Cancer Prevention Think Tank
December 8, 2006

Molecular Targets for Cancer Prevention

Moderators: Nancy Colburn (LCP, CCR) and Powell Brown (Baylor College of Medicine)
Panel Members: Powell Brown (Baylor College of Medicine), Giorgio Trinchieri (CIP, CCR), Jeff Green (LCBG, CCR), Glenn Merlino (LCBG, CCR), Mathew Meyer (MBTL, CCR), and Stuart Yuspa (LCBG, CCR)

Mouse Models: Major Discussion Points

1. Mouse models provide a valuable means to a) identify and validate molecular targets for prevention, and b)carry out pre-clinical prevention trials of candidate intervention agents.
2. Genetic models involving the stroma and the tumor microenvironment represent a major opportunity for target validation.
3. Mouse studies remain useful for pharmacokinetic and pharmacodynamic studies of compounds for cancer prevention as long as differences between mice and human metabolism are recognized. There were varying levels of enthusiasm regarding humanizing mice for drug metabolism. In cases in which a chemopreventive agent is known to be metabolized by an enzyme that differs in mice and humans, these humanized models may be useful. Such cases have not yet been defined.

Recommendations

1. Develop and utilize chemical carcinogenesis models alone and in combination with genetically engineered models, particularly the more sophisticated models of tissue specific and single allele expression.
2. Encourage models that address the contribution of the stroma and the microenvironment in the development of carcinomas.
3. Develop tools that allow the prediction of human efficacy and toxicity based on either humanized mouse models or current knowledge of the relationship between mouse and human metabolism.

Microenvironment, Inflammation and Cancer Prevention: Major Discussion Points

1. We need to understand the balance between inflammation and immune response and how this affects tumorigenesis and tumor progression. There is a trade-off between protective inflammation (usually acute) and inflammation as a tumor promoter (usually chronic).
2. The pro-inflammatory molecules responsible for an inflammation response are also effectors of tumor promotion.
3. It is not just the epithelial cells that are important but also immune cells and stromal fibroblasts that produce angiogenic factors.
4. Chronic infection affects the microenvironment, and a high proportion of cancers (possibly >10%) arise in part from infection.
5. Important microenvironment targets include angiogenic factors VEGF and VEGFR,,macrophages, chemokines and basophils.
6. Promising proinflammatory *molecular targets* include: COX-2, NFκB, AP-1, and STAT-3 all of which are elevated during human cancer progression and have been validated in mouse models.

Recommendations

1. Continue to support basic research aimed at understanding the role of inflammation in inducing cancer.
2. Encourage collaborations between basic researchers and clinicians to develop noninvasive ways to detect inflammation.

3. Support the development of 3D culture based systems, so that interactions among the cells and cell types can be studied.

Stem Cells and Cancer Prevention: Major Discussion Points

1. We need to identify cancer stem cells from more tissue types and understand the origin of the cancer stem cell; does it arise from a normal adult stem cell or from a more lineage-restricted cell that has regained self-renewal properties?
2. We need to understand the relationship between normal adult stem cells and cancer stem cells.
3. Ideal therapy would be one that kills the cancer stem cell in a single pulse.
4. The need to use a drug that differentiates between a cancer stem cell and a normal stem cell may be tissue specific. If targeting an organ that no longer needs the stem cell (i.e. prostate or breast), then differentiation between normal and cancer stem cells is unnecessary, in contrast to treating tissue that uses stem cells for continuous renewal (i.e. skin or colon).
5. If we understand the process of how a stem cell becomes cancerous, then we could target the process, not necessarily the cell.
6. The cancer stem cell provides a likely cell for acquiring genetic hits due to its long life span. Therefore, risk factors may occur at a young age and interventions may need to be targeted to younger persons. An ideal prevention agent may be one that can be used for a short time relatively early in life, but will give lifetime protection to the high risk patient. Examples include lactation for prevention of breast cancer and protection from sun exposure in children to reduce melanoma risk.

Recommendations

1. Support initiatives to study the relationship between normal adult and cancer stem cells.
2. Provide increased resources for the isolation of stem cells, i.e. flow core facilities.
3. Encourage interdisciplinary research that includes basic researchers from disciplines such as developmental biology and cancer biology, as well as clinicians.
4. Develop strategies to target cancer stem cells for the prevention of metastatic disease.

Priorities: How do we hit the target?

