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P6

The presence of HOFI promotes tumor progression

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HOFI (homologue of FISH, SH3PXD2B) is a typical adapter protein with an N-terminal phagocyte oxidase homology (PX)-domain followed by a set of four SH3-domains. Its involvement in the regulation of cell migration, the development of functional podosomes and lamellipodia suggested that it may play a role in tumor progression. The fundamental role of HOFI in the regulation of mammalian development strongly suggests its involvement in the development of a functional tumor-associated stroma (TAS). TAS is considered to be a major contributing factor to tumor progression. In this work, first we investigated the role of HOFI in the regulation of tumor cell proliferation both in vitro and in vivo. Next, we studied the contribution of HOFI in the organization of TAS in various murine models. We found decreased proliferation in vitro and diminished growth in SCID mice when HOFI expression was silenced in A2058 human melanoma cells. In addition, subcutaneous injection of B16-F10 murine melanoma cells into HOFI-deficient animals resulted in a significant reduction of tumor growth compared to wild type animals. To examine the contribution of HOFI to the immune compartment of the TAS we also injected B16-F10 cells into bone marrow chimeras that received either wild-type or HOFI-deficient bone marrow. Interestingly, tumor growth was also impaired in chimeras, receiving HOFI-deficient bone marrow suggesting a role for HOFI in tumor-specific immunosurveillance. Taken together, HOFI appears to be an intrinsic tumor promoting factor controlling the growth rate of transformed cells as well as extrinsic, indirect regulator of TAS. Based on our bone marrow transfer experiments, HOFI should control one or more subsets of tumor-infiltrating immunocytes involved in anti-tumor responses. This work was supported by the Hungarian Research Fund OTKA K 109444.

P7

Beyond initiation: Human P53 plays role in transcription elongation

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The P53 tumor suppressor regulates the transcription initiation of selected genes by binding to specific DNA sequences at their promoters. Here we report a novel role of P53 in transcription elongation in human cells. Upon transcription elongation blockage P53 is associated with genes, which have not been reported earlier as its direct targets. P53 could be co-immunoprecipitated with active forms of RPB1, highlighting its association with the elongating RNAPII. During normal transcription cycle, P53 and RPB1 localized at distinct regions of selected non-canonical P53-target genes and this pattern of localization was changed upon transcription elongation block. Additionally, transcription elongation block induced the ubiquitylation and the proteosomal degradation of RPB1. Finally, we showed that the transcription block induced RPB1 degradation is mediated by P53. Our results reveal a novel role of P53 in human cells during transcription elongation blockage that might serve to facilitate the removal of RNAPII from DNA.

P8

Competition of apoptotic and necrotic cells for uptake by bone marrow-derived macrophages

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One of the major roles of professional phagocytes is the removal of dead cells. The uptake of apoptotic cells is well described as the final stage of programmed cell death including the sensing of corpses via „find me" signals, the recognition of apoptotic bodies via „eat me" signals, and the internalization mechanism. Without prompt and effective phagocytosis uncleared corpses can undergo secondary necrosis promoting inflammation and autoimmunity. In contrast to the apoptotic cell phagocytosis, much less is known about the clearance of necrotic cell debris. Since necrotic and apoptotic cell surface shares, at least partially, the same molecules the question arose which cell type is the preferred pray of macrophages, when both cell types are present and how effective is the engulfment of necrotic and apoptotic cells? We studied the phagocytosis of necrotic and apoptotic thymocytes and NB4 cells by mouse bone marrow-derived macrophages and measured the phagocytosis by two- or three-color flow cytometry and fluorescent microscopy. In our