



Ian Marc Bonapace

 UNIVERSITY OF INSUBRIA



[Printable Version](#)

Contact data

Assistant Professor

Department of Structural and Functional Biology
Via A. da Giussano, 12 – 21052 – Busto Arsizio (Va)
Tel: (office) +39 (0)331 339452 (lab) +39 (0) 331 339405
Fax: +39 (0) 331 339459
E-mail: ian.bonapace@uninsubria.it

Biography

Ian Marc Bonapace has obtained his degree in Biological Sciences on the in January 1982 - score 110/110 - University of Naples – Italy; and his Ph.D. in Cellular and Molecular Biology in 1990 at the IInd Faculty of Medicine - “Università Federico II” in Naples - Italy.
In 1982 he was Postdoctoral Fellow at the “Section of Molecular and Cellular Biology” - Cornell University – Ithaca, NY - USA.

In 1993-94 he was Assistant Professor at the Institute of General Pathology and Oncology of the 2nd University of Naples – Italy. In 1997-2000 he was Assistant Professor at the European Institute of Oncology – Milan – Italy; and since 2001 he has been an Assistant Professor at the School of Biological Sciences of the University of Insubria – Varese.

Research interests

In the last 7 years his research interests have been focused on the relationship between the transformation and the differentiation process.

Terminally differentiated cells (TD cells) constitute the larger part of the mammalian body and are characterised by two main features: i) they have irreversibly lost their ability to proliferate (post-mitosis) and ii) they have acquired specialised functions in a cell-type specific manner. The progression of differentiation is a co-ordinated event in which irreversible cell cycle arrest is coupled to the expression of tissue-specific genes. A large body of knowledge on the mechanisms governing progression through and/or arrest of cell cycle has been generated on cellular systems displaying reversible cell cycle. Surprisingly little is known about the mechanisms underlying the apparent inability of post-mitotic cells to respond to mitogenic stimuli. Therefore, studies of the mechanisms that determine the irreversible cell cycle arrest, which accompanies terminal differentiation, can increase our understanding of the control of the mutual exclusion of proliferation and differentiation and of the origin and progression of cancer.

To perform a biased approach to cancer transcriptomes, we utilized a model of terminally differentiated (TD) myotubes in vitro, induced to re-enter the cell cycle by the E1A viral oncogene, an early gene product of

tumorigenic adenovirus. While the action of E1A has been largely linked to its interference with the growth suppression function of pRb-family proteins, this event in itself is not capable of causing re-entry into the cell cycle of TD myotubes.

In human cancers, alterations of the pRb-pathway are a frequent occurrence. However, they are thought to be insufficient by themselves to cause neoplasia, as also shown by recent evidence in a mouse retinoblastoma model. Thus, E1A might provide a useful tool to uncover pathways, concomitantly needed with the inactivation of the pRb pathway, which might be directly relevant to human carcinogenesis.

To isolate cDNAs specifically induced and repressed by the action of E1A on TD myoblasts, we have chosen to use the PCR selection cDNA subtraction method (Clontech). The following major classes of genes could be identified:

Class-A. Pocket protein-dependent (not induced, or scarcely induced, by YH47/dl928; induced by Rb removal), E2F1-dependent (induced by E2F1 overexpression) genes.

Class-B. Pocket protein-dependent, E2F1-independent (or scarcely-dependent) genes. Interestingly, a subset of genes in this class (MCM 4, 6, and 7), which is known to be under the transcriptional control of E2F1 in non-post-mitotic cells, was not responsive to the overexpression of this protein in a TD environment, despite retaining pocket protein-dependence.

Class-C. Pocket protein-indifferent genes (induced by YH47/dl928, but also activated by Rb removal). Almost all of these genes were E2F1-independent, with the exception of K0648.

Class-D. Pocket protein-independent, or substantially-independent, genes. This group of 5 genes was activated by YH47/dl928 and scarcely by Rb removal. These genes were also E2F1-independent.

One interesting protein that emerged from the screen was: Np95. We have demonstrated that this protein was specifically induced by E1A, but not by over expression of E2F-1 or of the *cycE/cdk2* complex. In addition, the concomitant expression of Np95 and of *cycE/cdk2* was alone sufficient to induce S phase in TD cells. In NIH-3T3 cells, the expression of Np95 was tightly regulated during the cell cycle and its functional ablation resulted in abrogation of DNA synthesis. Thus, expression of Np95 is essential for S phase entry (Bonapace et al, 2002).

