c-MYB and TGFβ: EMT's dynamic duo in breast cancer

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c-MYB is the prototype member of a small family of transcription factors that include B-MYB and A-MYB, involved in cell survival, proliferation, differentiation and transformation.[1]

c-MYB has been studied extensively in the hematopietic system, where it plays an important role in the maintenance and differentiation of stem cells, explaining its frequent deregulation in leukemias.[2] Recent evidence corroborates the hypothesis that a key function of c-MYB is to control stem cells in different tissues, and it is thought to exert its physiological and cancer-promoting functions by transactivating key target genes involved in cell growth, self-renewal and anti-apoptosis.[1,3]

A recent study by the group of Giuseppe Raschellá has established that c-MYB activates epithelial-to-mesenchymal transition (EMT) in human cancer cells of different origin by transactivating SLUG.[4] SLUG is a developmentally regulated gene important for specification of the neural crest, aberrantly expressed in aggressive, metastatic forms of cancer. Other groups have independently demonstrated that c-MYB activity is required for EMT in the neural crest and the development of SLUG-expressing neural crest structures in lower vertebrates, suggesting that regulation of EMT by c-MYB occurs in different patho-physiological settings and is evolutionary conserved.[5,6]

In a new study published in the December 1st issue of *Cell Cycle*, Raschellá and coworkers show that c-MYB is a TGFβ-regulated gene in estrogen receptor-positive (ER+) mammary cancer cells. Using different approaches, they demonstrate that c-MYB is upregulated by TGFβ, at least in part by suppression of the miR200 network. "Seed" sequences belonging to members of miR200 family are identified in the 3′ untranslated region of c-MYB and are shown to be essential for miR downregulation. In the presence of TGFβ, the miR200 members are inactivated, resulting in stabilization of c-MYB. Notably, the expression of BCL2 and SLUG evoked by TGFβ is blunted after silencing c-MYB in breast cancer cell lines. The authors conclude that c-MYB is a new TGFβ target gene, explaining how mechanistically TGFβ promotes EMT in breast cancer cells.

A limitation of the study is that it has been conducted with cell lines in vitro, so it will be important to corroborate the findings in mouse models of breast cancer and in the context of primary human tissues. Notwithstanding this limitation, the paper is consistent with recent investigations from the Ramsay and Gonda laboratories, also suggesting that c-MYB has a promoting role in ER+ breast cancer.[1] This unified picture is somewhat complicated by other studies in which the expression of c-MYB has been associated with very good prognosis in breast cancer.[7] Furthermore, c-MYB transcriptionally activates Hep27, resulting in attenuation of Mdm2 and stabilization of p53 in ER+ breast cancer cells.[8] To explain these contradictory results, one could hypothesize that the phenotypic outcome of c-MYB activation in breast cancer cells depends on signals from the microenvironment. For example, TGFβ is produced by stromal myofibroblasts to support breast cancer progression.[9] In this context, c-MYB could promote a more aggressive tumor phenotype by activating SLUG. In other circumstances, c-MYB expression could be beneficial to patients' prognosis by supporting the function of p53, thus imparting a more benign phenotype to breast cancer cells. Whatever the case may be, the new study from the Raschellá group further brings c-MYB at the center stage of EMT signaling and breast cancer, reiterating the fundamental importance of this oncoprotein in development and disease.

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A double whammy for aging? Rapamycin extends lifespan and inhibits cancer in inbred female mice

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Aging is a highly complex, multifactorial process. Evidence collected over the last two decades has nonetheless vividly demonstrated that specific genetic mutations can extend lifespan, and that the pathways involved are highly conserved across wide evolutionary distances.[1,2] The nutrient-sensing target of rapamycin (TOR) pathway plays a key role in cellular growth and metabolism and is a highly conserved modulator of aging.[2-4] At the core of this pathway lies the TOR kinase, which forms the catalytic subunit of two distinct complexes; TOR complex 1 (TORC1) and TORC2.[4] TOR primarily mediates its metabolic effects through the phosphorylation of

downstream effectors such as S6 kinase 1 (S6K1) and eIF4E-binding protein1 (4E-BP1).[2,4] Critically, the TOR pathway is also highly accessible to pharmacological intervention, with rapamycin specifically inhibiting the ability of TORC1 to phosphorylate its downstream effectors. Rapamycin treatment has been shown to increase lifespan in yeast, Drosophila and genetically heterogeneous mice,[5-8] to augment stress resistance in Drosophila[2] and to delay and/or reduce pathology in several mouse models of disease.[4] These findings have pushed rapamycin and associated rapalogs to the forefront of candidate drugs that could ultimately be capable of improving health during aging in humans.

