The Metastasis Research Network (MetNet)

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Metastasis and the “Metastatic Cascade”

• Metastasis accounts for the vast majority of deaths in patients with solid tumors, yet therapeutic strategies to manage metastatic disease are lacking.

• Metastasis was considered the late end product of a linear process, the “metastatic cascade”.

The metastatic cascade
1. Local Invasion & Intravasation
   Angiogenesis, EMT, migration
2. Survival in circulation
   Immune evasion, CTC clusters, platelets binding
3. Arrest in distant organ
   Trapping/specific adhesion
4. Extravasation:
   Physical barriers, seeding
5. Micrometastasis:
   Survival on arrival, dormancy
6. Macrometastatic growth
Metastasis can occur early and often

- Detect disseminated cells in circulation and in secondary sites even before diagnosis
- The likelihood, timing, frequency, and mechanisms of early dissemination for many cancers are unknown
Metastasis can result from concurrent overlapping routes

- Cartoon depicts relationships between the primary tumor and metastatic clones

Monoclonal sequential seeding

Polyclonal seeding

Cross-metastatic seeding

LN = lymph node
M = metastatic clone

Current Challenges in metastasis research

• Tumors preferentially metastasize to specific organs and tissues
  • In general, mechanisms that regulate tropism are not well understood

• Metastatic cells can remain dormant for weeks, months, or years before clinical manifestations
  • In general, mechanisms that regulate dormancy are poorly understood, and likely include strong microenvironmental and systemic components

• Phenotypic plasticity of metastatic cells can underlie therapeutic resistance
  • The role of dynamic molecular, cellular, and microenvironmental interactions are not well characterized and experimental systems are lacking

• Current model systems are not representative
  • Physiologically relevant in vitro and in vivo models that capture the entire metastatic process to mimic that seen in humans are lacking

Obenauf AC, Massague J. Trends in Cancer, 2015
A comprehensive picture of metastasis does not currently exist

Rapid autopsy studies have provided a catalog of sites of metastasis, however:

• Knowledge of metastasis is fragmented because of siloed studies that concentrate on one stage of the “metastatic cascade”
  • Studying each stage in isolation misses the others

• Approaches and technologies that provide a physiological description of overlapping, non-linear processes are limited (i.e., approaches that span scales from cell → tissue → organ → body).

Need: A new view of metastasis that accounts for the dynamic, non-linear, multi-scale physiological interactions required for tumor cell dissemination, colonization, growth, and drug resistance.
Opportunities to advance metastasis research

• New viewpoints on “old” ideas are percolating within the community
  • Metastasis occurs early, is dynamic, and non-linear
  • Cell plasticity is not limited to EMT or MET
  • Cooperativity between multiple cell types contributes to metastasis

• New approaches and tools will facilitate a comprehensive view
  • Surgical approaches that improve human relevance
  • *In vivo* bar coding and lineage tracing tools
  • Advanced imaging techniques for *in vivo* and multi-modal measurements
  • Single cell data collection and integrative analyses
Proposal: The Metastasis Research Network

• Develop a network of 4 – 5 Metastasis Research Centers (U54 mechanism)
• Each center will focus on the intersection of two or more emerging themes that span the metastatic process:
  • The likelihood, timing, and frequency of early dissemination
  • The interactions and crosstalk between metastatic cells, including circulating tumor cells, and other host non-cancer cells or systems (e.g., immune or nervous)
  • The acquisition of, maintenance of, or emergence from metastatic dormancy
  • The response of metastatic cells, including those that are dormant, to therapies
• Teams will be expected to propose multidisciplinary approaches that incorporate appropriate technology and analysis capabilities that lead to a comprehensive and mechanistic understanding of metastasis
What would a Center look like?

• A multi- and inter-disciplinary effort involving:
  • cancer biology, physiology and pathology, bioengineering, biophysics, systems biology, computational analyses

• Encompassing multiple themes simultaneously, for example:
  • From different primary sites to same secondary site
    • Focus: determinants of organotropism
    • Themes: early dissemination and interactions
  
  • How treatments influence the metastatic process
    • Focus: treatment-associated cell phenotypic and metabolic plasticity
    • Themes: early dissemination, dormancy, and treatment
Portfolio Analysis

- Despite advanced techniques and knowledge, the metastasis-related portfolio across NCI has remained static over the past 5-10 years.

- Portfolio consists of a spectrum of awards, with the majority being investigator-initiated R01 awards that focus on single elements of the metastatic cascade
  - Early events and late events poorly represented
  - Invasion/Migration more readily adaptable to in vitro study

- Portfolio also contains several projects within on-going programs that complement the MetNet, including:
  - DCB: CSBC, PS-ON
  - Trans-NCI: HTAN
Budget and Review considerations

- 4-5 Centers (U54 mechanism)
  - 2-3 projects
  - Shared resources cores (up to 2)
  - Administrative core
    - Dedicated data manager and coordinator
- $1.5M/ U54 total cost per year
- 5 years of support
- $37.5M total costs over 5 years

- Review:
  - Two receipt dates, one per year (2020, 2021).
  - Require review by a Special Emphasis Panel
Justification for use of the RFA and Cooperative Agreement U54 mechanism

• RFA:
  • Dedicated set-aside provides indication of NCI commitment
  • Energize the metastasis research community, and encourage new researchers to the field
  • Multidisciplinary effort using system-level approaches
    • Portal for bringing new researchers to the field

• Cooperative Agreement:
  • Foster interaction and collaboration across the network and with other programs
  • Facilitate interactions and opportunities for junior investigators
  • Facilitate interactions between the network and larger research community
    • Admin supplements for collaborations
    • Borrow from the RAS Initiative playbook for hosting a biannual meeting and/or blog discussion forum
  • Substantial NCI programmatic involvement to help maximize resources for PIs and the NCI
Evaluation of the Network

• Two-tier evaluation process:
  • Annual evaluation of individual centers and projects
    • Consider network participation, progress, accomplishments, publications
  • Evaluation of the network overall
    • Establishment of productive cross-network collaborations (publications/research grant applications),
    • Retention of junior investigators within the metastasis research field,
    • Development/sharing of new technologies and models,
    • Deposition of data in appropriate data bases,
    • Interaction with additional NCI-sponsored programs.
Measurements for the Overall Success of the MetNet

• A more comprehensive understanding of metastasis and how that knowledge can be translated into intervention strategies
• Sustained influx of new R01 applications into the biology of metastasis using systems-level approaches
• Generated resources accessible and useful to the larger research community
• Promotion and sustainability of the metastasis workforce
Pursuing a comprehensive and mechanistic understanding that accounts for the dynamic, non-linear, multi-scale physiological interactions required for metastasis.