We studied the role of Np95 in chromatin interactions. We show that Np95 is tightly bound to chromatin *in vivo* and that it binds to histones *in vivo* and *in vitro*. The binding to histones is direct and shows a remarkable preference for histone H3 and its N-terminal tail. A novel protein domain, the SRA-YDG domain, contained in Np95 is indispensable both for the interaction with histones and for chromatin binding *in vivo*. Np95 contains a RING finger. We also demonstrate that this domain confers E3 ubiquitin ligase activity on Np95, which is specific for core histones, *in vitro*. Finally, Np95 possess specific E3

activity for histone H3 when the endogenous core octamer, coimmunoprecipitating with Np95, is used as a substrate (Citterio et al. 2004).

Teaching experience and appointments

Since 2001 he is the head teacher of the course of 'General Pathology'. In 2002, 2003 and 2005 he has been also the head teacher of the class 'Immunology'.

Since 2002 he is the Lecturer of 'Biology of tumors' within the course of 'Biology and Pharmacology of neoplastic transformation'.

Representative publications

1. F. Nicassio, F. Bianchi, M. Capra, M. Vecchi, S. Confalonieri, M. Bianchi, D. Pajalunga, M. Crescenzi, Ian Marc Bonapace, and Pier Paolo Di Fiore. (IMB and PPDF are both 'Corresponding authors') A cancer-specific transcriptional signature in human neoplasia *Journal of Clinical Investigation*. In the press.

2. Citterio E., Papait R., Nicassio F., Vecchi M., Gomiero P., Mantovani R., Di Fiore P.P. and Bonapace I.M. Np95 is a histone-binding protein endowed with ubiquitin ligase activity *Molecular and Cellular Biology* – 24(6):2526-35 (2004)

3. Bonapace I.M, Latella L., Papait R., Nicassio F., Sacco A., Muto M., Crescenzi M. and Di Fiore P.P Np95 is regulated by E1A during mitotic reactivation of terminally differentiated cells and is essential for S phase entry *The Journal of Cell Biology* 157, 909–914 (2002)

4. Bonapace I.M, Addeo R., Altucci L., Cicatiello L., Bifulco M., Laezza C., Salzano S., Sica V., Bresciani F., Weisz A. 17 β -estradiol overcomes a G1 block induced by HMG-CoA reductase inhibitors and fosters cell cycle progression without inducing ERK-1 and -2 MAP kinase activation. *Oncogene* 12, 753-763, (1996).

5. Addeo, R; Altucci L., Battista T., Bonapace I.M., Cancemi M., Cicatiello L., Germano D., Pacillo C., Salzano S., Bresciani F., Weisz A. Stimulation of Human Breast Cancer MCF-7 cells with Estrogens prevents cell cycle arrest by HMG-CoA reductase inhibitors *Biochemical and Biophysical Research Communications* 220, 864-870 (1996).

6. Gallo A., Benusiglio E., Bonapace I.M, Feliciello A., Cassano S., Garbi C., Musti A.M., Gottesman M.E. and Avvedimento E.V. (Please note that the first three authors have contributed equally to the research – see acknowledgements) v-Ras and Protein Kinase C de-differentiate thyroid cells by down-regulating nuclear cAMP-dependent Protein Kinase A. *Genes and Development* 6, 1621-1630, (1992).

7. Bonapace I.M., Sanchez M., Obici S., Gallo A., Garofalo S., Gentile R., Coccozza S. and Avvedimento V.E. Extinction and activation of the thyroglobulin promoter in hybrids of differentiated and transformed thyroid cells. *Molecular and Cellular Biology*. 10, 1033-1040, (1990).

8. Avvedimento V.E., Musti A.M., Fusco A., Bonapace I.M. and Di

Lauro R. Neoplastic transformation inactivates specific trans-acting factor(s) required for the expression of the thyroglobulin gene. Proc. Natl. Acad. Sci USA. 85, 1744-1748, (1988).

9. Polito L.C., Furia M., Cavaliere D. and Bonapace I.M. Analysis of rDNA magnification process in mei9bb mutant of *Drosophila melanogaster*. Genetics Supplement - 1980.