Tumour cells can escape antiproliferative pressure by interferon-β through immunoediting of interferon receptor expression

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Abstract

Type I interferons (IFNs) play a central role not only in innate immunity against viral infection, but also in the antitumour response, e.g. through a direct impact on cell proliferation. Particularly for cancer arising in the context of chronic inflammation, constant exposure to IFNs may constitute a strong selective pressure during tumour evolution. Expansion of neoplastic subclones resistant to the antiproliferative effects of IFNs may contribute to immunoediting of tumours, leading to more aggressive disease. Experimental evidence for this development of IFN-insensitivity has been scarce and its molecular mechanism is unclear. In this study we demonstrate that six weeks exposure of cells to IFN-β in vitro reduces their sensitivity to its antiproliferative effects, and that this phenotype was stable for up to four weeks. Furthermore, we observed substantial differences in cellular sensitivity to growth inhibition by IFN-β in a panel of ten different liver cancer cell lines, most prominently in a pair of highly dedifferentiated cell lines, and least in cells from well-differentiated tumours. In both, long-term IFN selection and in dedifferentiated tumour cell lines, we found IFNAR2 expression to be substantially reduced, suggesting the receptor complex to be a sensitive target amenable to immunoediting. Beyond new insights into possible molecular processes in tumour evolution, these findings might prove valuable for the development of biomarkers allowing to stratify tumours for their sensitivity to IFN treatment in the context of patient tailored therapies.