Recommendations

1. Use a combinatorial approach for cancer prevention. This approach can include:
   - Hitting the primary target with more than one therapy
   - Hitting more than one target
   - Hitting more than one pathway leading to the target
   - Sequentially changing therapy regimens to avoid resistance
2. Approach nutritional interventions in the same way as drugs or other compounds when considering mouse models and prevention. For example, assume that drugs and nutritional interventions alike can carry risks of toxicity.
3. Recommend that NCI develop mechanisms to work with drug companies in order to perform clinical trials involving multiple agents manufactured by different companies.
4. Pursue promising targets such as oncogenic molecules AP-1, NFκB, COX-2, EGFR, STAT-3, and ER. All of these targets are elevated during human cancer progression and have been validated in mouse models. Despite setbacks with particular drugs, COX-2 remains an important target for which better agents and combinations need to be identified. In addition, consider stabilizing or elevating tumor suppressors such as Pdcd4 or p27 as both have been found to be underexpressed during human cancer progression and have been validated in mouse models.

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Nutritional and Pharmacological Interventions to Prevent Cancer

Moderators: Elaine Lanza (LCP, CCR), Monica Bertagnolli (Brigham & Women's Hospital)
Panel Members: Monica Bertagnolli (Brigham & Women's Hospital), Jennifer Eng-Wong (MOB, CCR), John Milner (NSRG, DCP), Asad Umar (GOCRG, DCP), Jim Crowell (CADRG, DCP), Pat Steeg (LMP, CCR), James McMahon (MTDP, CCR)

Individualized Prevention: Major Discussion Points

1. The future will be individualized cancer prevention. Promising bio-molecular techniques, such as multiplexing genes and biomarkers are now available; however, the repeatability and accuracy of these techniques and bioinformatics tools must be improved before they can be used in a clinical setting.
2. Any method of classifying individuals would qualify as a 'device' according to FDA regulations and would have to meet specific predetermined criteria.
3. There is a lack of prospective evidence regarding biomarkers. Initial gene/biomarker screening for eligible participants would require a large part of the budget of any prevention trial. The additional costs would have to be weighed against the potential benefits of targeted cancer prevention.

Recommendations

1. Develop, using mouse and human studies, biomarker panels that can predict with sufficient diagnostic accuracy and repeatability, an individual's risk of cancer and his/her response to treatment on a molecular level.
2. Gather prospective data within current prevention trials to test the predictive power of biomarker panels in determining an individual's cancer risk.

Human Prevention Trials: Major Discussion Points

1. Planning a randomized control trial must include dose-response data, phase 1 trials, mechanistic studies, structure studies, epidemiologic evidence, and animal studies. Consider timing and duration of administration in relation to the subjects' age, risk profile and co-morbidities when determining eligibility requirements. Intermittent dosage based on age or cancer progression 'windows', rather than continuous administration, may also be important.
2. Determination of the risk-benefit ratio is needed in selecting the appropriate target population. It is impossible to completely prevent toxicity/side effects for some participants; thus, identification and exclusion of those expected to be most vulnerable to side effects is prudent.
3. The risk of side effects must be weighed against the potential benefits, with the understanding that some individuals will be at high risk for developing cancer and/or side effects. Currently, there is limited availability of chemopreventive agents for these high risk individuals.
4. Early trial termination due to a small number of adverse events may preclude determining efficacy of a preventive intervention in a high risk group of individuals.

Recommendations

1. Support research regarding timing and duration of dose, particularly with respect to identifying periods at which intervention is most efficacious.
2. Seek evidence for any experimental preventive agent, whether a drug or a nutritional intervention, from a number of fields.
3. Encourage clinicians to adequately communicate the risk-benefit ratio to patients. It may be necessary to stratify participant groups according to risk-benefit ratios so that individualized approaches can be developed.

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Secondary/Metastasis Prevention Trials: Major Discussion Points

1. Imaging techniques that can detect micrometastases will be valuable. These will aid investigation of efficacy as well as the 'therapeutic window' of a therapy.
2. Organ-specific adjuvant therapies should be developed and tested. More information is needed regarding differences in the efficacy of a therapy according to organ site or primary or secondary tumor.
3. It may be possible to produce biomarker panels that predict, with sufficient diagnostic accuracy and repeatability, those individuals most likely to develop secondary tumors at a specific organ site.
4. Identification of intermediary endpoints to predict whether a therapy was successful should also be encouraged.

Recommendations

1. Support multidisciplinary teams for detecting micrometastases through advanced biomedical technologies such as imaging techniques, and those that are developing organ-specific adjuvant therapies.
2. Include detection of cancers not yet evident but predicted by a molecular profile of biomarkers.

Priorities for human prevention studies

Recommendations

1. Increase interactions with clinicians for testing the effectiveness of pharmaceuticals/food factors/natural factors/exercise, molecular targets, and biomarkers in humans. Research priorities should be partly determined by CCR clinical researchers, with molecular research developed from these studies. Use a multidisciplinary 'bench-to-bedside' framework in directing organ-specific or mechanistic research.
2. Increase collaborations with the Division of Cancer Prevention to identify and validate markers for exposure, effect and susceptibility for delivery of effective approaches for cancer prevention, particularly in high risk groups.