Alpha interferon induces long-lasting refractoriness of JAK-STAT signaling in the mouse liver through induction of USP18/UBP43

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Recombinant alpha interferon (IFN-alpha) is used for the treatment of viral hepatitis and some forms of cancer. During these therapies IFN-alpha is injected once daily or every second day for several months. Recently, the long-acting pegylated IFN-alpha (pegIFN-alpha) has replaced standard IFN-alpha in therapies of chronic hepatitis C because it is more effective, supposedly by inducing a long-lasting activation of IFN signaling pathways. IFN signaling in cultured cells, however, becomes refractory within hours, and little is known about the pharmacodynamic effects of continuously high IFN-alpha serum concentrations. To investigate the behavior of the IFN system in vivo, we repeatedly injected mice with IFN-alpha and analyzed its effects in the liver. Within hours after the first injection, IFN-alpha signaling became refractory to further stimulation. The negative regulator SOCS1 was rapidly upregulated and likely responsible for early termination of IFN-alpha signaling. For long-lasting refractoriness, neither SOCS1 nor SOCS3 were instrumental. Instead, we identified the inhibitor USP18/UBP43 as the key mediator. Our results indicate that the current therapeutic practice using long-lasting pegIFN-alpha is not well adapted to the intrinsic properties of the IFN system. Targeting USP18 expression may allow to exploit the full therapeutic potential of recombinant IFN-alpha.

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