

DISCUSSION SESSION ON LECTURE #10: STUDY QUESTIONS

ASSIGNED PAPER: Dai C, Whitesell L, Rogers AB, Lindquist S (2007) Heat shock factor 1 is a powerful multifaceted modifier of carcinogenesis. *Cell* 130: 1005-1018.

1. Eukaryotic cells that have become fully malignant contain many genetic and epigenetic alterations (including point mutations, deletions, rearrangements, amplifications, translocations, and transcriptional silencing). A select few of these changes are causal for driving cell proliferation and survival, but others arise as a consequence of unchecked and unregulated proliferation. The results in this paper suggest that such cancer cells are, in essence, under constant stress and become "addicted" to the need for the normal cellular functions of certain proteins that are not themselves considered oncogenes *per se*.
2. What is HSF1? What does it normally do in cells? How is its function turned on? What products and/or processes are under its control?
3. What model systems did these investigators use to determine whether HSF1 function has any role in supporting or sustaining the ability of tumorigenic cells to form overt tumors? How did they extend their findings to human cancers?
4. To date, no somatic mutations in the *HSF1* gene that alter its properties or its level of expression have been identified in any human cancers; yet, based on the studies in this paper, how might HSF1 function in or contribute to tumorigenesis?

QUANTITATIVE QUESTION: Ionic strength (μ) is a measure of the effect of the dissolved ions in solution and is defined by the equation $\mu = \frac{1}{2} \sum_i M_i z_i^2$, where M_i is the molarity of ion i and z_i is the charge on ion i , summed over all of the ions present. Increasing the ionic strength decreases the "sphere of influence" of any given charged site on a protein in aqueous solution. The effective sphere of influence of a charge in solution is $1/b$ (the so-called Debye length), where $b^2 = (4 \pi e^2 / \epsilon k T) \sum_i M_i z_i^2$, and e is the charge of the electron, ϵ is the dielectric constant of the solvent (a measure of the charge-shielding effect of the medium), k is the Boltzmann constant, and T is absolute temperature ($^{\circ}\text{K}$). Thus, the Debye length is proportional to $1 / \sqrt{\mu}$. (a) How much higher is the ionic strength of a 1 M solution of NaCl than that of a 1 M solution of $(\text{NH}_4)_2\text{SO}_4$? (b) Given the above considerations, provide a reasonable physicochemical explanation for (i) why essentially all globular proteins aggregate and precipitate when placed in a solution that has an ionic strength below that equivalent to a solution of 10 mM NaCl and, conversely, (ii) why essentially all globular proteins require a moderate amount of salt (equivalent to >100 mM NaCl) in the purification and/or assay buffer to remain soluble and be active.