HMW-FGF2 DID NOT INDUCED THE SENESCENCE CAUSED BY LMW-FGF2 IN RAS-TRANSFORMED CELLS.

Dermargos, A., Murata, G. M. and Armelin, H. A.

Departamento de Bioquímica, Instituto de Química, Universidade de São Paulo, São Paulo, Brasil. e-mail: dermagos@iq.usp.br

The isoforms of FGF2, the founder of the large FGF family, have regulatory roles in mitogenesis, cellular differentiation, organ morphogenesis and tissue repair. Translation from a single mRNA yields different molecular isoforms of FGF2 displaying a common C-terminal sequence. The 18 kDa form (LMW-FGF2) is released to the extra-cellular milieu and binds to FGFRs with paracrine and autocrine functions. On the other hand, higher molecular weight forms (HMW-FGF2: 21, 22, 22,5 and 34 kDa) are intracellular species that interact with unknown partners and remain without defined intracrine functions. Recently we demonstrated that recombinant LMW-FGF2 inhibits proliferation by inducing senescence in Ras-dependent malignant mouse cells (Costa et al., 2008). Herein, we report that recombinant HMW-FGF2 does not trigger this LMW-FGF2 toxic effect in Ras-dependent malignant cells. Y1 adrenocortical malignant cells were treated with recombinant HMW-FGF2 (22.5 kDa) and analyzed by : growth curves, clonogenic assays, ^{3}H-timidine uptake into DNA and ERK ½ activation. Our results demonstrated that HMW-FGF2 stimulated ERK 1/2, but, differently from LMW-FGF2, did not induce senescence in Y1 cells. In addition, non tumorigenic Balb 3T3 cells displayed the same mitogenic response to both LMW or HMW FGF2. These results suggest that both FGF2s (18 and 22,5 kDa) activate ERK 1/2, a key kinase downstream of FGFR, but only the LMW-FGF2 induces senescence in Ras-dependent malignant cells.

Supported by: FAPESP and CNPq