

Irinotecan treatment and senescence failure promote the emergence of more transformed and invasive cells that depend on anti-apoptotic Mcl-1.

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Résumé en anglais	<p>Induction of senescence by chemotherapy was initially characterized as a suppressive response that prevents tumor cell proliferation. However, in response to treatment, it is not really known how cells can survive senescence and how irreversible this pathway is. In this study, we analyzed cell escape in response to irinotecan, a first line treatment used in colorectal cancer that induced senescence. We detected subpopulations of cells that adapted to chemotherapy and resumed proliferation. Survival led to the emergence of more transformed cells that induced tumor formation in mice and grew in low adhesion conditions. A significant amount of viable polyploid cells was also generated following irinotecan failure. Markers such as lgr5, CD44, CD133 and ALDH were downregulated in persistent clones, indicating that survival was not associated with an increase in cancer initiating cells. Importantly, malignant cells which resisted senescence relied on survival pathways induced by Mcl-1 signaling and to a lesser extent by Bcl-xL. Depletion of Mcl-1 increased irinotecan efficiency, induced the death of polyploid cells, prevented cell emergence and inhibited growth in low-adhesion conditions. We therefore propose that Mcl-1 targeting should be considered in the future to reduce senescence escape and to improve the treatment of irinotecan-refractory colorectal cancers.</p>
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Liens

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