

BOLSA DE INVESTIGAÇÃO (M/F)

Referência: PTDC/SAU-OBD/100261/2008 - FCOMP-01-0124-FEDER-011264

Título do Projecto: “Dissecting the cross-talk between mitotic checkpoint, ageing and cancer: towards the understanding of cell fate after mitotic slippage”

Código interno: PR223305

Está aberto concurso para recrutamento de um(a) bolseiro(a) de Investigação para colaborar no projecto acima referido, financiado pelo programa COMPETE - Programa Operacional Factores de Competitividade na sua componente FEDER e pelo orçamento da Fundação para a Ciência e a Tecnologia na sua componente OE.

A bolsa, em regime de exclusividade, terá a duração de 6 meses, eventualmente renováveis, com início previsto em 1 de Julho de 2010.

O valor mensal da bolsa será de € 745,00, pago por transferência bancária (preferencialmente).

Local de trabalho: IBMC - Instituto de Biologia Molecular e Celular (Grupo de Dinâmica e Instabilidade Cromossómica), Porto, Portugal

Programa de trabalho: (ver sumário em anexo).

Perfil pretendido:

Os candidatos devem possuir licenciatura na área das Ciências Biológicas, Bioquímica ou afins. Dá-se preferência a candidatos com experiência comprovada de laboratório e domínio de biologia molecular e cultura celular.

O prazo para recepção de candidaturas decorre de 25 de Maio a 8 de Junho de 2010.

As propostas deverão incluir carta de motivação, CV, e duas cartas de recomendação e ser enviadas por correio electrónico para candidaturas@ibmc.up.pt com indicação do código interno (PR223305).

Após avaliação do CV, os candidatos pré-seleccionados poderão ser chamados para entrevista.

A contratação será regida pelo estipulado na legislação em vigor relativamente ao Estatuto de Bolseiro de Investigação Científica, nomeadamente a Lei 40/2004, de 18 Agosto, e o Regulamento de Bolsas de Investigação Científica do IBMC (www.ibmc.up.pt/fellowships.php).

“Dissecting the cross-talk between mitotic checkpoint, ageing and cancer: towards the understanding of cell fate after mitotic slippage”

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Project Summary:

During mitosis, the spindle assembly checkpoint (SAC) acts to prevent exit from mitosis until all kinetochores (KTs) are stably attached to spindle microtubules (MTs). The SAC “wait anaphase signal” is generated by several Mad and Bub proteins, which accumulate only on unattached or weakly attached KT. These proteins catalyze the formation of an inhibitory complex that prevents anaphase-promoting complexes (APCs) from ubiquitinating those proteins required for chromatid cohesion and the mitotic state.

Drugs that interfere with MT assembly or dynamics, such as vinca alkaloids and taxanes, have been used extensively to treat cancers as they activate the SAC inducing mitotic delay (D-mitosis). However, the delay is seldom permanent, and even in the presence of an active SAC, most cells ultimately escape mitosis, a process commonly termed checkpoint adaptation or mitotic slippage. The factors that control the duration and fate of a D-mitosis remain largely unexplored. Depending on these factors, the cell will either i) die in mitosis or ii) exit mitosis as a 4N entity that can then enter apoptosis, senescence or a new cycle. One determinant factor seems to be the cell’s molecular phenotype, especially regarding SAC and apoptosis proficiencies.

SAC appears to be the only pathway that operates in vertebrates to delay progression through mitosis. Whereas a completely inactive SAC results in cell autonomous lethality, cells with a weakened SAC survive and exhibit chromosome instability. Mouse models of checkpoint gene haploinsufficiency exhibit susceptibility to carcinogenesis, and a transgenic mouse model of MAD2 overexpression suggests that an overactive checkpoint may also lead to chromosomal instability. Consistently to evidence from animal and cellular models, inactivating mutations in SAC genes have not been detected in human cancers, though these genes are expressed at reduced levels in a subset of tumors, most likely through epigenetic mechanisms.

Recently, SAC proteins have been directly implicated in the regulation of KT-MT attachments. RNAi depletion of BubR1, Bub1 and Bub3 proteins to levels below 15% leads to an accumulation of prometaphase cells with improperly attached chromosomes. This raises the question whether a weakened SAC might be able to induce a D-mitosis due to the presence of defective KT-MT attachments. Importantly, the outcomes from this mitotic delay should be examined to provide insight into the mechanisms leading to cancer susceptibility. Furthermore, since SAC senses the KT-MT attachments, its function may be important in modulating the effect of spindle poisons. Indeed, association between SAC defects and resistance to chemotherapeutic drugs, such as paclitaxel, has been reported, even though remains unexplored.

Another emerging area of interest related with SAC function is its unanticipated role in the ageing process. Mice expressing reduced levels of BubR1 and Bub3 proteins display an array of early ageing-associated phenotypes which strongly correlates with the severity of chromosome instability. This suggests a role for SAC in the development of progeroid features, perhaps by eliciting signals that drive cells into a senescent state.

In light of the present data, we propose to address the following problems regarding SAC implication in both cancer and ageing. First, examine the duration of mitosis and cell fate (aneuploidy, apoptosis, senescence) of non-transformed human cells with a weakened or overactive SAC. Second, identify differences in phenotypic responses and cell fate between normal and cancer cells with dysfunctional SAC. Third, examine the effect of anti-tumor drugs in the fate of SAC defective cells with normal and cancer genetic backgrounds. Fourth, dissect the roles of transcription, translation and proteolysis of key mitotic regulators and pro-apoptotic proteins in mitotic slippage outcomes. Fifth, analyze the effect of ageing in mitotic slippage rate as well as in SAC function. Previous approaches for studying exit from a D-mitosis have been collected largely on cancer cells, and have used flow cytometry and immunoblotting to score responses, which average cell populations. To resolve these issues, we propose to systematically investigate cell fate after D-mitosis both in normal and cancer cell lines using long-term time-lapse microscopy to score the response of individual cells in vivo. The team has the necessary background knowledge and technical expertise required for the successful execution of this project.