4th Geneva Aging Workshop - Aging and Cancer at the Crossroads

MOUSE MODELS TO STUDY THE INTERACTION BETWEEN MYC AND TELOMERASE

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Deregulation of Myc is a frequent event in human cancer, suggesting a critical role of Myc activation during tumor formation and/or maintenance. In support of this idea, evidence obtained over the last two decades indicates that Myc activation triggers a plethora of events that are advantageous for both tumor formation and maintenance, such as enhanced proliferation, differentiation blockage or angiogenesis. But, at the same time, Myc activation can be detrimental for tumor growth as increases the probability of neoplastic cells to be eliminated through apoptosis. To exploit Myc-induced sensitization to apoptosis in tumor therapy, an attractive strategy would be, instead of inhibiting Myc, to specifically target Myc effectors involved in its procarcinogenic functions.

One of the pro-carcinogenic effectors of Myc could be the enzyme telomerase, whose catalytic subunit has been recently identified as a transcriptional target of Myc using *in vitro* systems. Telomerase has been considered an attractive target for therapeutic strategies since it is reactivated in the vast majority of human cancers. Recent reports indicate that telomerase not only might promote tumorigenesis stabilizing chromosome ends, but also affecting cell proliferation.

Here, we present data demonstrating that Myc activates telomerase *in vivo*, and that this is an event required to elicit a full hyperplastic Myc-induced response in a switchable skin tumorigenesis model. The presence of critically short telomeres in the absence of telomerase activity further reduces the hyperplasia induced by Myc. On the other hand, telomerase overexpression accelerates Myc-induced hyperplasia without changing telomere length, suggesting a direct role of telomerase in the hyperplastic response independent of telomere maintenance. Finally, a possible mechanism by which telomerase gene dosage and telomere length could influence Myc-induced skin hyperplasia involving skin stem cell number and capability to mobilize is also discussed.