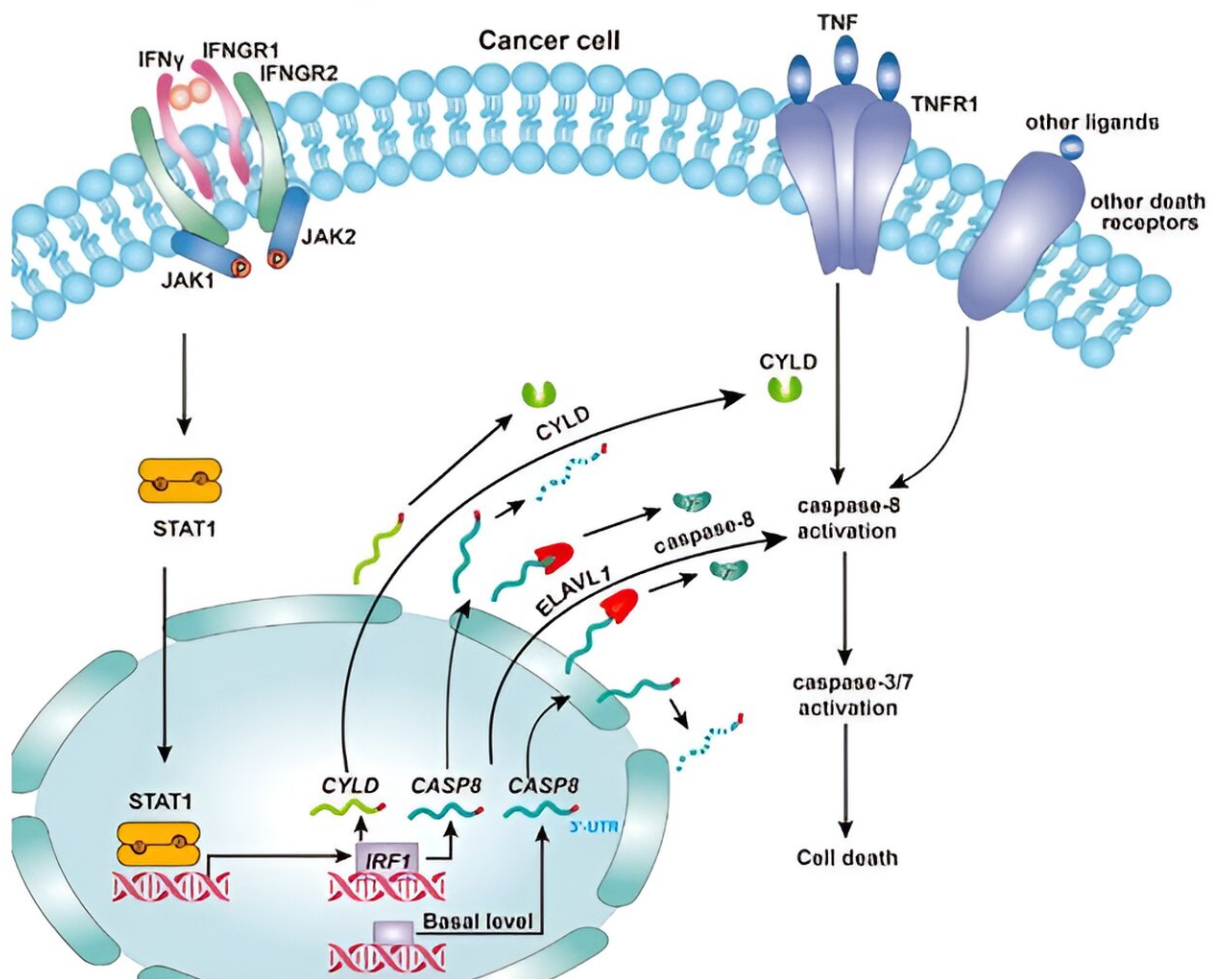


# Researchers reveal novel biochemical mechanism of cytokine-induced cell death

February 19 2024, by Zhang Nannan



Biochemical mechanism of TNF and IFN $\gamma$ -induced cancer cell death. Credit: IGDB

Uncovering the biochemical mechanisms underlying different types of cell death has the potential to provide targets for the treatment of various diseases. A physiological cytokine combination (TNF+IFN $\gamma$ ) has been identified that induces cell death in several cell lines in vitro. However, because TNF and IFN $\gamma$  are multi-effector cytokines, their individual and combined use has complex effects. In disease situations, it is difficult to distinguish which effects are triggered by TNF+IFN $\gamma$  cell death.

The latest discovery by a research team led by Prof. Ai Youwei from the Institute of Genetics and Developmental Biology (IGDB) of the Chinese Academy of Sciences provides new insights into answering this scientific question. [The work](#) is published in the *Journal of Cell Biology*.

In this study, the researchers used RNA-seq and CRISPR-Cas9 genetic screening to show that IFN $\gamma$  activates its transcription factor IRF1. It directly binds to specific interferon-sensitive response element (ISRE) positions in the CASP8 and CYLD promoters, upregulating their expression and promoting TNF-induced cell death through a synergistic effect.

In addition, they found that the IFN $\gamma$ -upregulated CASP8 mRNA has a short half-life and requires stabilization by the RNA-binding protein ELAVL1 to translate sufficient protein to mediate cell death.

Therefore, in the future, simultaneous mutation of CASP8 and CYLD ISRE motifs in the promoter region in [cancer cells](#) or mouse genomes could be used to abolish the regulation of IFN $\gamma$  on cell death and inhibit TNF+IFN $\gamma$ -induced cell death. This allows researchers to evaluate the role of TNF+IFN $\gamma$ -induced [cell death](#) in immunotherapy and tissue damage.

**More information:** Buhao Deng et al, TNF and IFN $\gamma$ -induced cell death requires IRF1 and ELAVL1 to promote CASP8 expression,

*Journal of Cell Biology* (2024). [DOI: 10.1083/jcb.202305026](https://doi.org/10.1083/jcb.202305026)

Provided by Chinese Academy of Sciences

Citation: Researchers reveal novel biochemical mechanism of cytokine-induced cell death (2024, February 19) retrieved 16 May 2024 from <https://phys.org/news/2024-02-reveal-biochemical-mechanism-cytokine-cell.html>

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