S.II.1.

Cancer immunoprevention

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The immune system effectively prevents tumor onset, and immunodeficiencies predispose to cancer. Unfortunately, a functional immune system is not 100% efficient in preventing either infections or tumors. However, the correlation between immune suppression and excessive cancer risk suggests that immune *stimulation* could prevent tumor onset, or at least reduce the risk.
In humans, cancer immunoprevention is already operative at the population level, in the form of vaccines against oncogenic viruses. The hepatitis B vaccine reduced by two-thirds the risk of hepatocellular carcinoma, and papilloma virus (HPV) vaccines almost completely prevented the development of cervical carcinoma in pre-approval trials. Widespread adoption of the HPV vaccine could lead, for the first time in human history, to the disappearance of a deadly cancer, just as vaccination eradicated smallpox in the past.
Is immunoprevention also applicable to the vast majority (>80%) of human tumors, not related to oncogenic viruses? Preclinical studies performed in my Laboratory, and in many others throughout the world, demonstrated that immunological stimuli do indeed prevent tumor onset.
Studies in HER-2 transgenic mice, which are prone to mammary carcinogenesis, showed that vaccination of young, healthy mice with cells or DNA encoding HER-2, coupled with potent biological adjuvants, could completely prevent tumor onset later in life. Immunity from mammary carcinoma was regulated by T cell cytokines and effected by anti-HER-2 antibodies. The fact that HER-2 is an *oncoantigen*, i.e. an antigenic molecule causally involved in carcinogenesis, was a key element in determining long-term immunoprevention.
Clinical development of cancer immunoprevention depends on the discovery of suitable oncoantigens in high-risk individuals, such as HER-2 itself, which is frequently amplified in breast cancers of Li-Fraumeni carriers. MUC-1, a cell surface mucin aberrantly expressed in colorectal carcinoma, is the target of early clinical studies that are paving the way to human cancer immunoprevention.

Key words: cancer vaccines; oncoantigens; HER-2

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S.II.2.

Chemopreventive agents targeting cancer stem cells for novel prevention approaches

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Cancer stem cells are known to play a role in tumorigenesis, invasion, recurrence, and metastasis. Characterization and better understanding of cancer stem cells offers an exciting strategy in cancer prevention and treatment. Targeting cancer stem cells by cancer preventive agents, such as vitamin D, triterpenoids, tocopherols, stilbenoids and other nutritional factors, may provide a promising approach to blocking the progression of premalignant tumors into invasive and metastatic cancer. Ductal carcinoma *in situ* (DCIS) is an early precursor in breast carcinogenesis, which progresses to invasive ductal carcinoma (IDC) if left untreated. Using mammosphere culture and DCIS xenograft studies, we have been investigating the role of nutritional and dietary factors as well as synthetic drug candidates on regulation of breast cancer stem cells and inhibition of cancer progression. Among chemopreventive agents tested, vitamin D compounds are potent inhibitors of cancer stem cells that they reduce the tumor-initiating subpopulation *in vitro* and repress the DCIS progression *in vivo*. Treatment with these cancer preventive agents decreases markers associated with the stem cell-like phenotype and pluripotency in mammospheres. Epigenetic changes introduced by cancer preventive agents during cancer progression are important, and the effects of these agents on regulation of microRNAs are being investigated. Regulation of breast cancer stem cells may potentially contribute to the inhibition of breast cancer progression. Identification of new targets and pathways in cancer stem cells may provide a new direction in cancer prevention research.

Key words: cancer stem cells; vitamin D; cancer prevention

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S.II.3.

Mortalin and cancer therapeutics

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Mortalin/mthsp70, a stress protein, is enriched in cancer cells and tissues. It was first cloned in our laboratory while screening to identify proteins associated with mortal or immortal phenotype. It has been shown to play several life essential functions including chaperoning, intracellular trafficking, mitochondrial import of proteins, cell proliferation, control of ROS production and apoptosis. It has been established that mortalin interacts with tumor suppressor protein, p53, and causes inactivation of its transcriptional function, control of centrosome duplication and apoptotic activities; all the three are tightly related to cancer development. Most recently, we found that mortalin promotes cancer aggressiveness and metastasis by multiple pathways including activation of telomerase, hnRNP-K, and several other factors involved in epithelial-mesenchymal transition (EMT). Mortalin knockdown in cancer cells, by a variety of anti-mortalin molecules, was shown to cause apoptosis in cancer cells *in vitro* and *in vivo*. Thus, mortalin is proposed as a potential target for cancer therapeutics.

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S.II.4.

TAp73 activation in cancer

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p53 is a transcription factor regulating a plethora of mechanisms leading to tumor suppression. Although p53 activation causes tumor regression *in vivo*, the fact that *TP53* gene is mutated in more than 50% human cancers has proven this strategy difficult to implement therapeutically. Results from cell lines and mice models demonstrate that the p53 family member, p73, can compensate for p53 tumor suppressive functions in cancers with p53 mutations and deletions. Mutations of *TP73* gene occur in less than 0.1% of all cancers, which makes p73 a promising target for cancer therapy.

Withaferin A (WA) is one of the most bioactive compounds of *Withania somnifera*, exerting anti-inflammatory, anti-angiogenic, chemotherapeutic and chemopreventive effects in *in vivo* models. Protoporphyrin IX (PpIX), was shown to induce death of colon cancer and cervical cancer cell lines HCT 116 and HeLa. Both WA and PpIX trigger apoptosis of cancer cells in a p53-related manner.

Basing on structural and functional homology between p53 family members, the aim of our research was to analyze the role of tumor suppressive isoforms of p73 (TAp73) in cancer cells response to small molecules WA and PpIX, for further validation of TAp73 as a potential target for cancer prevention and therapy.

We showed that oxidative stress induced by withaferin A led to JNK-mediated TAp73 phosphorylation and activation. Stabilization of TAp73 upon WA resulted from an enhanced binding to NQO-1, which protected TAp73 from degradation.

Protoporphyrin IX was shown to bind to the N-terminal domain of TAp73 *in vitro* and stabilize TAp73 in cancer cell lines and xenograft mouse model. PpIX-mediated stabilization of TAp73 was a consequence of modulating its interactions with protein regulators. Knockdown of *TAP73* significantly inhibited cell death induced by both WA and PpIX highlighting its role in stress-induced cancer cells response and pointing to TAp73 as a promising candidate for cancer prognosis and therapy.

Key words: small molecules; oxidative stress; p53 family

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