cell it came from (if the receptor is present) or of another cell.

6. The amino acid sequence folds into a 3-dimensional structure, and is now an active protein (in this case, a cytokine).

5. The cytokine gene RNA is exported from the nucleus to the cytoplasm. The RNA is translated into a sequence of amino acids.