In the December 15th issue of *Cell Cycle*, a study by Anisimov and colleagues demonstrates that lifelong rapamycin treatment extends the lifespan of inbred female 129/Sv mice.[9] Notably, the drug improved survival to extreme older ages, with 31% of the rapamycin treated group but only 10% of the control group alive at 900 d of age. Importantly, this research shows that rapamycin's positive effects on lifespan appear consistent across different genetic backgrounds in mice, with the earlier work undertaken using heterogeneous (UM-HET3) mice[6,7] or cancer-prone HER-2/neu mice.[8] These data are reassuring, given that genetic background can profoundly influence the effect of a particular intervention on lifespan.[10,11] In addition, it is crucial that the effects on lifespan of particular pharmacological agents are consistent across different mouse strains if they are eventually to be clinically tested.[7] The study also demonstrated that, irrespective of how rapamycin is delivered, be it via diet[6,7] or via subcutaneous injection (this study), the beneficial effects on lifespan are demonstrable. Interestingly, in the study by Anisimov et al., the rapamycin was injected three times weekly only every second fortnight, indicating that intermittent treatment is sufficient to increase adult lifespan. It has been suggested that one possible drawback of early-life treatment with rapamycin is that it could potentially affect growth during critical developmental stages. However, rapamycin treatment in this study was initiated from 2 mo of age with no apparent effect on growth during development, although the rapamycin treated mice were significantly lighter later in life, associated with a reduction in food intake. There could also have been metabolic effects on body weight, because a previous study reported that rapamycin retarded an age-related decline in spontaneous activity, but only in male mice.[6]

Another striking finding was that significantly fewer of the rapamycin-treated mice had tumors (specifically uterine tumors) compared with control mice despite the incidence of chromosomal aberrations in bone marrow cells being significantly higher at 26 mo of age. These findings contrast with other studies,[6,7] where comprehensive pathological investigation indicated that rapamycin did not alter the presumed cause of death. The reason for this discrepancy is unclear, but one could certainly speculate that life-long supplementation is necessary to induce this anticancer effect. Again, it is remarkable that this effect on tumorigenesis was observed despite rapamycin being administered only intermittently. A detailed study of the effects of rapamycin on the incidence and timing of different types of tumor would seem warranted.

This work raises several important questions regarding rapamycin and its impact on lifespan and health. First, it is critical to now determine exactly what causes of death are ameliorated by rapamycin to extend lifespan, beyond the implicated effects on cancer. Second, interventions that increase lifespan are often sex-specific in their effects, and, indeed, rapamycin seems to increase lifespan more in female mice[7] and Drosophila[5] compared with males. A comparable study of effects of rapamycin on lifespan and causes of death in male mice is needed. Third, as the authors themselves suggest, it is now critical to determine whether later-life rapamycin treatment (e.g., 9 or 20 mo) using this same protocol for delivery of the drug has as great an effect on health and survival as does lifelong administration. We do not yet know if it will be possible to obtain the full protective effects by starting drug treatment in older animals. Fourth, it will be important to understand exactly how rapamycin increases lifespan. An obvious first step will be to determine how the drug alters downstream cellular processes, such as autophagy and translation, by determining if mutations that block these responses abrogate the effects of the drug. It will also be important to determine if TOR inhibition by rapamycin has effects beyond those of other pathways that extend lifespan, such as reduced insulin/IGF signaling. This will start to reveal whether pharmacological inhibition of more than one target is needed to maximize health benefits during aging. Ultimately the aim is to translate this knowledge into interventions that can increase healthy lifespan in humans. Excitingly, from this perspective, recent data from the Leiden longevity study suggests that individuals from long-lived families have decreased expression of genes associated with the mTOR pathway.[12]

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