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Résumé du Projet de Stage (en 300 mots, 1 à 5 mots clés en gras)

In a way very analogous to phosphorylation/dephosphorylation, the addition of N-Acetylglucosamine (GlcNAc) on serines and threonines represents a reversible mechanism of regulation of cytosolic and nuclear proteins. Our group has recently published the first evidence showing that **FoxO1** is subject to **O-GlcNAc glycosylation**, and that this modification increases its transcriptional activity. FoxO1 can function as a **tumor suppressor**, by inhibiting cell proliferation and by stimulating apoptosis. Since glucose constitutes an important metabolic substrate for cancer cells, we propose to characterize FoxO1 O-glycosylation and its consequences on the expression of genes involved in proliferation and apoptosis. These studies will be performed in HEK293 cells transfected with reporter genes, as well as in cancer derived cell lines (HepG2, MCF7, MDA-MB-231). **Interfering RNA technology** will be used to establish the implication of FoxO1 O-glycosylation on proliferation and apoptosis in **cancer cells**.

Publications récentes de l'équipe, relatives au stage proposé

Nouaille S, Blanquart C, Zilberfarb V, Boute N, Perdereau D, Roix J, Burnol AF, Issad T. (2006) Interaction with Grb14 results in site-specific regulation of tyrosine phosphorylation of the insulin receptor. **EMBO Reports**. 7: 512-518.

Issad T. and Jockers R. Bioluminescence Resonance Energy Transfer (BRET) to monitor protein-protein interactions (2006) **Methods in Molecular Biology: Transmembrane signaling protocols** (Humana Press) 332:195-209

Blanquart C, Gonzalez-Yanes C, Issad T. Monitoring the activation state of insulin/insulin-like growth factor-1 hybrid receptors using bioluminescence resonance energy transfer. (2006) **Mol Pharmacol**. 70:1802-1811

Nouaille S, Blanquart C, Zilberfarb V, Boute N, Perdereau D, Burnol AF, Issad T. Interaction between the insulin receptor and Grb14: A dynamic study in living cells using BRET. (2006) **Biochem Pharmacol**. 72:1355-1366

Issad, T., Blanquart, C. and Gonzalez-Yanes, C. The use of Bioluminescence Resonance Energy Transfer (BRET) for the study of therapeutic targets: application to tyrosine kinase receptors (2007) **Expert. Opin. Ther. Targets** 11: 541-556

Kuo MS, Zilberfarb V, Gangneux N, Christeff N, Issad T. O-glycosylation of FoxO1 increases its transcriptional activity towards the glucose 6-phosphatase gene. **FEBS Letters** 2008; 582: 829-34.

Kuo, M.-S., Zilberfarb, V., Gangneux, N., Christeff, N., Issad, T. O-GlcNAc modification of FoxO1 increases its transcriptional activity: A role in the glucotoxicity phenomenon? (2008) **Biochimie**. 90:679-85.

Kuo, M.-S., Zilberfarb, V., Gangneux, N., Christeff, N., Issad, T. A new mode of regulation of FoxO1 by O-GlcNAc glycosylation: involvement in the glucotoxicity phenomenon. (2008) **Med Sci (Paris)**. 24(4):369-71.